Pachyonychia Congenita Project

15 March 2005

Use of Articles in the Pachyonychia Congenita Bibliography

The articles in the PC Bibliography may be restricted by copyright laws. These have been made available to you by PC Project for the exclusive use in teaching, scholarship or research regarding Pachyonychia Congenita.

To the best of our understanding, in supplying this material to you we have followed the guidelines of Sec 107 regarding fair use of copyright materials. That section reads as follows:

> Sec. 107. - Limitations on exclusive rights: Fair use
> Notwithstanding the provisions of sections 106 and 106A, the fair use of a copyrighted work, including such use by reproduction in copies or phonorecords or by any other means specified by that section, for purposes such as criticism, comment, news reporting, **teaching (including multiple copies for classroom use), scholarship, or research**, is not an infringement of copyright. In determining whether the use made of a work in any particular case is a fair use the factors to be considered shall include - (1) the purpose and character of the use, including whether such use is of a commercial nature or is for nonprofit educational purposes; (2) the nature of the copyrighted work; (3) the amount and substantiality of the portion used in relation to the copyrighted work as a whole; and (4) the effect of the use upon the potential market for or value of the copyrighted work. The fact that a work is unpublished shall not itself bar a finding of fair use if such finding is made upon consideration of all the above factors.

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

The Phenotypic and Molecular Genetic Features of Pachyonychia Congenita

W.H. Irwin McLean[1], C. David Hansen[2], Mark J. Eliason[2] and Frances J.D. Smith[1]

Pachyonychia congenita (PC) is an autosomal dominant genodermatosis caused by heterozygous mutations in any one of the genes encoding the differentiation-specific keratins K6a, K6b, K16, or K17. The main clinical features of the condition include painful and highly debilitating plantar keratoderma, hypertrophic nail dystrophy, oral leukokeratosis, and a variety of epidermal cysts. Although the condition has previously been subdivided into PC-1 and PC-2 subtypes, the phenotypic characterization of 1,000 mutation-verified PC patients enrolled in the International PC Research Registry, coordinated by the patient advocacy group PC Project, shows that there is considerable overlap between these subtypes. Thus, a new genotypic nomenclature is proposed, in which PC-6a represents a patient carrying a mutation in the *K6a* gene, etc. Although a rare disorder, PC represents a good model for therapy development, and international efforts are ongoing to develop and deliver siRNA, gene, correction, small molecule, and other strategies to treat this painful, disabling skin condition. The special relationship between PC Project and the PC research community has greatly accelerated the development pathway from gene identification to clinical trials in only a few years and represents a paradigm of hope for other orphan diseases.

Journal of Investigative Dermatology advance online publication, 24 March 2011; doi:10.1038/jid.2011.59

INTRODUCTION

Pachyonychia congenita (PC) is an uncommon autosomal dominant disorder of keratinization caused by mutations in any one of a number of keratin genes that are expressed in differentiated epithelial tissues. The condition was first described in the early twentieth century (Jadassohn and Lewandowski, 1906; Jackson and Lawler, 1951) but it was not until the early 1990s, with the emergence of molecular genetics technology, that the causative gene in a large Scottish PC family was mapped to one of the keratin gene clusters (Munro *et al.*, 1994). Shortly thereafter, the causative mutations were identified in several PC patients in the *KRT6A*, *KRT6B*, *KRT16*, and *KRT17* genes, encoding the keratin proteins K6a, K6b, K16, and K17, respectively (Bowden *et al.*, 1995; McLean *et al.*, 1995; Smith *et al.*, 1998).

Keratins are the intermediate filament proteins specifically expressed by epithelial cells, in which they form a dense cytoplasmic network (Irvine and McLean, 1999; Omary *et al.*, 2004). The primary function of the keratin cytoskeleton is to impart mechanical strength and resilience to epithelial cells and tissues. Disruption of this cytoskeletal system due to a genetic mutation in a keratin gene leads to extreme fragility of the epithelial cells and tissues in which the mutated keratin is expressed. Similar to several other keratin disorders, the vast majority of causative mutations in the PC-related keratins are heterozygous missense mutations or small insertion/deletion mutations that disrupt cytoskeletal function via dominant-negative interference and lead to epithelial cell fragility (McLean *et al.*, 2005). In PC, this is manifest as cytolysis and hyperkeratosis in the subset of differentiated epithelial tissues in which K6a, K6b, K16, and K17 are predominantly expressed (Lane, 1993), specifically the palmoplantar epidermis, nail bed, mucosae, and the pilosebaceous unit. Thus, the cardinal phenotypic features of PC are palmoplantar (predominantly plantar) keratoderma; hypertrophic nail dystrophy; oral leukokeratosis; and a variety of cysts arising from hyperkeratosis of pilosebaceous apparatus (Figure 1).

