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.

2386 East Heritage Way, Suite B, Salt Lake City, Utah 84109 USA
Phone +1-877-628-7300 • Email—Info@pachyonychia.org
www.pachyonychia.org

FEATURE ARTICLE

Pachyonychia Congenita Project

A Partnership of Patient and Medical Professional

Mary E. Schwartz, Gail M. Zimmerman, Frances Smith, Eli Sprecher

ABSTRACT: A rare disease like pachyonychia congenita (PC) poses barriers to the patient, medical professional, and scientist. The patient has challenges connecting to information, the medical professional has challenges connecting to patient experience, and the scientist has challenges connecting to a sufficient number of patients to do meaningful research. Recent collaboration between these groups has transformed our understanding of PC and its symptoms and method of diagnosis. PC Project is at the center of this collaboration and is providing new insights for the dermatologist and dermatology nurse, enabling better diagnosis of PC and counseling of a PC patient. The PC patient, medical professional, and scientist have an international advocate in PC Project, a patient-led, nonprofit project committed to connecting all these communities to the tools they need to improve the lives of those living with PC.
Key words: Blisters, Cysts, Keratoderma, Nail dystrophy, Pachyonychia, Partnership

> ***"I was one proud mama! I watched my son hand PC brochures out to people (at our PC Awareness Day Event). When they asked questions, he answered them. If my grandmother was still alive she would be so proud to know how far we've come. No longer are we sitting on fingers at the dinner table, hiding our PC as she did…instead we are sharing with anyone information about PC, proud that we have an organization that stands by us. And, most importantly, we are not alone with PC. It may be rare…but we have met friends with it thanks to last year's PC Patient Support Meeting. We are not alone!" (Jessica, pachyonychia congenita [PC] patient).***

These words of joy reflect the power that can come from shared experience—knowing you are part of a larger community. This joy of knowing can be especially empowering when living with a rare disease like PC.

PC is an ultra-rare skin disorder that affects 2,000–10,000 people worldwide. The rarity of PC means that a person with PC usually never meets anyone else with PC other than affected family members. It means that researchers are challenged to find a sufficient number of PC patients to do meaningful research. It means that medical professionals do not have easy access to broad patient experience on which to base diagnosis or to learn if a treatment really works.

In 2004, PC Project [a patient-led 501(c)(3) charity based in Salt Lake City, Utah] set out to eliminate these barriers of isolation by creating an international collaborative network of patients, medical professionals, and scientists to be a catalyst to find effective treatments for the disease. Using high-technology tools, including custom software for the PC registry and database, an interactive Web site (www.pachyonychia.org), Webinars, and Web meetings (as well as E-mail, conference calls, and VoIP services or Skype), PC Project has connected researchers interested in keratin disorders, multidisciplinary specialists, and dermatologists to conduct basic and clinical research. This group of specialists is known as the International PC Consortium (IPCC). PC Project has also identified and recruited patient volunteers to provide personal histories and has in turn provided physician consultations and

***Mary E. Schwartz, AA**, Pachyonychia Congenita Project, Salt Lake City, Utah.*
***Gail M. Zimmerman, BA**, Pachyonychia Congenita Project, Salt Lake City, Utah.*
***Frances Smith, PhD**, Division of Molecular Medicine, University of Dundee, Dundee, United Kingdom.*
***Eli Sprecher, MD, PhD**, Department of Dermatology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, and Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel.*

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Correspondence concerning this article should be addressed to Mary E. Schwartz, AA, Pachyonychia Congenita Project, 2386 E. Heritage Way, Suite B, Salt Lake City, UT 84109.
E-mail: mary.schwartz@pachyonychia.org

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genetic testing for these patients through the International PC Research Registry (IPCRR). PC Project continues to seek dermatologists and dermatology nurses to be partners in this international community.

Through this collaborative effort, researchers have made several discoveries that have transformed the understanding of PC and treatment for PC. These new insights have significance for the dermatologist and dermatology nurse in diagnosing and counseling a PC patient.

PC: WHAT WE HAVE LEARNED

The disease is characterized by accumulation of keratin in the skin and nails, which manifests as calluses, thickened nails, and cysts (see Figures 1–3). Under the calluses are extremely painful blisters on the soles and sometimes on the palms. Pain is one of the most consistent features of PC and a key in differential diagnosis (Eliason, Leahman, Feng, Schwartz, & Hansen, 2012). PC is caused by a single mutation in one of at least five keratin genes, KRT6A, KRT6B, KRT6C, KRT16, or KRT17 (Akasaka et al., 2011; Wilson et al., 2010, 2011). As PC is an autosomal-dominant disorder, there is a 50% chance of passing on the mutation with each conception. However, more than 45% of PC cases appear spontaneously where there is no family history of the disease.

The condition was first described in the early 20th century (Jadassohn & Lewandowski, 1906) as "pachyonychia," which means "thickened nails." However, PC refers to a spectrum of symptoms, which is determined by both the location and the nature of the causative mutation as well as by yet unknown additional genetic and environmental factors (which explain the fact that individuals carrying the very same mutation can display divergent clinical features). From detailed questionnaires gathered from nearly 500 patients participating in the IPCRR, those with genetically confirmed PC are consistently found to have a triad of features including nail dystrophy, palmar/plantar keratoderma (e.g., thickening of the skin), and pain.

PC shares symptoms with a number of disorders like epidermolysis bullosa simplex and some connexin disorders (e.g., Clouston syndrome). In PC, the unrelenting pain from blisters under the thick calluses on the soles of the feet is the principal life-altering feature for most with this disease. The callus usually begins when the child with PC first begins to walk, and the pain is usually constant by age of 10 years. It requires regular trimming of the callus and activity planning to limit time on one's feet. Many must use canes, crutches, or wheelchairs or must crawl on their knees to manage the pain. In some forms of PC, the prevalent cysts are the most painful feature.

Documenting the variability of the symptoms across mutations and genes has led to a new classification system of PC to help clinicians improve their diagnostic and prognostic accuracy and improve therapeutic development. Rather than refer to PC-l and PC-2, which inaccurately groups PC patients, the new nomenclature, a diagnosis of

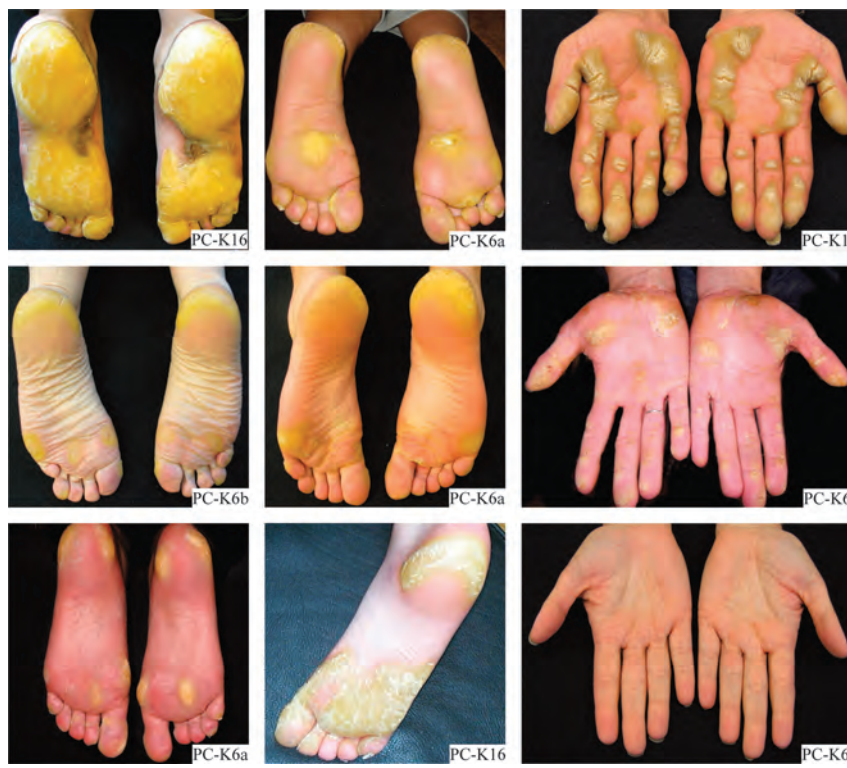

FIGURE 1. Focal plantar keratoderma, with painful blistering underneath the callus, is the main source of pain and disability in PC. Palmar keratoderma may also be found in patients with PC. Abbreviation: PC = pachyonychia congenita.

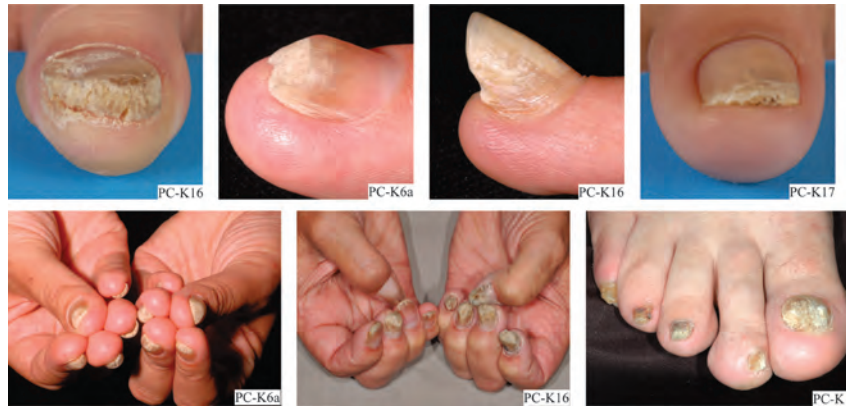

FIGURE 2. Nail changes in PC are quite varied across PC patients even among family members or those with the same mutations. Abbreviation: PC = pachyonychia congenita.

PC-K6a, PC-K6b, PC-K6c, PC-K16, and PC-K17, corresponds to mutations in the KRT6A, KRT6B, KRT6C, KRT16, and KRT17 genes, respectively, and PC-U indicates those with an unconfirmed genetic mutation (McLean, Hansen, Eliason, & Smith, 2011).

THE ROLE OF THE DERMATOLOGY NURSE

Although there is no effective treatment for PC at this time, the dermatology nurse can be a very helpful partner to the PC patient by helping with diagnosis, care techniques, and provision of accurate information. Those with PC may require medical assistance when they experience an infection of the nails or cysts. A good relationship with a dermatology nurse can be extremely beneficial to patients with PC.

Also, the dermatology nurse can effectively assist the patient in participating in the IPCRR. Through the IPCRR, the patient can obtain genetic testing to determine whether the patient has a mutation in one of the genes associated with PC. Details regarding the gene and the specific mutation are provided with the test results, and genetic counseling is available. If the patient is found not to have PC, genetic testing is conducted for a number of other similar conditions with the overall goal to assist the patient and medical providers with a definitive answer regarding the condition. All PC Project services are provided at no cost to the patient and referring specialist.

The IPCC experts welcome the opportunity to support the nurse and/or doctor in diagnosis, treatment options, and care. The dermatologist or dermatology nurse may contact us directly or refer the patient to PC Project. Individual consultations for patients, physicians, and dermatology nurses treating PC patients may be scheduled with physicians serving on the PC Project Medical and Scientific Advisory Board.

Once the diagnosis of PC is confirmed, the PC patient's de-identified data will be made available to researchers around the world (while preserving patient privacy and anonymity), and the patient will be eligible to participate in future studies and clinical trials.

Diagnosis

It is not uncommon for a person to reach his or her 40s or 50s before getting a correct diagnosis. Data from patients participating in the IPCRR have now revealed that plantar pain is a key diagnostic clue. In a recent study of 254 PC patients, plantar pain was reported by 225 of 254 (89%) surveyed patients. Only three patients older than 10 years old did not report plantar pain. The researchers concluded that plantar pain is the most important feature of PC affecting quality of life. The pain is related to the underlying blisters, and the thickness or extent of the visible callus may not reflect the degree of pain a patient experiences (Eliason et al., 2012).

Main Features of PC

Because of the IPCRR, the clinician who only rarely encounters these disorders now has better guidance and a more robust framework to make a clinical diagnosis (Irvine, 2012, p. 1758).

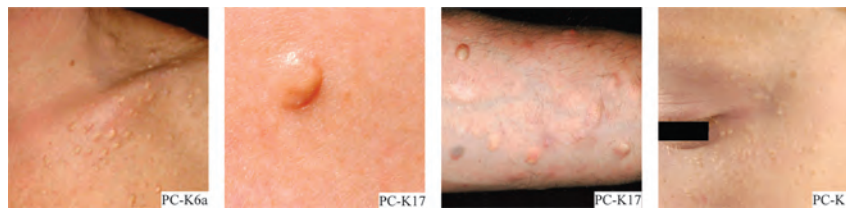

FIGURE 3. PC patients experience a variety of epidermal cysts. Those with PC-K17 have the greatest abundance of steatocystomas. Abbreviation: PC = pachyonychia congenita.

- Nail dystrophy (or thickening) often does not affect all 10 fingernails or all 10 toenails.
- Only toenails may be affected with fingernails remaining normal.
- Calluses on the soles of feet have underlying hidden blisters and are usually extremely painful with plantar pain being the number one concern for PC patients.
- Cysts are the second most common cause of pain in PC, and pain may also be from infected nails or follicular hyperkeratosis.
- Both steatocystoma and pilosebaceous cysts are found in nearly all types of PC, although those with PC-K17 have a greater number of steatocystomas.
- Nail infections may be initiated by nail trauma or excessive trimming.

Other Features of PC

- Follicular hyperkeratosis (most prominent in children and young teens)
- Oral leukokeratosis (often misdiagnosed as thrush or leukoplakia)
- Prenatal or natal teeth (usually PC-K17)
- Acute pain related to "first bite syndrome" (often misdiagnosed as "ear" pain)
- Laryngeal problems: thickening or nodules on the vocal chords causing hoarseness or, sometimes, difficulty in breathing (Treatment of the larynx may cause increased overgrowth but may sometimes be necessary to avoid obstruction.)

The rarity of the disease and its overlapping symptoms with other skin disorders make diagnosis a challenge. Commonly, people with PC may be misdiagnosed with onychomyciosis or fungal infection of the nails or with other causes for palmar/plantar keratoderma. At the same time, people with only thickened or dystrophic nails may be told that they have PC. Furthermore, previously misattributed features such as deafness, mental retardation, diabetes, bony abnormalities, early menarche, corneal lesions, and cataracts can be safely excluded from the canon of PC manifestations (Irvine, 2012, p. 1758).

Genetic testing can confirm the clinical diagnosis of PC and is the only way to verify that the patient's condition is in fact PC and not a related disorder.

Treatment

Review of the experience of PC patients in the IPCRR has shown that, although traditional therapeutics such as urea, salicylic acid, or oral retinoids may soften or reduce calluses, most patients abandon those therapies for lack of sufficient benefit (Eliason et al., 2012). When oral retinoids were recently assessed, findings show that, for most patients, there was no benefit and, instead, increased pain or the adverse side effects outweighed the benefits (Gruber et al., 2011). Because we cannot predict which patients may benefit from oral retinoids, an empirical trial with variable dosing is being evaluated as well as a topical retinoid application for PC.

Patients typically manage their own symptoms through careful mechanical trimming of the calluses to ensure a "not too thick and not too thin" result. Aggressive debridement may increase pain. Frequent filing and trimming of the nails is also necessary. Patients who experience PC with numerous cysts find that these must be drained or the cysts may need to be surgically removed because of pain or infection.

The results of a formal survey of patient experience with treatment and self-care will also be published soon. The survey collected detailed responses on treatment and care used by PC patients for specific conditions including keratoderma; cysts; follicular hyperkeratosis; and fingernails, toenails, and nail infections. The results will be published shortly and will provide a good reference for both the dermatologist and dermatology nurse.

Patients may need one or more medical services on a regular basis including quick access to prescriptions for antibiotics when infections arise, removal of cysts, pain medication, or other care related to the varied symptoms of PC. The dermatology nurse/dermatologist may need to help the PC patient find treatment for one or more of these issues.

PC PROJECT: A RESOURCE FOR THE PC PATIENT AND MEDICAL PROFESSIONAL

Major benefits for PC patients and medical professionals are available through the PC Project, the IPCRR, and IPCC members. Participation in the IPCRR provides access to clinical trials, information on care techniques, publications from dermatology journals, annual patient support meetings, and Webinars. Through the IPCC, medical professionals have a team of support and information for their patients' care.

Through the Web site (www.pachyonychia.org), both the patient and medical professional can stay informed about opportunities to participate in educational meetings, Webinars, and clinical trials. The Web site features the latest research news, extensive images, a complete bibliography of scientific articles, patient education brochures, a quarterly scientific newsletter, and a monthly news brief as well as an annual report. PC Project also maintains a Facebook page through which PC patients in the IPCRR can connect with each other.

Patient success with various care techniques does vary. To help PC patients find what may work for them, PC Project has catalogued patient reports into a PC Wiki section available on the Web site. Techniques used to manage the symptoms of PC are shown on a "Caring For PC" DVD, which is available upon request. The DVD and all printed materials are provided at no charge to patients and medical professionals.

The annual PC Patient Support Meeting (in Europe or the United States) is an especially important way a PC patient can meet, connect, and share with others who have PC. To help every PC patient who wants to attend, PC Project offers scholarships to patients in the IPCRR to attend the meeting.

To learn directly from physician experts about PC, interested dermatology nurses can sign up for one of the quarterly educational Webinar sessions sponsored by PC Project. There are also educational brochures specifically for medical professionals. In addition, for patients in the IPCRR, medical experts are available to provide counseling with a physician or nurse to individual patients.

We recognize that most medical professionals will rarely see a PC patient, so PC Project has set up a resource for those medical professionals wanting to confirm diagnosis or get the latest advice on management of the disease or clinical trials that may be ongoing.

WORKING TO CHANGE THE FUTURE: MAINTAINING RESEARCH MOMENTUM

PC Project is collaborating on a number of research strategies to develop an effective PC treatment. One of these research strategies is gene silencing. By inactivating the mutant keratin gene, researchers hope to eliminate PC symptoms. PC Project, through its biotech partner TransDerm, has completed a Phase 1b, FDA-approved clinical trial of a gene silencing strategy using siRNA therapy (Leachman et al., 2010). A second clinical trial of an improved siRNA developed by TransDerm will begin in 2013 (Hickerson et al., 2011). This second trial will involve use of dissolvable microneedles developed to deliver drugs in a more patient-friendly manner (Gonzalez et al., 2010). Two additional clinical studies (oral statins and topical rapamycin) will also enroll patients in 2013.

PC Project provides fellowship and grant funding to a variety of universities for the support of PC research. Since 2004, when the IPCC was formed with 23 physicians and researchers, PC Project has recruited 150 members of the consortium, each with a pledge to collaborate to improve treatment for PC. A number of ground-breaking basic and clinical research reports have been published in the last couple of years by members of the IPCC in leading dermatology journals. These reports are accessible to everyone through a searchable bibliography on the PC Project's Web site or can be requested on a CD or in booklet format.

Topics of articles, which will be published shortly based on the results of current studies, include PC best practices, life history of PC, pathology of PC nails, pathology of PC cysts, and over 50 additional case studies including novel mutations as well as a revised PC summary article. The National Institutes of Health Office of Rare Disease Research and National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin have been very helpful to PC Project in our research and outreach efforts.

RAISING RARE DISEASE AWARENESS

As PC is ultra-rare, the public and medical community are generally not aware of PC or the challenges it can present. This lack of awareness contributes to the isolation of many PC patients. The empathy and understanding of the general public will create a more supportive environment for those experiencing rare diseases like PC and generate more public support of rare disease research.

Raising funds for rare disease research and patient support has been challenging in terms of recruiting volunteers and supporters. However, because of the profound impact this disease can have on the life of both children and adults, parents, spouses, and family members are highly motivated to help improve their future. PC Project launched its first annual PC Awareness Day in 2012 to begin connecting and empowering the PC patient community in its support of public awareness. This first international effort resulted in dozens of local events in 10 countries and reached thousands around the world through print, TV, and radio media. PC Project just completed a 5- to 6-minute public awareness video on PC that can be found on YouTube. PC Awareness Day provided a new source of funds as well as an opportunity to increase awareness of PC. All 2012–2013 donations are matched $2-for-$1 by an anonymous individual sponsor, which triples each dollar received.

PC Project participates with other nonprofit groups, which specialize in areas important to PC research and patient support. These include Genetic Alliance (focuses on genetic disorders), National Organization for Rare Disorders (focuses on rare disorders), and the Coalition of Skin Diseases (focuses on skin disease research and patient advocacy). The American Academy of Dermatology and the Society of Investigative Dermatology are important partners in the effort to raise awareness and provide support for skin disease research. The best part of PC Project is the partnerships—helping people connect with each other and to connect the patients and scientists. PC Project was started to help one person, but now, it serves and unites more than 1,000 people with PC in over 50 countries. People with PC need to know that, by sharing information and working with others in the PC community, they can advance research and change the future. The growing number of patients, physicians, and scientists in our network of collaborators will move us more rapidly to an effective, patient-friendly treatment. ■

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