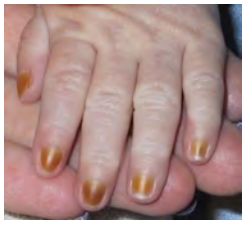
PC PROJECT

Mission Statement

Find a Cure for Pachyonychia Congenita (PC)



INFORMATION FOR PEOPLE WITH PC

DISCLAIMER

The information in this pamphlet has been carefully prepared by PC Project as a public service for educational purposes. It is provided as general information only. It is not intended as medical advice and is not tailored to the needs of your specific situation.

No diagnosis or decision regarding treatment should be based on the information in this pamphlet without consultation with medical professionals.

The information is intended to be accurate and any mistakes are unintentional. No guarantee is made or implied regarding these materials.

If you have any questions about information in this pamphlet or if you find any incorrect information, please contact us at the address given on the back page.

Mary Schwartz, Director
PC Project

What is Pachyonychia Congenita?

Pachyonychia Congenita (PC) is a rare genetic skin disorder. The name means:

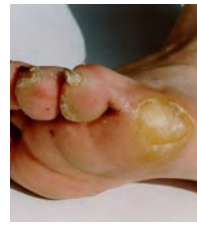
Pachy — thick

onychia — refers to nails

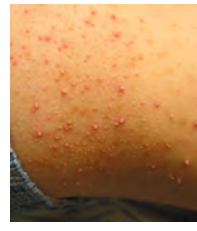
Congenita — a condition present at birth

Your symptoms may include some or all of these features:

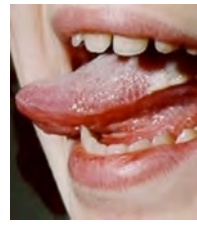
- Thickened **fingernails** and/or **toenails.** Infections are painful.



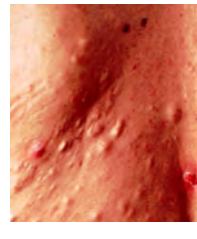
- **Keratoderma** — thickened skin and calluses on palms of hands (palmar) and soles of feet (plantar). The blisters and calluses on the feet are often extremely painful and walking may be difficult or impossible without assistance. [See page 3 for more information on keratin.]



- **Follicular hyperkeratoses** — thickened skin or bumps around hair follicles which are often on arms, legs, the waist and/or other areas of friction. This usually lessens after teenage years.



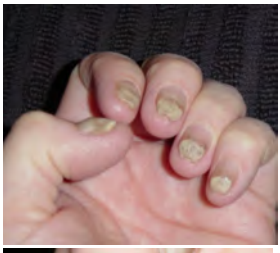
- **Leukokeratosis** — white film inside the mouth and on the tongue (mucosa). This may be misdiagnosed as thrush in newborns.

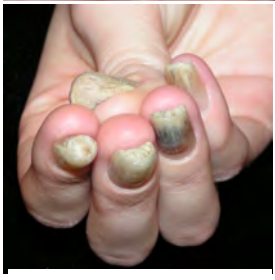


- **Cysts** — several different kinds of skin cysts are part of PC. Cysts are another cause of pain.

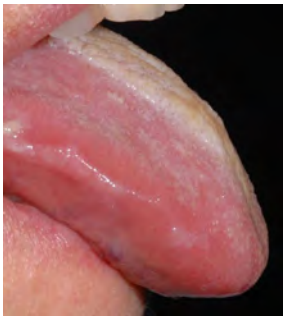
PC may also cause

- Acute pain in the ears or salivary glands when drinking or eating with first swallow or taste.
- Pre-natal or natal teeth — teeth present at birth or first months of life which are soon lost.
- Larynx problems — thickening or nodules on the vocal chords causing hoarseness or sometimes difficulty in breathing.