A MOLECULAR CLASSIFICATION FOR PC SUBTYPES

In 2003, a patient advocacy group—Pachyonychia Congenita Project—was established to support those affected by PC and to both encourage and fund research into a cure for the condition (www.pachyonychia.org). To achieve this goal, the International PC Consortium (IPCC) was founded in early 2004. This is a group of clinicians and scientists actively researching the causes of PC and importantly, the development of new treatments for PC. The IPCC has met annually since 2004 and its membership is listed at www.pachyonychia.org.

An important part of the ongoing PC research program is the International PC Research Registry (IPCRR), in which detailed phenotypic data are collected from patients and linked to genetic data. At the time of writing, close to 1000 PC patients have been identified by the PC Project. This has

[1]*Division of Molecular Medicine, University of Dundee, Dundee, UK and* [2]*Department of Dermatology, University of Utah, Salt Lake City, Utah, USA*

Correspondence: W.H. Irwin McLean, Division of Molecular Medicine, Medical Sciences Institute, University of Dundee, Dundee DD1 5EH, UK. E-mail: w.h.i.mclean@dundee.ac.uk

Abbreviations: IPCC, International Pachyonychia Congenita Consortium; IPCRR, International Pachyonychia Congenita Research Registry; K, keratin protein; KRT, keratin gene; PC, pachyonychia congenita

Received 26 August 2010; revised 2 February 2011; accepted 11 February 2011

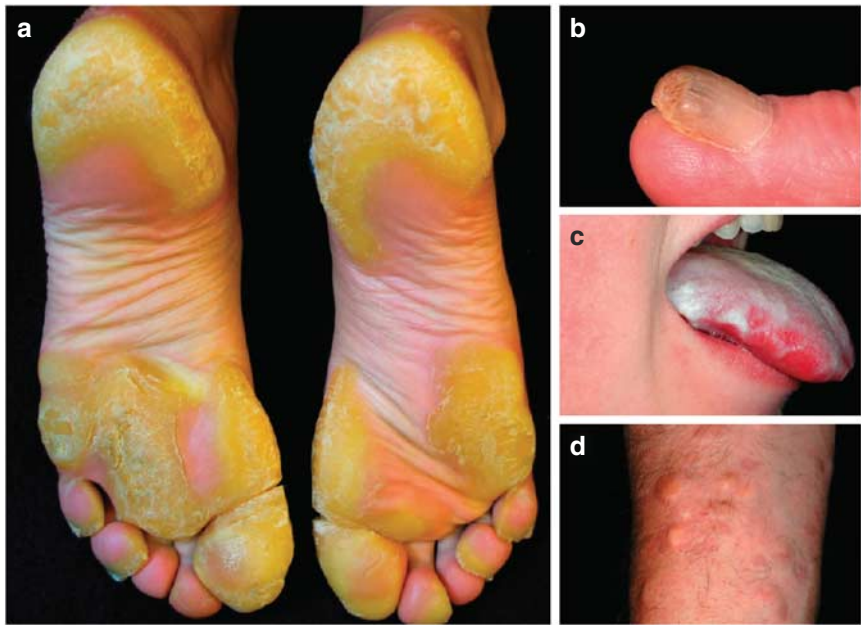

Figure 1. The cardinal clinical characteristics of PC. (**a**) Focal plantar keratoderma, with recurrent blistering underneath the callus, is the main source of pain and disability in PC. This individual is a heterozygous carrier of the K16 mutation L132P (p.Leu132Pro). (**b**) Typical hypertrophic nail dystrophy that gives the condition its name. The nail changes are quite variable in PC families, even among people with the same mutation. In some cases, the fingernails are spared. This patient carries the K17 mutation L95Q (p.Leu95Gln). (**c**) Oral leukokeratosis is a common feature of PC, readily seen here as lingual leukokeratosis in a patient carrying the most common PC mutation, N172del (p.Asn172del) in K6a. (**d**) PC patients suffer from a variety of epidermal cysts, including follicular keratoses and pilosebaceous cysts that can resemble steatocysts or epidermoid cysts. The latter are more abundant in patients with K17 mutations, as shown here in a patient carrying the K17 mutation N92D (p.Asn92Asp). PC, pachyonychia congenita.

