Pachyonychia Congenita Project

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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.

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GENEReviews
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Pachyonychia Congenita

[*Includes: Pachyonychia Congenita Type 1, Pachyonychia Congenita Type 2*]

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Summary

Disease characteristics. Pachyonychia congenita (PC) is characterized by hypertrophic nail dystrophy, focal palmoplantar keratoderma and blistering, oral leukokeratosis, cyst formation, palmoplantar hyperhydrosis, and follicular keratoses on the trunk and extremities. PC includes two main subtypes,

pachyonychia congenita type 1 (PC-1) and pachyonychia congenita type 2 (PC-2). Variants of PC include focal non-epidermolytic palmoplantar keratoderma (FNEPPK), with keratoderma occurring on the palms and soles but usually without nail dystrophy; steatocystoma multiplex (SM) with widespread cysts but with little or no nail involvement or palmoplantar keratoderma; and late-onset PC (PC tarda), which resembles either PC-1 or PC-2 and has onset from late childhood to middle age.

Diagnosis/testing. PC is diagnosed by clinical findings and by molecular genetic testing. The two keratin genes known to be associated with PC-1 are KRT6A (encoding keratin, type II cytoskeletal 6a) and KRT16 (encoding keratin, type I cytoskeletal 16). The two keratin genes known to be associated with PC-2 are KRT6B (encoding keratin, type II cytoskeletal 6b) and KRT17 (encoding keratin, type I cytoskeletal 17). Molecular genetic testing of these four genes is available on a clinical basis.

Management. Treatment of manifestations: Pain from the palmoplantar keratoderma can be reduced by limiting friction and trauma to the feet by minimizing walking or standing, reducing hydration of the stratum corneum by using wicking socks and ventilated footwear, selecting comfortable shoes, and maintaining ideal body weight. Foot care includes paring down hyperkeratotic areas and topical therapies for hyperkeratosis including emollients and lotions containing keratolyics. Early detection permits treatment of secondary bacterial and yeast/fungal infections on the feet and nails and in the mouth. Care of thickened nails often requires the use of surgical or razor blades or sanders such as a Dremel® tool. Troublesome nails can be removed surgically. Frequent brushing of teeth can improve the appearance of thick, white patches on the tongue and oral mucosa. Poor feeding in infants with leukokeratosis may require use of a bottle with a soft nipple and an enlarged opening. Rarely, emergency surgical intervention may be needed to re-establish the airway in young children with laryngeal thickening/growths. Steatocystoma multiplex and other pilosebaceous cysts can be treated initially by incision and drainage. Prevention of secondary complications: attention to pre- and post-grooming hygiene to prevent infection. Agents/circumstances to avoid: trauma, friction, and sheer forces to the skin and nails. Therapies under investigation: Studies on the use of a K6a mutation-specific siRNA, rapamycin, anti-TNF biologics, and botulism toxin are underway.

Genetic counseling. Pachyonychia congenita is inherited in an autosomal dominant manner. Approximately 50% of cases appear to result from a de novo mutation. Offspring of an affected individual have a 50% chance of inheriting the disorder. Prenatal diagnosis is possible for pregnancies at increased risk if the disease-causing mutation in the family is known.

Diagnosis

Clinical Diagnosis

Pachyonychia congenita (PC) encompasses a range of inherited ectodermal dysplasias, divided into two main subtypes, pachyonychia congenita type 1 (PC-1, Jadassohn-Lewandowski syndrome) and pachyonychia congenita type 2 (PC-2, Jackson-Lawler syndrome), which can usually be distinguished by clinical examination [Terrinoni et al 2001, Leachman et al 2005, Liao et al 2007]. Considerable overlap can occasionally exist between PC-1 and PC-2, which can make diagnosis difficult. In particular, cysts, though more common and severe in PC-2, are now recognized as a feature of PC-1 as well.

The predominant and most common clinical feature in PC is hypertrophic nail dystrophy in association with a focal, painful palmoplantar keratoderma.

Other findings common to both PC-1 and PC-2:

- Palmoplantar blistering
- Oral leukokeratosis
- Follicular keratoses on the trunk and extremities
- Pilosebaceous cysts
- Palmoplantar hyperhydrosis

Other findings observed only in PC-2:

- Natal or prenatal teeth, present at birth or within one month of birth
- Widespread steatocystomas (benign lesions)
  Note: Steatocystomas normally develop at puberty, making it difficult to distinguish PC-1 from PC-2 in young children without molecular genetic testing.
- Pili torti (twisted hair), observed in a very small subset of individuals

Variants of PC (based on shared keratin mutations)

- Focal non-epidermolytic palmoplantar keratoderma (FNEPPK). Keratoderma of varying severity occurs on the palms and soles as in PC-1, but there is usually no nail dystrophy.
- Steatocystoma multiplex (SM). Widespread steatocystomas develop at puberty as in PC-2, but there is little or no nail involvement or palmoplantar keratoderma.
- Late-onset PC (PC tarda) resembles either PC-1 or PC-2. Onset ranges from late childhood to about age 20 years [Hannaford & Stapleton 2000]

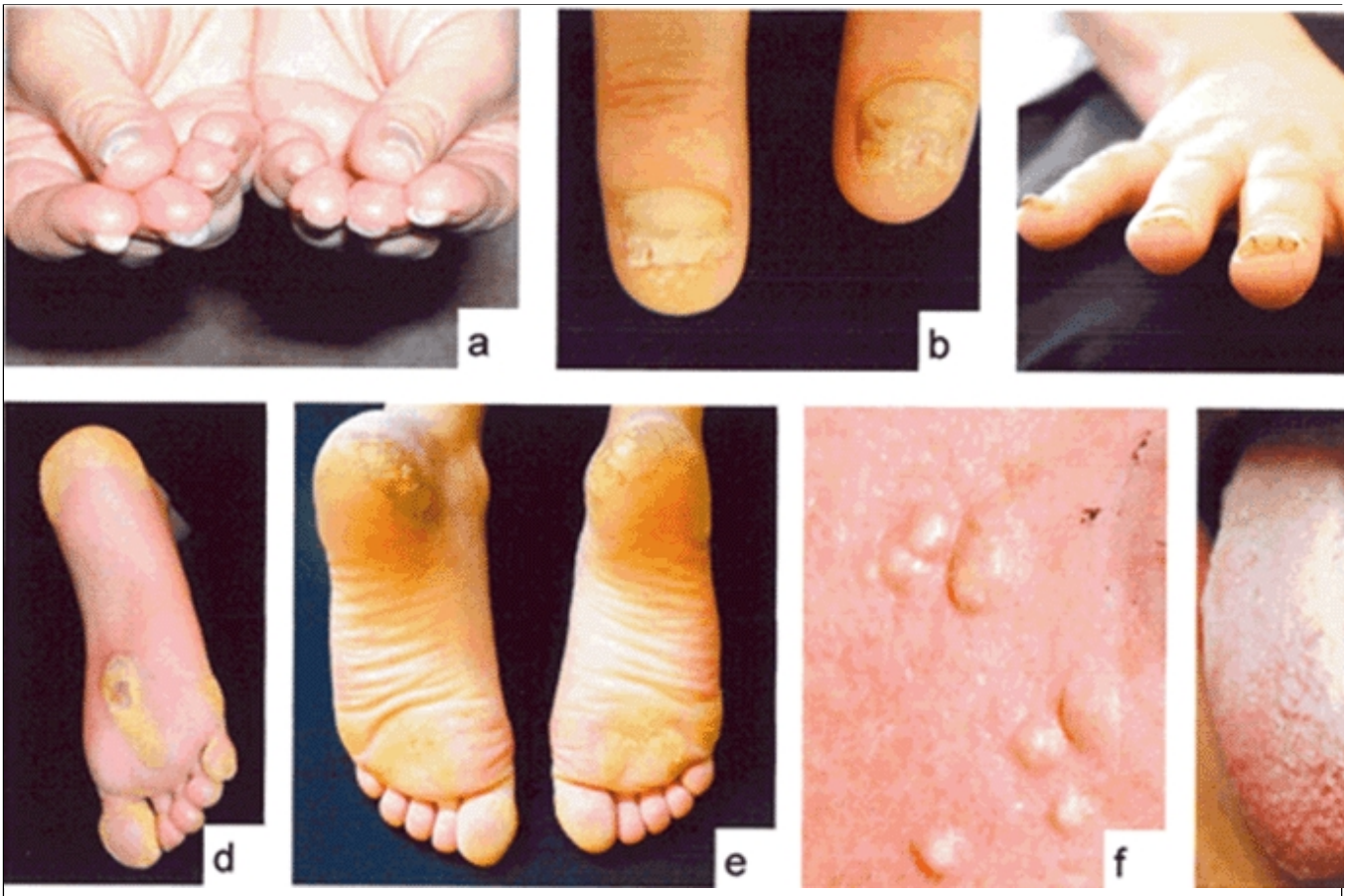

Figure 1. Common findings of pachyonychia congenita include: thickened and dystrophic nails (both fingernails and toenails) (a-c); bullae (usually on the pressure points of the heels and soles); hyperkeratosis (d-e); cysts (f); and oral leukokeratosis (g).

See Figure 1.

Testing

Biopsy examination. Histologic, immunohistologic, or electron microscopic examination of the nails or skin from individuals with PC is not helpful in confirming the diagnosis of PC.

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.

Genes. The four keratin genes known to be associated with pachyonychia congenita and the subtype of pachyonychia congenita:

- PC-1
  - KRT6A (encoding keratin, type II cytoskeletal 6a)
  - KRT16 (encoding keratin, type I cytoskeletal 16)
- PC-2
  - KRT6B (encoding keratin, type II cytoskeletal 6b)
  - KRT17 (encoding keratin, type I cytoskeletal 17)

Clinical testing

- Sequence analysis

