桜 Sakura:
Renewal and Hope for PC

International Pachyonychia Congenita Consortium (IPCC) Symposium

May 10, 2023 | 8:00 am to 1:00 pm
Takao Room | 42nd Floor
Keio Plaza Hotel Tokyo, Japan

Sakura: Our Season of Optimism

Sakura 桜, or the cherry blossom, is the national flower of Japan. Sakura season represents a time of renewal and optimism, hope, and new dreams. The first pops of pink mark the end of winter and the beginning of spring. When the cherry blossoms are in full bloom, they signify that the future is bursting with beautiful possibilities.

What a perfect way to describe our experience with pachyonychia congenita! For too long, PC patients have felt the "winter" of pain, discouragement, and physical limitations. However, because of the work of this dedicated group – the International Pachyonychia Congenita Consortium - the future is bright and hopeful.

Our journey is much like the Sakura, the cherry blossom cycle. As we gather again this year, we do so with a sense of renewal to these patients. Our symposium program takes us through the first stage, the **Tsubomi,** or the first buds of research. Then, we move to **Kaika**, the first blossoms, or emerging therapies. Next, we reach the **Mankai**, the peak blooming of Sakura, where the previous stages are finally translating into an extraordinary flower.

Finally – and we are not quite there yet, but we plan to be – we reach the ultimate stage of our journey, **Hanafubuki** – a cherry blossom blizzard.

Thank you for joining us and working with us to achieve our goal for patients - a spectacular Sakura "storm" of treatments, where all hopes and expectations are realized, and pain and suffering are no more.

Tender feet may ache
But with hope and care, they'll heal
Stronger steps await

—Haiku by Nathan, PC patient

Program at a Glance

8:00 AM **Welcome and PC Project Update**
Janice Schwartz, BA
Pachyonychia Congenita Project, Utah, USA

蕾 Tsubomi (Pathogenesis session)
Chair: Edel O'Toole, MD, PhD, FRCP
Blizard Institute, Queen Mary University of London, England, UK

8:10 AM **Palmoplantar keratodermas in 5 steps**
Eli Sprecher, MD, PhD
Division of Dermatology, Tel Aviv Medical Center, Israel

8:30 AM **Effects of keratin gene loss on epidermal keratinization programs**
Leopold Eckhart, PhD
Medical University of Vienna, Austria

8:45 AM **Experience with autograft therapy using revertant keratinocytes in severe recessive epidermolysis bullosa.**
Akiharu Kubo, MD, PhD
Kobe University Graduate School of Medicine, Japan

9:00 AM **Neuronal control of sweat gland stem cells in the palmoplantar skin**
Catherine Pei-ju Lu, PhD
New York University Grossman School of Medicine, New York, USA

9:15 AM **Molecular mechanisms of intermediate filament tetramerization**
Christopher G. Bunick, MD, PhD
Yale University, Connecticut, USA

9:30 AM **Connecting skin inflammation and morphogenesis through desmosomes**
Kathleen J. Green, PhD
Northwestern University Feinberg School of Medicine, Illinois, USA

9:45 AM **Pachyonychia congenita keratin isoforms modulate motility signals during wound healing**
Benjamin A. Nanes, MD, PhD
University of Texas Southwestern Medical Center, Texas, USA

10:00 AM **BREAK—Group Photo**

開花 Kaika (Emerging therapies session)
Chair: Roger Kaspar, PhD
Ayni Therapeutics, Santa Cruz, CA, USA

10:15 AM **Towards an in vitro model of pachyonychia congenita**
Laura Ramos, PhD
Blizard Institute, Queen Mary University of London, England, UK

10:25 AM **Innovations in CRISPR gene editing for epidermolysis bullosa**
Joanna Jacków, PhD
King's College London, England, UK

10:40 AM **Personalized preclinical gene editing protocols for in vivo correction of pachyonychia congenita**
Marta Garcia Diez, PhD
Universidad Carlos III de Madrid (UC3M), Spain

10:55 AM **Gene therapy for epidermolysis bullosa**
M. Peter Marinkovich, MD
Stanford University, California, USA

11:10 AM **BREAK**

滿開 Mankai (Clinical insights and disease modeling session)
Chair: Alain Hovnanian, MD, PhD
Imagine Institute, Paris, France

11:25 AM **Mouse models for pachyonychia congenita**
Pierre A. Coulombe, PhD & Amanda Orosco, PhD Candidate
University of Michigan Medical School, Michigan, USA

11:40 AM **Lessons learned from pachyonychia congenita may provide clues to the pathogenesis of hidradenitis suppurativa**
Michelle Lynn Kerns, MD, MS
Cleveland Clinic, Ohio, USA

11:55 AM **Erythromelalgia: A newly identified feature of pachyonychia congenita**
Rebecca McCarthy, BMBS (Hons), BSc (Hons)
Blizard Institute, Queen Mary University of London, England, UK

12:05 PM **Palmoplantar keratodermas in The Netherlands, a continued learning experience**
Antoni Gostynski, MD, PhD
Maastricht University Medical Center, The Netherlands

12:20 PM **Complicated genetic background of palmoplantar keratoderma in Japanese: A heterozygous SERPINB7 variant is a possible modifying factor for clinical features.**
Masashi Akiyama, MD, PhD
Nagoya University Graduate School of Medicine, Japan

花吹雪 **Hanafubuki –**
Renewed commitment and a brighter future for patients!

12:35 PM **Lunch & Symposium Adjourns**

1:10 PM **PC Project's Medical & Scientific Advisory Board Meeting**
By invitation only

Detailed Program

8:00 AM

Welcome and PC Project Update

Janice Schwartz, BA

Executive Director, Pachyonychia Congenita Project

蕾 Tsubomi (Pathogenesis session)

Chair: Edel O'Toole, MD, PhD, FRCP

Professor of Molecular Dermatology, