GENEReviews

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Pachyonychia Congenita

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

Frances JD Smith, PhD
Epithelial Genetics Group
Human Genetics Unit
Division of Pathology and Neuroscience
Ninewells Medical School
Dundee, United Kingdom
fjsmith@hgmp.mrc.ac.uk

Roger L Kaspar, PhD
Transderm, Inc
Santa Cruz
roger.kaspar@transderm.org

Mary E Schwartz
PC Project
Salt Lake City
mary.schwartz@packyonychia.org

WH Irwin McLean, DSc, FRSE
Epithelial Genetics Group
Human Genetics Unit
Division of Pathology and Neuroscience
Ninewells Medical School
Dundee, United Kingdom
w.h.i.mclean@dundee.ac.uk

Sancy A Leachman, MD, PhD
Department of Dermatology
University of Utah
Salt Lake City
sancy.leachman@hci.utah.edu

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Summary

Disease characteristics. Pachyonychia congenita (PC) is characterized by hypertrophic nail dystrophy, focal palmoplantar keratoderma, blistering oral leukokeratosis, 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). Findings only observed in PC-2 include widespread steatocystomas, twisted hair, and natal teeth. 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) and 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). Sequence analysis of these mutations is available on a clinical basis.

Management. Treatment of PC primarily provides symptomatic relief. Pain from 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. Essential grooming of the feet includes paring down hyperkeratotic areas. Topical therapies for hyperkeratosis include emollients such as Vaseline™, lanolin-containing products, or creams and lotions containing keratolytics such as urea, lactic acid, salicylic acid, or propylene glycol and sometimes oral retinoids. Grooming of thickened nails to prevent infection often requires the use of surgical or razor blades or sanders such as a Dremel™ tool; oral antibiotics are used to treat infections and oral antifungals to treat secondary fungal infections. Troublesome nails can be removed surgically. Frequent brushing of teeth can improve the appearance of thick, white patches on the tongue and oral mucosa; in some individuals, antibiotics reduce leukokeratosis. Poor feeding in infants with leukokeratosis may require use of a bottle with a soft nipple with an enlarged opening. Follicular hyperkeratosis can be treated with alpha-hydroxy acid creams or lotions or keratolytic emollients. 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 by stab incision and expression of the contents. Reduction of trauma, friction, and sheer forces to the skin and nails helps prevent manifestations.

Genetic counseling. Pachyonychia congenita is inherited in an autosomal dominant manner. About 50% of cases result from a *de novo* mutation. If a parent of the proband is affected, the risk to the sibs is 50%. Prenatal diagnosis by molecular genetic testing for pregnancies at increased risk is possible 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]. 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.

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

- Focal palmoplantar keratoderma
- Blistering, oral leukokeratosis
- Palmoplantar hyperhydrosis
- Follicular keratoses on the trunk and extremities
- Pilosebaceous cysts

Other findings observed only in PC-2:

- Widespread steatocystomas, the main feature distinguishing PC-2 from PC-1

  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)
- Natal teeth

Variants of PC

- **Focal non-epidermolytic palmoplantar keratoderma (FNEPPK).** Keratoderma of varying severity occurs on the palms and soles similar to PC-1, but there is usually no nail dystrophy [Shamsher et al 1995].
- **Steatocystoma multiplex (SM).** Widespread steatocystomas develop at puberty as in PC-2, but there is little or no nail involvement or palmoplantar keratoderma [Smith et al 1997].
- **Late-onset PC (PC tarda)** resembles either PC-1 or PC-2. Onset ranges from late childhood to middle age [Hannaford & Stapleton 2000] (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.

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

- *KRT6A* (encoding keratin, type II cytoskeletal 6A) and *KRT16* (encoding keratin, type I cytoskeletal 16): PC-1
- *KRT6B* (encoding keratin, type II cytoskeletal 6B) and *KRT17* (encoding keratin, type I cytoskeletal 17): PC-2

Clinical uses

- Confirmatory diagnostic testing
- Prenatal diagnosis

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

- 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

Phenotype	Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
PC-1/FNEPPK [2]	Sequence analysis	*KRT6A* & *KRT16* sequence variants	90%	Clinical Testing
PC-2/SM [3]		*KRT6B* & *KRT17* sequence variants		Clinical Testing

1. Proportion of affected individuals with a mutation(s) as classified by gene, phenotype, and/or test method
2. Focal non-epidermolytic palmoplantar keratoderma
3. Steatocystoma multiplex

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

Testing Strategy

- **PC.** If no mutation is identified in the predicted two keratin genes for PC-1, the other two keratin genes associated with PC-2 should be screened, and vice versa.
- **Focal non-epidermolytic palmoplantar keratoderma (FNEPPK).** All mutations to date are in *KRT16*, but mutations may occur in *KRT6A*.
- **Steatocystoma multiplex (SM).** Screen for mutations in *KRT17* and *KRTK6*B 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.