  Sequence analysis of KRT6A and KRT16 identifies mutations in approximately 90% of individuals with PC-1 [Terrinoni et al 2001, Smith et al 2005, Liao et al 2007].

  Sequence analysis of KRT6B and KRT17 identifies mutations in approximately 90% of individuals with PC-2. [Terrinoni et al 2001, Smith et al 2005, Liao et al 2007].

  The highly conserved helix boundary domains, the site of the majority of mutations, are screened first; the remaining exons are screened as needed.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Pachyonychia Congenita

Gene Symbol	Phenotype	Test Method	Mutations Detected	Mutation Detection Frequency	Test Availability
KRT6A, KRT16	PC-1 / FNEPPK [1]	Sequence analysis	Sequence variants	90%	Clinical
KRT6B, KRT17	PC-2 / SM [2]	Sequence analysis	Sequence variants	90%	Clinical

1. Focal non-epidermolytic palmoplantar keratoderma
2. Steatocystoma multiplex

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

Confirming/establishing the diagnosis in a proband. Molecular genetic testing is guided by clinical

phenotype:

- PC. If no mutation is identified in the predicted two keratin genes for PC-1 or PC-2, the other two keratin genes associated with PC should be screened as the clinical features of the two types overlap.
- Focal non-epidermolytic palmoplantar keratoderma (FNEPPK). All mutations to date are in KRT16, but mutations may theoretically occur in KRT6A.
- Steatocystoma multiplex (SM). Screen for mutations in KRT17 and KRTK6B as for PC-2.
- Late-onset PC (PC tarda). Screen for mutations in KRT6A and KRT16 if the phenotype resembles PC-1 or for mutations in KRT6B and KRT17 if the phenotype resembles PC-2.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) Disorders

No other phenotypes are associated with mutations in KRT6A, KRT6B, or KRT17.

Unilateral palmoplantar verrucous nevus (UPVN). In one person, mosaicism for a KRT16 mutation was present in the affected, but not unaffected, palm skin [Terrinoni et al 2000].

Clinical Description

Natural History

The severity of all symptoms can vary widely, both within the same family and among families with the same disease-causing mutation.