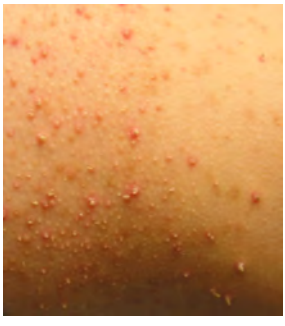




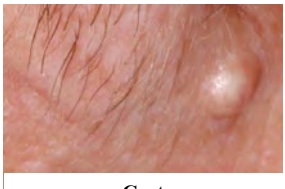
Thickened Nails



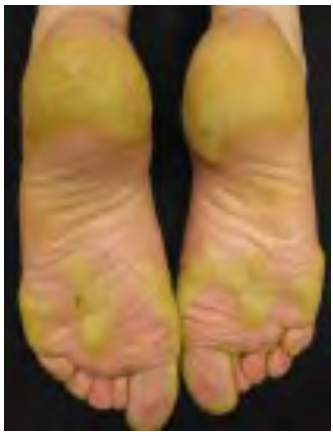
Leukokeratosis

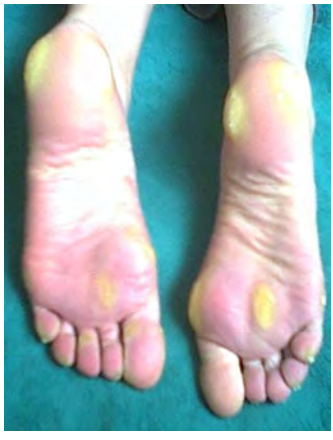


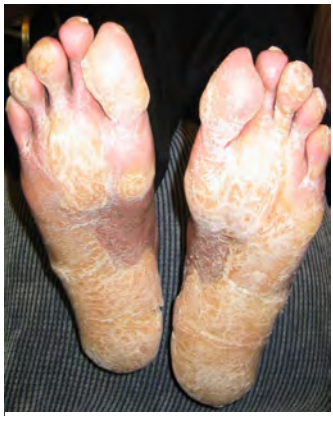
Follicular Hyperkeratosis



Cyst







Plantar Hyperkeratosis

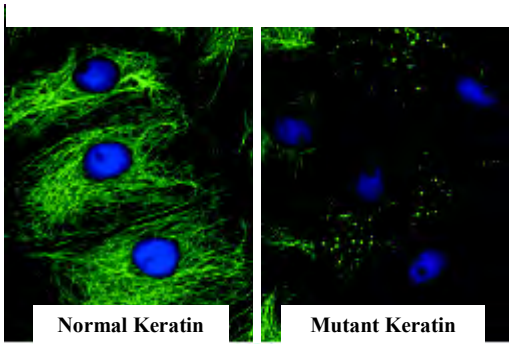
PC symptoms vary greatly from person to person even for those with the identical genetic mutation [see page 4.]

What is role of keratin in skin, hair & nails?

Skin is our largest organ. Our skin protects the network of muscles, bones, nerves, blood vessels, and everything else inside our bodies.

Every square centimeter of skin contains thousands of **cells,** hundreds of sweat glands, oil glands, nerve endings, hair follicles, and blood vessels. Skin is made up of three layers**.** The upper layer of our skin, the **epidermis**, is the tough, protective outer layer which is most affected in PC.

The **epidermis** has several layers of cells called keratinocytes that are constantly flaking off and being renewed. The keratinocytes cells contain lots of **keratin.**



Keratin Immunofluorescence
Photo courtesy of Prof. Irwin McLean, University of Dundee, Scotland

Keratin is a tough, fibrous protein that doesn't dissolve in fluid. Keratin is one of the structural proteins that supports keratinocyte cells and gives them shape and strength. Nails and hair are almost pure keratin.

You might compare keratin in cells to the framework of a building. When one of the keratin genes has a mistake (mutation), the framework is fragile and cells are weakened. This can cause rupture of the cells, blistering and pain. The body compensates by producing more of the defective keratin, leading to further fragility and callus buildup over time.

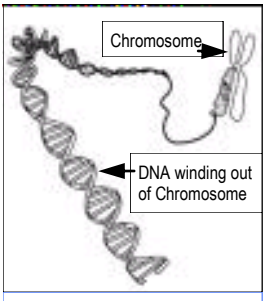
The photographs above show the difference between a cell with normal keratin with a strong network, structure and form within the cell (left photo) and the mutant keratin that does have any real structure or form within the cell (right photo).

What causes PC?

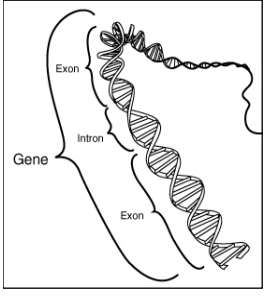
Pachyonychia Congenita is caused by a change in one keratin gene. PC is an **autosomal dominant**, **genetic disorder**. What does this mean?