led to the largest collection of linked clinical and genetic information yet assembled for a rare keratin disorder. Historically, PC has been split into two subtypes (PC-1, or Jadassohn–Lewandowski subtype; and PC-2, or the Jackson–Lawler subtype) on the basis of subtle differences in phenotype, primarily the presence or absence of pilosebaceous cysts (Jadassohn and Lewandowski, 1906; Jackson and Lawler, 1951). At present, with analysis of hundreds of patients in the IPCRR, limitations in the older classification, which was based on only a handful of non-genotyped cases, have become clear. In particular, many PC patients, regardless of genotype, have some form of epidermal cysts (see Wilson *et al.*, 2011). Therefore, on the basis of the more comprehensive IPCRR data, a more rational and useful classification based on the mutated gene was proposed at the 2010 IPCC Symposium and has been adopted throughout the research papers in this issue of the *JID*. The new classification is PC-6a, PC-6b, PC-16, and PC-17, for a patient with a mutation in the gene encoding K6a and others proteins (the complete data set underlying this new nomenclature will be published elsewhere; Eliason *et al.*, unpublished data). In cases in whom PC is suspected but no mutation has been found (or not looked for), the term PC-U (for unknown) will be used.

The predominant symptom in PC is plantar pain

Although hypertrophic nail dystrophy is the phenotypic feature that gave rise to the name of the condition, the most problematic symptom reported by PC patients is focal plantar keratoderma that is associated with severe pain. The plantar pain in PC is often highly debilitating and has considerable negative effect on quality of life. The reason for the pain is not fully understood but is thought to be related to blister formation deep underneath the thick callus that develops over the pressure points of the plantar surface (see Figure 1a). Plantar blistering, together with accompanying pain, is a common feature of PC that is under-reported in the literature (Eliason *et al.*, unpublished data).

Nail dystrophy (Figure 1b), which can occur from a very early age, is variable in severity and in many cases not all 20 nails are affected. Toenails are more commonly affected than fingernails, which could be because of greater trauma exerted from shoes. Another feature of PC is oral leukokeratosis (Figure 1c). This is often one of the first signs of PC in babies and may lead to difficulty in feeding and is often mistaken for candidiasis in infants. Follicular keratoses are present in many cases of PC. Some individuals also develop cysts in the form of steatocysts (steatocystomas) and/or pilosebaceous cysts (Figure 1d). This feature is particularly associated with patients with a K17 mutation (see Wilson *et al.,* this issue), in whom sometimes it is necessary to remove cysts surgically. The severity of the clinical features of PC can vary quite widely both among and within families. This may partly be because of individual lifestyle and care of PC and could also be because of the specific type of mutation, as well as other genetic and/or environmental factors.

Rapid therapy development in PC

Although it is a rare condition, PC is at the forefront of genetic therapy development in the dermatology field. In particular, the dominant-negative genetic mechanism in PC contributes to therapeutic strategies based on RNA interference (RNAi), especially in the form of short interfering RNA (siRNA). It has been demonstrated that mutant keratin alleles differing from wild type by a single-nucleotide point mutation can be potently and specifically silenced by carefully designed siRNA (Hickerson *et al.*, 2008). This mutation-specific siRNA therapy approach has been progressed into the recently reported small-scale human clinical trial, in which efficacy was demonstrated (Leachman *et al.*, 2010). This was the first time that siRNA had been used to treat a human skin disorder. The keratins involved in PC also show considerable functional redundancy, in particular when K6 is involved. Humans have three copies of a nearly identical *KRT6* gene, encoding the K6a, K6b, and K6c proteins. Mouse knockout experiments strongly suggest that loss of one of these keratins may be tolerated (Wong *et al.*, 2000; Wojcik *et al.*, 2001) and therefore an alternative therapeutic approach would be to completely silence the defective keratin, regardless of mutation. To this end, highly potent gene-specific siRNA has been developed for PC (Smith *et al.*, 2008). The major technical hurdle yet to overcome in both these therapeutic approaches is the development of a safe, effective, and patient-friendly method for routine delivery of siRNA into the epidermis. This is currently a major goal of the IPCC research groups, in addition to development of alternative therapies that include gene correction methodology, small molecule therapy, and other strategies (Kaspar *et al.*, this issue).