Pachyonychia Congenita Type I (PC-1, Jadassohn-Lewandowski Syndrome)

Hypertrophic nail dystrophy, the predominant clinical feature of PC-1, is typically noted within the first few months of life. The nail dystrophy appears to fall into two phenotypes:

- Nails that grow to full length and have an upward slant caused by the prominent distal hyperkeratosis (often with an accentuated curvature of the nail)
- Nails that have a nail plate that terminates prematurely leaving a gently sloping distal region of hyperkeratosis and exposed distal finger tip

Focal palmoplantar keratoderma usually presents during the first few years of life when a child starts bearing weight and walking. Blisters can develop beneath the keratoderma. For many individuals, blisters and the constant foot pain are more severe in warmer weather. The pain associated with plantar focal blistering often results in the use of crutches, canes, or wheelchairs.

Oral leukokeratosis (thickened white patches on the tongue and cheek) is often present; in babies, it can cause feeding difficulties.

Follicular keratosis, usually on the elbows and knees, occurs in some persons.

Other findings that may occur:

- Excessive sweating of the palms and soles (palmoplantar hyperhydrosis) observed in approximately 50% of individuals with PC-1 and PC-2
- Axillary and inguinal cyst formation
- Excessive production of waxy material in the ear
- Hoarseness (laryngeal involvement), reported primarily in young children. Although rare, laryngeal involvement may cause life-threatening respiratory distress.

Pachyonychia Congenita Type II (PC-2, Jackson-Lawler Syndrome)

Clinical findings are similar to PC-1.

The focal palmoplantar keratoderma in PC-2 may be less severe than in PC-1.

The clinical features present in PC-2 that distinguish it from PC-1:

- Widespread steatocystomas. Cysts normally do not develop until puberty, although early onset has been reported [Feng et al 2003].
- Natal teeth or prenatal teeth. Some individuals have a few prenatal or natal teeth, but this finding is not consistently present even within the same family [Leachman et al 2005]. Primary and secondary dentition is normal.
- Pili torti (twisted hair). Mainly affecting eyebrows and body hair, pili torti occurs in a small subset of individuals with PC-2. Vellus hair on the arms may appear wavy (see Table 2).

Table 2. Phenotypic Features of PC-1 and PC-2

Phenotypic Feature	Percent of Individuals with PC-1 [1]	Percent of Individuals with PC-2 [2]
Dystrophic toenails	98%	100%
Dystrophic fingernails	98%	96%
Plantar keratoderma	90%	95%
Oral leukokeratosis	83%	40%
Palmar keratoderma	64%	82%
Follicular keratoses	59%	67%
Cysts (any type)	26%	96%
Laryngeal involvement (hoarseness)	26%	Unknown [3]
Hyperhydrosis	82%	Unknown [3]
Hair abnormalities	26%	36%
Natal/prenatal teeth	0	50%

Adapted from Leachman et al [2005]
1. Confirmed as having mutations in KRT6A or KRT16
2. Confirmed as having mutations in KRT6B or KRT17
3. Insufficient data

Genotype-Phenotype Correlations

Even within the same family, the same mutation can result in variable severity (e.g., mild versus severe keratoderma) or variable extent (e.g., some members with oral findings and others without oral findings). For example, the same KRT17 mutation in the highly conserved helix initiation motif has been observed in PC-2 and in the milder variant SM with little or no nail changes. The modifying factors responsible for this variability in expressivity are not known.

In a few reports of late onset, PC mutations have been identified outside the helix boundary domains [Connors et al 2001, Xiao et al 2004], but numbers are too small to speculate whether this will hold true for all late-onset cases.

Penetrance

Within families studied to date, inheritance of a pathogenic mutation is uniformly associated with some manifestation of disease, suggesting that penetrance is 100%.

Nomenclature

The subclassification systems suggested for PC prior to the identification of the genetic basis of the disease were based solely on clinical findings [Irvine & McLean 1999]. There are two major subtypes of PC that show variable phenotypic features as discussed above:

- PC-1 (Jadassohn-Lewandowski syndrome)
- PC-2 (Jackson-Lawler syndrome)

As the number of mutations identified in persons with PC increases it may be clearer to classify the disorder according to the gene involved. For example those with mutations in KRT6B appear to have a milder and slightly different clinical phenotype to those with mutation in KRT17.