Genes are recipes or sets of instructions in the cells of the body. For example, **keratin genes** tell the body how to make keratin proteins. If the recipe (gene) is changed (called a mutation) the cells may not make a normal protein.

The basic unit of any living thing is called a cell. It is a small, watery, compartment filled with chemicals and contains a complete copy of all the genes for that living thing. Within each cell, there is a nucleus which holds the genes in structures called chromosomes. Humans have 22 pairs of **autosomal** (non-sex) chromosomes plus one male and one female sex chromosome. These chromosomes hold the DNA or sequence of genes.



Images courtesy of www.genome.gov



During the last few years, it has been possible to decode the entire human genome — all of the human genes have been located and named or numbered. In 1995, scientists discovered that a mutation in **K**eratin genes named **K**6a or **K**16 or **K**6b or **K**17 causes PC. A person with PC has just one mistake in the complex code for any one of those keratin genes.

Autosomal—mutation on a non-sex chromosome
Dominant—one gene causes the disorder
Out of the 30,000-40,000 human genes a person has, researchers estimate there are usually about six which have **mutations** (changes). Most of the time we aren't even aware of the defective genes we have as there aren't any harmful effects. This is because we have two copies of nearly all genes (one from our mother and the other from our father) and the healthy gene just carries out the work for the pair. In PC, however, the gene that has the mutation is **dominant** and won't allow the other gene in the pair to take over. PC doesn't hide. If you have a mutation in a PC gene, you will have PC and PC symptoms.

How did I get PC?

If your mother or father do not have PC, and you do have PC, then you have what is called a **spontaneous mutation** (not an inherited mutation). A mutation is a change or an error in the code in a gene. This is thought to happen when cells are dividing and replicating (copying) in the earliest stages of development. There is no specific cause for this. Statements that the PC mutation is caused by a virus or other illness of the mother during pregnancy, or that the mutation is caused by other actions of the parents are not substantiated by any accepted research findings.

If either your mother or father has PC, then you have what is called **inherited** or **familial** PC (meaning it comes through your family). [See page 9 for more information on inherited or familial PC].

All relatives in a family who have PC will have the identical mutation (genotype), so it is only necessary to test one member of a family to know the specific mutation for all the family members. However, because each person has their own set of genes in addition to the PC gene, the PC symptoms (phenotype) may be very different from person to person even in the same family. [See page 6 for more information on genetic testing].

Whether **spontaneous** or **inherited**, if you have PC then you have a change or mutation in a **keratin gene**. The table shows an example of gene pairs with a change in K6a. A change in one partner of the pair in either K6a, K6b, K16 or K17 causes a person to have PC. It seems amazing that one single change in one copy of one gene can cause so many changes in skin, hair and nails!

The example shows a change in keratin gene K6a. However, a mutation in any one of these four keratin genes causes a person to have PC. All of the symptoms associated with PC are from the change in just one gene partner!

This person does not have PC— all 4 pairs of genes are okay

K6a	K6a
K6b	K6b
K16	K16
K17	K17

This person has **PC** — one of the genes in one pair has a change

K6a	**K6a**
K6b	K6b
K16	K16
K17	K17

What is learned through genetic testing?

Phenotype describes how PC looks and the symptoms that can be seen and felt. **Genotype** is the specific change (mutation) inside the body which causes PC. Previously, medical articles divided PC into two types:

PC-1 Jadassohn-Lewandowsky type
PC-2 Jackson-Lawler type

However, with data now available on nearly 500 genetically confirmed PC patients, it is clear these classifications are not accurate. In 2011 a better system has been proposed using PC-6a, PC-6b, PC-16, and PC-17 to identify the type of PC. There are many overlapping features among these types.

PC symptoms vary from person to person even among people with exactly the same mutation. The reasons for this variation are not completely known. Some factors which cause individual differences may include (1) the specific gene (2) the type of mutation in that gene (3) the place in the gene where the mutation occurs (4) other genes a person has which may make the change better or worse. Therefore, a diagnosis based only on the physical symptoms will not provide an accurate diagnosis of the specific mutation.