CONCLUSION

Over the past 7 years, the PC research field represents a great example of how a small group of highly motivated patients and their families, together with a group of interested clinicians and scientists, can rapidly progress research from knowing only the identity of a gene defect to having new therapies that show efficacy in cells, in animal models, and in patients. Hopefully, this sustained, highly focused effort will shortly lead to a successful and widely applicable treatment for PC and the lessons learned along the way can be translated to other genetic skin disorders.

CONFLICT OF INTEREST

Dr McLean and Dr Smith filed a patent on therapeutic siRNA for PC. The other authors state no conflict of interest.

ACKNOWLEDGMENTS

We thank Pachyonychia Congenita Project for their continued enthusiasm, constant encouragement, and financial support of their research.

REFERENCES

Bowden PE, Haley JL, Kansky A *et al.* (1995) Mutation of a type II keratin gene (K6a) in pachyonychia congenita. *Nat Genet* 10:363–5

Hickerson RP, Smith FJD, Reeves RE *et al.* (2008) Single-nucleotide-specific siRNA targeting in a dominant-negative skin model. *J Invest Dermatol* 128:594–605

Irvine AD, McLean WHI (1999) Human keratin diseases: the increasing spectrum of disease and subtlety of the phenotype-genotype correlation. *Br J Dermatol* 140:815–28

Jackson ADM, Lawler SD (1951) Pachyonychia congenita: a report of six cases in one family with a note on linkage data. *Ann Eugen* 16:142–6

Jadassohn J, Lewandowski F (1906) *Pachyonychia congenita: keratosis disseminata circumscripta (follicularis). Tylomata. Leukokeratosis linguae*. vol. 1. Berlin: Urban and Schwarzenberg, 29

Kaspar RL, Leachman SA, McLean WHI, Schwartz ME (2011) Toward a Treatment for Pachyonychia Congenita: Report on the 7th Annual International Pachyonychia Congenita Consortium Meeting. *J Investig Dermatol* 131:1011–4

Lane EB (1993) Keratins. In *Connective Tissue and its Heritable Disorders. Molecular, Genetic and Medical Aspects*. Royce PM, Steinmann B (eds). New York: Wiley-Liss Inc, 237–47

Leachman SA, Hickerson RP, Schwartz ME *et al.* (2010) First-in-human mutation-targeted siRNA phase Ib trial of an inherited skin disorder. *Mol Ther* 18:442–6

McLean WHI, Rugg EL, Lunny DP *et al.* (1995) Keratin 16 and keratin 17 mutations cause pachyonychia congenita. *Nat Genet* 9:273–8

McLean WHI, Smith FJD, Cassidy AJ (2005) Insights into genotype-phenotype correlation in pachyonychia congenita from the human intermediate filament mutation database. *J Investig Dermatol Symp Proc* 10:31–6

Munro CS, Carter S, Bryce S *et al.* (1994) A gene for pachyonychia congenita is closely linked to the keratin gene cluster on 17q12-q21. *J Med Genet* 31:675–8

Omary MB, Coulombe PA, McLean WHI (2004) Intermediate filament proteins and their associated diseases. *N Engl J Med* 351: 2087–100

Smith FJD, Hickerson RP, Sayers JM *et al.* (2008) Development of therapeutic siRNAs for pachyonychia congenita. *J Invest Dermatol* 128: 50–8

Smith FJD, Jonkman MF, van Goor H *et al.* (1998) A mutation in human keratin K6b produces a phenocopy of the K17 disorder pachyonychia congenita type 2. *Hum Molec Genet* 7:1143–8

Wilson NJ, Leachman SA, Hansen CD *et al. J Invest Dermatol*; e-pub ahead of print 17 February 2011

Wojcik SM, Longley MA, Roop DR (2001) Discovery of a novel murine keratin 6 (K6) isoform explains the absence of hair and nail defects in mice deficient for K6a and K6b. *J Cell Biol* 154:619–30

Wong P, Colucci-Guyon E, Takahashi K *et al.* (2000) Introducing a null mutation in the mouse K6alpha and K6beta genes reveals their essential structural role in the oral mucosa. *J Cell Biol* 150:921–8