Prevalence

The rarity of PC makes it difficult to accurately assess its prevalence. Recent registry data show nearly 400 individuals with confirmed mutations and another 300 with a clinical phenotype of PC who have not yet undergone genetic testing (see www.pachyonychia.org).

Differential Diagnosis

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

Onychomycosis. Although the hyperkeratotic nail thickening seen in pachyonychia congenita (PC) is similar to that of onychomycosis, fungal infections do not typically affect all nails from a few months of age or have a hereditary component (with the exception of rare disorders such as autoimmune endocrinopathy-candidiasis-ectodermal dystrophy (APECED) or systemic mucocutaneous candidosis, in which all nails can be affected).

Oral leukokeratosis is often mistaken for thrush and /or leukoplakia if no other findings of PC are apparent. A KOH preparation can be examined to determine if yeast is present. This should also be differentiated from white sponge nevus if other PC signs are mild.

Epidermolysis bullosa simplex (EBS) or other palmoplantar keratodermas can result in a similar pattern of plantar blister formation or hyperkeratosis, respectively; however, they do not share the characteristic nail changes of PC.

Note: EBS may be incorrectly diagnosed in young children with PC because they have a greater tendency toward blister formation and lesser tendency toward keratoderma.

Clouston syndrome, caused by mutations in GJB6, the gene encoding the gap junction protein connexin 30, can also mimic PC [van Steensel et al 2003].

Hidradenitis suppurativa and follicular occlusion triad caused by GJB2 mutations may possibly be confused with the axillary and inguinal cyst formation of PC. Clinical signs such as deafness in the former and molecular genetic testing help differentiate between these two disorders.

Palmoplantar keratoderma striata et areata of Siemens can be confused with focal non-epidermolytic palmoplantar keratoderma (FNEPPK).

Familial onychogryposis without the associated palmoplantar keratoderma or other features of PC can be confused with the syndrome. Patients that only have nail findings are unlikely to demonstrate a

mutation in one of the PC keratins.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with pachyonychia congenita (PC), the following evaluations are recommended:

- Thorough clinical examination to assess each affected area and the degree of involvement
- Culture if infection is suspected
- Genetic testing of one affected individual in the family

Treatment of Manifestations

The current treatment modalities primarily center on symptomatic relief, hygienic grooming practices, and treatment of secondary infection when indicated.

Palmoplantar keratoderma. Painful plantar keratoderma is the most problematic finding among individuals with PC.

Pain can be reduced by limiting the friction and trauma to the feet by minimizing walking or standing, reducing hydration of the stratum corneum by using wicking socks and ventilated footwear, selecting shoes that are comfortable (possibly with insoles), and maintaining an ideal body weight.

Routine grooming of the feet is essential and includes paring down the hyperkeratotic areas to avoid painful buildup of the callosities that can add further friction and trauma to the foot. Soaking the feet prior to the paring is helpful when the callosities are hard. The surface of the skin and the instruments used should be clean to avoid infection.

Topical therapies to reduce the hyperkeratosis:

- Emollients such as Vaseline®, lanolin-containing products, or creams and lotions containing keratolyics such as urea, lactic acid, salicylic acid, or propylene glycol. These are the most frequently used.
- Oral retinoids. Although they reduce the keratoderma, they do not affect the underlying blistering and fragility of the skin, do not usually improve the pain, and are associated with side effects that may be poorly tolerated. Thus, they are less commonly used.

Nail thickening. The hard, thickened nails are not typically painful as long as they are well groomed. Grooming often requires the use of surgical or razor blades or sanders such as a Dremel® tool. Failure to keep the nails trimmed or over-trimming of the nails can result in infection. If infection occurs, oral antibiotics are indicated. Secondary fungal infections can also arise, which respond best to oral antifungals.

Particularly troublesome nails can be successfully removed surgically; however, the nails tend to re-grow if not completely ablated.