To have any successful gene-based therapy, the specific gene mutation has to be identified. If you have a mutation in the K6a gene, it is unlikely to help you to have a treatment which affects the K17 gene.

Genetic testing is a complex process which may cost from $2,000US to $3,000US. Through cooperative funding, PC Project is able to provide genetic testing without cost to those patients who enroll in the International PC Research Registry **(IPCRR).** [See page 11 for further details.]

Through genetic testing for PC, a determination is made as to whether or not there is a mutation (change) in keratin genes K6a, K6b, K16 or K17. The exact **location** where the gene is changed is identified and the **type** of genetic change is also found. The report will provide the full information, such as:

[1] **Deletion** means part of the code is left out of the gene.
Example K6a N171del [a deletion of N at 171]
[2] **Missense** means one amino acid is replaced by another.
Example K6a L170F [L is replaced by F at 170]
[3] **Insertion** means an extra part of code adds onto the gene.
Example K6a p.D432_E470dup
[the code beginning with D432 is repeated after E470]
[4] **Nonsense** means the code stops before the end.

What research is being done on PC?

Of the more than 50 **keratin genes** in humans, those that cause PC are unusual because they can be switched on and off in a number of natural situations. For example, they are **switched on** when the skin is wounded and **switched off** again when the wound is fully healed. UV light and certain chemicals are also known to activate these genes and, once these agents are removed, they are switched off again. Researchers believe an effective treatment may be to find ways to permanently 'switch off' the defective PC keratin gene. Since 2004, more than 12 research grants specifically for PC research have been awarded by PC Project. Each has a different goal and together these will allow progress towards a cure.

***TransDerm, Inc.*, Santa Cruz, CA,**
Roger Kaspar has a partnership with PC Project and established a biotech company specifically focused on therapies for skin including development of siRNA and other treatments targeted for PC mutations.

Drug Discovery for the Treatment of PC
Irwin McLean, Frances Smith, Dundee University, search for drugs which may switch off the PC gene(s). Several clinical studies are underway on drugs identified.

International PC Research Registry (IPCRR)
The IPCRR has established a uniform method of collecting data from PC patients, confirming data by clinical consultation and genetic testing provided at no cost to patients; those in the IPCRR may be eligible for clinical trials sponsored by PC Project for new treatments.

Genetic Testing
Through grants to the McLean/Smith laboratory at the University of Dundee, and in cooperation with GeneDX, PC Project provides genetic testing to patients referred through the IPCRR.

Pachyonychia Congenita Fellowships
PC Project continues to sponsor fellowships and has funded PC fellowships at Stanford University, University of Utah and of University of Dundee.

Career Development Award (CDA) 2005-2007
Frances Smith received this award PC Project to focus on PC research and coordinate research efforts with other scientists.

siRNA Clinical Trial (2008)
PC Project sponsored the first-in-man clinical trial of an siRNA targeted to a specific keratin mutation.

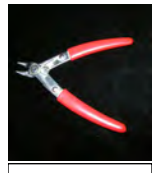
BioBank and PC models include samples collected from PC patients for improving the understanding of the disorder

Is there a cure for PC?

There is presently no cure for PC. A successful clinical trial using an siRNA drug was completed in 2008 and further research is being done on this technology. The benefits of certain retinoid drugs have been reported in some patients; however, the effects appear to be temporary. Patients report the side effects often outweigh the benefits. The main objective of PC Project is to find treatments and a cure for PC. Every activity supported by PC Project is based on that goal.

What are the current treatments for PC?

There are no standardized or effective treatments for PC. However, regular care for the feet and nails is required to reduce pain and manage the condition. Each patient manages the symptoms in a variety of ways. Two basic elements of care for the feet and nails are: (1) soaking to soften calluses and nails, then (2) removal of the excess calluses. The removal of the calluses (called debridement) may be done at home or with professional care. Tools used include clippers (including wire or pet clippers for thick nails), emery boards, pumice stone, Dremel-type sanders, razor blades and scalpels. Vaseline is consistently used. Also, ibuprofen or other pain medication is taken in some form by almost all those with PC. Some 'tips for care' from patients include:



Wire clippers

Surgical Scalpel

- Regular (often daily) care and removal of excess calluses
- Keep feet as dry and soft as possible (i.e. use wicking socks and a moisturizing cream or vaseline)
- Clip or file nails frequently
- Insoles made of 'memory' material are used by some
- Use a shower stool or stand on a soft cushion in the shower
- Use a bleach bath/soak (1 cap of bleach to 1 gallon water) to prevent infections
- Use open shoes or breathable leather shoes that reduce friction. Some prefer soft shoes such as moccasins; for others strong supportive lace-up shoes are better

The website at **www.pachyonychia.org** includes the PC Wiki which posts tips offered by PC patients.