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 palm skin, but not in the 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) — Hypertophic 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 wheelchair use.

Oral leukokeratosis (thickened white patches on the tongue and cheek) is often present; in babies, this 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)
- Axillary and inguinal cyst formation
- Excessive production of waxy material in the ear
- Hoarseness (laryngeal involvement). Although rare, laryngeal involvement may cause life-threatening respiratory distress. This has been reported primarily in young children.

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.** Although cysts normally do not develop until puberty, early onset is reported rarely [Feng et al 2003].
- **Natal teeth or prenatal teeth.** Some individuals have a few prenatal or a 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 some 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

Feature	Phenotype	
	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%.

Anticipation

Some families appear to demonstrate increasing severity of PC in subsequent generations; however, no data are available regarding genetic anticipation in these families and the numbers are too small to draw definitive conclusions.

Nomenclature

The subclassification systems suggested for PC prior to the identification of the genetic basis of the disease were based solely on clinical findings [Feinstein et al 1988, Dahl et al 1995, Irvine & McLean 1999]. It is now clear that there are two major subtypes of PC that show variable phenotypic features as discussed above: PC-1 (Jadassohn-Lewandowski syndrome) and PC-2 (Jackson-Lawler syndrome).

Prevalence

The rarity of PC makes it difficult to accurately assess its prevalence. Although it has been suggested that the worldwide PC population may be on the order of a few hundred individuals, recent registry data suggest that it is more likely to be on the order of a few thousand individuals (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 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, where all nails can be affected).

Oral leukokeratosis is often mistaken for thrush 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).

Management

Treatment of Manifestations

The current treatment modalities primarily center around symptomatic relief.

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.

Steatocystoma multiplex and other pilosebaceous cysts. Cysts can be treated by stab incision with a number 11 blade and subsequent expression of the contents of the cyst. 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.

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

Pachyonychia congenita 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 upon 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 upon the status of the proband's parents. If a parent is found to be 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 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.

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 in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

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 about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 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 in an affected family member in a research or clinical laboratory. 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 Pachyonychia Congenita

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

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 Pachyonychia Congenita

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

Table C. Genomic Databases for Pachyonychia Congenita

Gene Symbol	Locus Specific	Entrez Gene	HGMD
KRT16	KRT16	3868 (MIM No. 148067)	KRT16
KRT17	KRT17	3872 (MIM No. 148069)	KRT17
KRT6A	KRT6A	3853 (MIM No. 148041)	KRT6A
KRT6B	KRT6B	3854 (MIM No. 148042)	KRT6B

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

Note: HGMD requires registration.

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. PC keratins 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.

The majority of the mutations causing PC are in the highly conserved helix boundary domains at either end of the rod domain (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); in general, 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), adapted from www.interfil.org and Leachman et al 2005. A total of 82 mutations have been published to date [www.interfil.org]. The approximate location of mutations is indicated by numbered boxes. The numbers within the boxes indicate the number of families reported with mutations in this region, i.e. the number of independent occurrences of mutations. Note that the majority of mutations are found in or near the helix initiation motif in the 1A domain or the helix termination motif at the end of the 2B domain. The numbers below the schematic represent the amino acid residue number with the protein. The domains shown include the ISIS box (green), and homology subdomains H1 and H2 (blue), and the coiled coil domains 1A, 1B, 2A, and 2B (red), separated by non-helical linkers L1, L12, and L2 (black). Stutter sequences (S) are underlined.

KRT6A

Normal allelic variants: The cDNA comprises 2270 bp in nine exons [Takahashi et al 1995].

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 several recurrent mutations, the major one for PC-1 being K6a N171, which is either deleted (N171del) or a single base pair is mutated resulting in an amino acid change.

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 2218 bp in nine exons [Takahashi et al 1995].

Pathologic allelic variants: The mutations reported to date are heterozygous missense mutations in the highly conserved helix termination domain.