Oral leukokeratosis. Frequent and vigorous brushing with a toothbrush can significantly improve the appearance of the thick, white patches on the tongue and oral mucosa; however, this may also traumatize the mucosa resulting in reactive hyperkeratosis.

Some individuals have reported reduction of the leukokeratosis in response to oral antibiotics, suggesting a possible bacterial or inflammatory component.

Poor feeding in infancy may be ameliorated by the use of a bottle with a soft nipple with an enlarged opening.

Follicular hyperkeratosis. Rarely bothersome, this finding can be treated with alpha-hydroxy acid creams or lotions or keratolytic emollients.

Larygeal thickening/growths. The hoarseness associated with PC, especially following overuse, usually resolves spontaneously by resting the voice. However, the rare occurrence of respiratory insufficiency can be life-threatening, especially in young children, and requires emergent surgical intervention to re-establish the airway. The surgical procedures are repeated as necessary to maintain an open airway; however, unnecessary recurrent trauma to the larynx should be avoided as it may tend to worsen the condition.

Steatocystoma multiplex and other pilosebaceous cysts. Cysts can be treated by incision with a number 11 blade and subsequent expression of the contents of the cyst ("incision and drainage"). Oral antibiotics may be indicated in the case of secondary infection.

Prevention of Primary Manifestations

Reduction of trauma, friction, and sheer forces to the skin and nails improves the condition.

Prevention of Secondary Complications

Infection of the skin and nails following grooming is the most common secondary complication seen in PC. Pre- and post-grooming hygiene and use of clean instruments minimizes this complication. Antibiotics may be indicated when infection occurs.

Surveillance

In general, individuals with PC have no known associated systemic diseases or predispositions that require routine surveillance.

Agents/Circumstances to Avoid

Trauma, friction, or stress to the skin or nails should be avoided.

Heat and/or perspiration may worsen the condition.

Testing of Relatives at Risk

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

Therapies Under Investigation

Studies on the use of a K6a mutation-specific siRNA [Hickerson et al 2008, Leachman et al 2008], rapamycin, anti-TNF biologics, and botulism toxin are underway, but have not yet reached the point of being applied generally to treatment of the disorder. The siRNA trial included treatment of a single K6a mutation carrier in a dose-escalation trial of an siRNA directed against the N171K mutant allele and complete results have not been published. Similarly, results on the use of oral rapamycin have not been published to date. Botulinum toxin has been used in several patients with clinical findings consistent with PC but has not yet been replicated in mutation-tested individuals with PC [Swartling & Vahlquist 2006].

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Genetics clinics, staffed by genetics professionals, provide 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.

See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals.

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

Pachyonychia congenita (PC) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Up to 50% of individuals diagnosed with pachyonychia congenita have an affected parent.
- A proband with pachyonychia congenita may have the disorder as the result of a de novo gene mutation. The proportion of cases caused by de novo mutations is approximately 50%.
- Recommendations for the evaluation of parents of a proband with an apparent de novo mutation include a complete clinical examination by a dermatologist to confirm the lack of phenotype.

Note: Although up to 50% of individuals diagnosed with pachyonychia congenita have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. If the parent is the individual in whom the mutation first occurred, s/he may have somatic mosaicism for the mutation and may be mildly/minimally affected.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- If the disease-causing mutation cannot be detected in the DNA of either parent, the risk to sibs is low, but greater than that of the general population, because the possibility of germline mosaicism exists.
- The incidence of germline mosaicism is not known, but thought to be very low.

Offspring of a proband. Each child of an individual with pachyonychia congenita has a 50% chance of inheriting the mutation.

Other family members of a proband. The risk to other family members depends on the status of the proband's parents. If a parent is affected, his or her family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent de novo mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a de novo mutation. However, possible non-medical

explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

Because inheritance of the mutation appears to always be associated with some manifestation of disease, relatives are usually aware of whether they are affected without the need for genetic testing. However, in the case of mild or subtle disease manifestations, some individuals may wish to have confirmatory testing performed.

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 adults who are affected or at risk.

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 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 usually performed at approximately 15 to 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 .