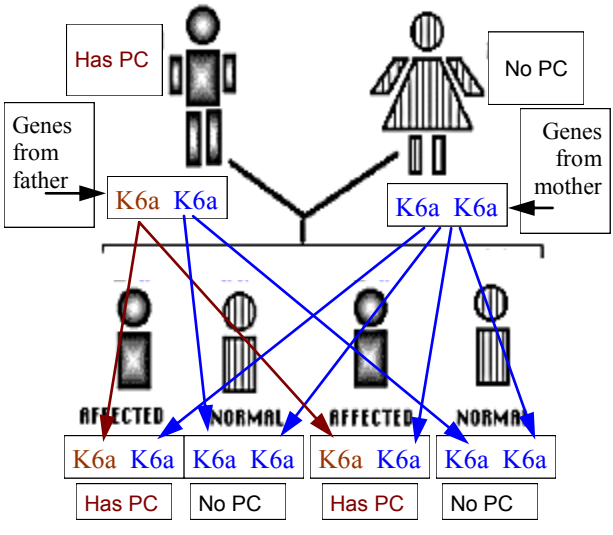
Will my children have PC?

Every person has two copies of every gene include the genes K6a, K6b, K16 and K17. One copy comes from their mother and one from their father.

A person who does not have PC cannot pass PC to their child even if their own mother or father has PC. If you don't have PC both copies of the PC genes are unchanged and you cannot pass on a mutation (changed) gene to your children or grandchildren.

A person who has PC has **one changed gene** (mutation) and **one unchanged gene** (normal) in either K6a, K6b, K16 or K17 keratin pair. Each time a baby is made, a person with PC has a **50/50** chance of either passing on the **changed gene** or passing on the **normal gene.**

Misinformation is sometimes provided about genetic inheritance in PC. In a recessive disorder, a disease can 'skip generations.' **That is not true for PC**. [See page 4 'What causes PC' for an explanation of PC as an autosomal **dominant** genetic disorder.]



NOTE - The gene with the mutation is shown in red. The example is shown with the father having PC. For familial or inherited PC, the inheritance factor is the same whether the father or the mother has PC.

What professional help is available?

Although there are currently no effective treatments for PC, patients may benefit from medical services on a regular basis including quick access to prescriptions for antibiotics when infections arise, removal of cysts, debridement of calluses, pain medication, treatment of laryngeal problems or other care related to the varied symptoms of PC.

A good relationship with caring and responsive medical professionals can make a great difference for patients. Because PC is so rare, even the most skilled and trained professionals may never have seen another case of PC. You can assist your care providers by providing quality reference materials available through PC Project. Although, some medical professionals will not welcome information from patients or may not have time to review such information, **it is worth every effort to find a care provider who will partner with you and establish an excellent doctor-patient relationship.**

You may find help from different specialists as you manage and care for your PC symptoms. It is important you know the qualifications of those helping you, be aware of the experience of other patients in any treatments offered and become a partner with the care provider to help them serve you better.

There are many different medical care providers:
A **general practitioner** — a medical doctor (MD) who treats general medical needs; this may be your main PC provider.
A **pediatrician** — a medical doctor (MD) with additional special training in treating children.
A **dermatologist** — a medical doctor with additional special training in diseases of the skin, but may have no experience with PC. Some may also have scientific training (MD, PhD). These doctors see patients and also are engaged in scientific research usually at a university.
A **nurse**, **nurse practitioner**, or **physician assistant** often assist MDs, and may also be helpful in the care of PC.
A **pain specialist** — a medical doctor (MD) with additional special training in chronic pain and pain medications
Scientists and researchers (often PhDs) do not treat patients, but work to find treatments and cures. .
A **podiatrist or chiropodist** is not a medical doctor (MD), but is specially trained in problems with the feet and often can provide debridement (removal of the calluses) and training in self care for PC patients.