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 1688 bp in eight exons.

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 1512 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 N92S.

Normal gene product: The protein, keratin, type I cytoskeletal 17 (K17), consists of 483 amino acids [Troyanovsky et al 1992]. 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

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.

Pachyonychia Congenita Project
2386 East Heritage Way Suite B
Salt Lake City UT 84109
Phone: 877-628-7300
Email: info@pachyonychia.org
www.pachyonychia.org

Epithelial Genetics Group
Department of Molecular & Cellular Pathology
University of Dundee Ninewells Hospital & Medical School
Dundee DD1 9SY
United Kingdom
Phone: 01382 425618
Fax: 01382 425619
Email: w.h.i.mclean@dundee.ac.uk
www.mcleanlab.com

National Institute of Arthritis & Musculoskeletal & Skin Diseases
www.niams.nih.gov

Pachyonychia Congenita Project Registry
Pachyonychia Congenita Registry

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.

Literature Cited

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Chapter Notes

Author Notes

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

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Revision History

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- 27 January 2006 (me) Review posted to live Web site
- 14 July 2005 (rlk) Original submission

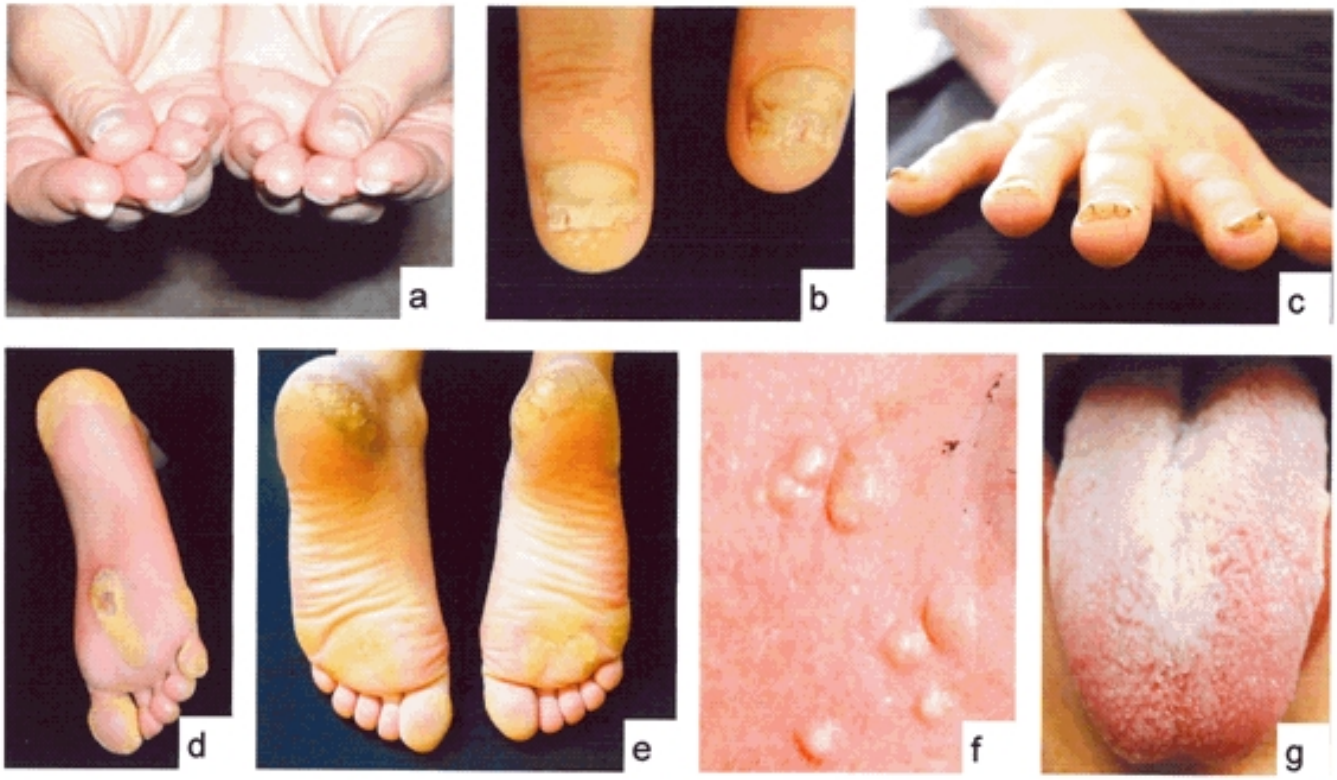

Figure 1. Common findings of pachyonychia congenita include: thickened and dystrophic nails (both finger nails and toe nails) (a-e); bullae (usually on the pressure points of the heels and soles); hyperkeratosis (d-e); cysts (f); and oral leukoplakia (g).