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. Pachyonychia Congenita: Genes and Databases

Gene Symbol	Chromosomal Locus	Protein Name	Locus Specific	HGMD
KRT16	17q12-q21	Keratin, type I cytoskeletal 16	Human Intermediate Filament Database KRT16	KRT16
KRT6A	12q13	Keratin, type II cytoskeletal 6A	Human Intermediate Filament Database KRT6A	KRT6A
KRT17	17q12-q21	Keratin, type I cytoskeletal 17	Human Intermediate Filament Database KRT17	KRT17
KRT6B	12q13	Keratin, type II cytoskeletal 6B	Human Intermediate Filament Database KRT6B	KRT6B

Data are compiled from the following standard references: gene symbol from HGNC; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from UniProt. For a description of databases (Locus Specific, HGMD) linked to, click here.

Table B. OMIM Entries for Pachyonychia Congenita (View All in OMIM)

148041	KERATIN 6A; KRT6A
148042	KERATIN 6B; KRT6B
148067	KERATIN 16; KRT16
148069	KERATIN 17; KRT17
167200	PACHYONYCHIA CONGENITA, TYPE 1; PC1
167210	PACHYONYCHIA CONGENITA, TYPE 2; PC2

Molecular Genetic Pathogenesis

Keratins form a cytoskeletal intermediate filament network within all epithelial cells. Epithelia in different body regions utilize a range of different keratins. Keratins associated with PC are constitutively expressed in the nail, palmoplantar skin, oral mucosa, and hair. Thus, mutations in these keratins lead to pathology in these major body sites.

Figure 2. Schematic diagram showing the basic protein structure of a keratin filament. The a-helical rod domain is divided into four domains: 1A, 1B, 2A, and 2B connected together by non-helical linkers L1, L12, and L2. At the ends of the rod domain are the helix initiation motif (shaded red) and helix termination motif (shaded red) that are highly conserved in sequence between keratins. The majority of mutations found in PC in KRT6A, KRT6B, KRT16, and KRT17 fall within these highly conserved domains.

The majority of the mutations causing PC are in the highly conserved helix boundary domains at either end of the rod domain (see Figure 2), consistent with the location of mutations in most other keratin disorders [Smith 2003, Smith et al 2005]. A genotype/phenotype correlation is observed in the keratin disorder epidermolysis bullosa simplex (EBS), where the more severe mutations occur in the helix boundary domains and those causing a milder phenotype occur within or outside these regions. So far, this has not been the case for PC. It could be that mutations in these less conserved regions in KRT6A, KRT16, KRT6B, or KRT17 are in general not severe enough to produce a clinical phenotype.

A schematic representation of the protein domain organization of each of the four keratins associated with PC is shown (K6a, K6b, K16, and K17) in Figure 2.

Mutations in 117 families have been published to date [www.interfil.org]. Mutations in KRT6A have been reported in 48 families, KRT6B mutations in four families, KRT16 mutations in 31 families, and KRT17 mutations in 34 families.

A number of the mutations are recurrent but others are family specific. More than 60 different mutations

have been identified; the majority are found in or near the helix initiation motif (shaded red; see Figure 2) in the 1A domain or the helix termination motif (shaded red) at the end of the 2B domain. The domains shown include the variable domains (V1 and V2), homology subdomains H1 and H2, and the coiled coil domains 1A, 1B, 2A, and 2B, separated by non-helical linkers L1, L12, and L2. Stutter sequences (S) are underlined.

KRT6A

Normal allelic variants. The cDNA comprises 2450 bp in nine exons.

Pathologic allelic variants. The majority of mutations are heterozygous missense mutations; in some individuals, small in-frame deletion/insertion mutations have been reported. Most mutations occur in the highly conserved helix boundary motif domains located at either end of the alpha-helical keratin rod domain. There are a number of recurrent mutations, the major one for PC-1, located at Asn171, is either a single amino-acid deletion (p.Asn172del) or a missense mutation involving the same residue (Table 3).