NOTE: If you are unable to locate medical professionals to provide care for you or your child, please contact PC Project. Our medical advisors will assist with referrals.

What is the IPCRR? How will it help me?

The first step in the scientific process is to gather information about a disease. The **International Pachyonychia Congenita Research Registry (IPCRR)** is the only Research Registry specifically designed to gather data from those with PC. An independent Institutional Review Board (IRB) regularly reviews the **IPCRR** to ensure compliance with guidelines concerning the privacy, safety, and security of the information collected from patients.

Only de-identified information is released outside the **IPCRR** without written permission from the patient. The non-personal, statistical data is made available only to qualified researchers for PC-related research studies.

We feel participation in the **IPCRR** is the **most important** thing you can do. Because PC is so rare, it is important every adult and child with PC in a family participate in the **IPCRR.** For information see **www.pachyonychia.org.**

When treatments are available, those participating in the **IPCRR** will have first access to those treatments, but will not be obligated to utilize any treatment or participate in any clinical study or trial unless they wish to do so.

How can I help in research?

Because PC is very rare, articles may be published on just one case or one family. The conclusions may not be correct. By providing information to the **IPCRR**, patients can directly ensure that more accurate information on PC is available.

In addition to participation in the **IPCRR**, patients may be invited to participate in Grand Rounds. There are for held for physician education and a group of doctors/residents may examine you at a university or hospital. By coordinating these with PC Project, a group of patients can participate to allow much better physician education and knowledge of PC.

Patients may also have an opportunity to donate skin samples for use in research focused on PC.

As clinical studies and trials are developed, patients have a chance to directly participate in research. Without patient participation, clinical studies and trials cannot take place.

Thank you for helping move research forward!

What activities are funded by PC Project?

The **PC website at** www.pachyonychia.org is a tool for patients, researchers and clinicians. It features extensive, fully searchable reference materials on PC. Information on all PC Project activities, research grants, patient meetings and rare disease news is available on the website.

Beginning in 2004, annual **Patient Support Meetings (PSM)** have been sponsored by PC Project. At these meetings, PCers, family members, scientists and physicians join in educational and support activities.

The International PC Research Registry (**IPCRR)** is an IRB-approved registry with patient data gathered through an in-depth questionnaire and validated by a physician consultation. Images and a genetics report are also included in the IPCRR which now has data on over 500 PC patients.

Genetic Testing to identify the specific mutation for each patient s is fully funded by PC Project for patients in the IPCRR. The results of the testing now available on hundreds of PC patients show that PC is a spectrum of disorders and provide an excellent foundation for research studies.

The International PC Consortium (**IPCC)** was formed to bring together researchers and clinicians in collaborative research efforts related to PC. The IPCC Genetics Team, IPCC Research Team and the IPCC Physician Network coordinate the major research efforts around the world.

Grants awarded include projects on specific gene inhibitors, small molecule drug screening, a PC mouse model, designs for clinical trials, tests for specific inhibitors in established stable cell lines, development of a biobank and immortalized cell lines and stem cells from PC patients.

Numerous **publications** on PC and related PC research have regularly appeared in leading journals and are available through PC Project. In 2011-2012 a 'Best Practice' guideline is being developed. Educational brochures for friends, schools and for medical professionals are also available.

PC Project has established a **partnership with TransDerm,** a biotech firm which specializes in delivery of therapeutics for skin and provides scientific resources for PC.

Clinical Trials and Studies are sponsored by PC Project including a Phase 1b FDA-approved clinical trial. These studies lead to better understanding of PC and to development and delivery of therapeutics to PC patients.

Where can I get further information?

The PC Project website at **www.pachyonychia.org** provides additional information including

- a complete bibliography of scientific articles published about PC
- Educational videos and presentations from Patient Support Meetings and other events
- News and notes blog about PC Project activities, research related to PC, and PC treatments
- Information on the PC registry, where PC patients are located, lists of genetic mutations in PC, images of PC, PC Wiki and care tips...and more

NOTES & QUESTIONS

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