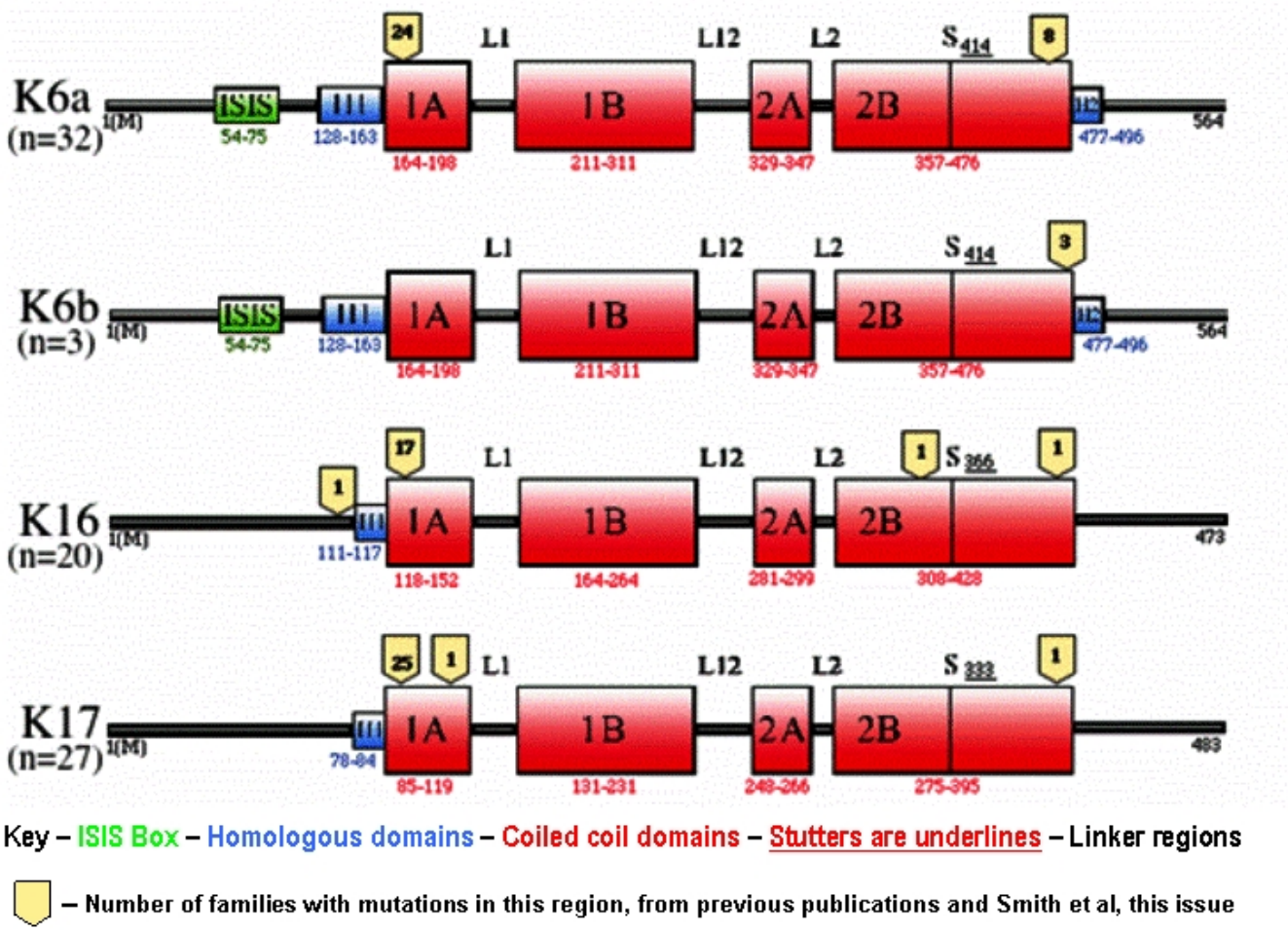

Figure 2. Keratin mutations in pachyonychia congenital