Table 3. Selected KRT6A Pathologic Allelic Variants

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequences
c.511A>G	p.Asn171Asp	NM_005554.3 NP_005545.1
c.511A>T	p.Asn171Tyr	
c.512A>G	p.Asn171Ser	
c.513C>A	p.Asn171Lys	
c.514_516delAAC	p.Asn172del	

See Quick Reference for an explanation of nomenclature. GeneReviews follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

Normal gene product. The protein, keratin, type II cytoskeletal 6A (K6a keratin), consists of 564 amino acids. Keratins form a cytoskeletal intermediate filament network within all epithelial cells.

Abnormal gene product. Mutations cause disruption of the cytoskeleton resulting in keratin filament aggregation leading to collapse of the cytoskeleton and cell fragility. The highly conserved helix boundary domains where the majority of mutations occur are critical during normal keratin filament assembly.

KRT6B

Normal allelic variants. The cDNA comprises 2331 bp in nine exons (reference sequence NM_005555.3).

Pathologic allelic variants. The mutations reported to date are heterozygous missense mutations in either the highly conserved helix initiation or helix termination domains.

Normal gene product. The protein, keratin, type II cytoskeletal 6B (K6b keratin), consists of 564 amino acids. Keratins form a cytoskeletal network within all epithelial cells.

Abnormal gene product. Mutations cause disruption of the cytoskeleton resulting in keratin filament aggregation leading to collapse of the cytoskeleton and cell fragility. The highly conserved helix boundary domains where the majority of mutations occur are critical during normal keratin filament assembly.

KRT16

Normal allelic variants. The cDNA comprises 1720 bp in eight exons (reference sequence NM_005557.3).

Pathologic allelic variants. The majority of mutations are heterozygous missense mutations; in some individuals, small in-frame deletion mutations have been reported. Most mutations occur in the highly conserved helix boundary motif domains located at either end of the alpha-helical keratin rod domain.

Normal gene product. The protein, keratin, type I cytoskeletal 16 (K16), consists of 473 amino acids. Keratins form a cytoskeletal network within all epithelial cells.

Abnormal gene product. Mutations cause disruption of the cytoskeleton resulting in keratin filament aggregation leading to collapse of the cytoskeleton and cell fragility. The highly conserved helix boundary domains where the majority of mutations occur are critical during normal keratin filament assembly.

KRT17

Normal allelic variants. The cDNA comprises 1574 bp in eight exons.

Pathologic allelic variants. In PC-2, the majority of mutations are in the helix initiation motif of KRT17, in which several recurrent mutations have been observed, particularly p.Asn92Ser (Table 4).

Table 4. Selected KRT17 Pathologic Allelic Variants

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequences
c.275A>G	p.Asn92Ser	NM_000422.2 NP_000413.1

See Quick Reference for an explanation of nomenclature. GeneReviews follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

Normal gene product. The protein, keratin, type I cytoskeletal 17 (K17), consists of 432 amino acids. Keratins form a cytoskeletal network within all epithelial cells.

Abnormal gene product. Mutations cause disruption of the cytoskeleton resulting in keratin filament aggregation leading to collapse of the cytoskeleton and cell fragility. The highly conserved helix boundary domains where the majority of mutations occur are critical during normal keratin filament assembly.

Resources

See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals. GeneTests provides information about selected organizations and resources for the benefit of the reader; GeneTests is not responsible for information provided by other organizations.—ED.

References

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

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Published Statements and Policies Regarding Genetic Testing

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

Suggested Reading

Smith FJD, Hickerson RP, Sayers JM, Reeves RE, Contag CH, Leake D, Kaspar RL, McLean WHI. Development of therapeutic siRNAs for pachyonychia congenita. J Invest Dermatol. 2008; 128: 50–8. [PubMed]

Chapter Notes

Author Notes

TransDerm, Inc is a therapeutic company dedicated to finding treatment for rare skin disorders.

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Revision History

- 25 June 2009 (me) Comprehensive update posted live
- 6 December 2007 (cd) Revision: clarification of PC phenotypes
- 27 January 2006 (me) Review posted to live Web site
- 14 July 2005 (rlk) Original submission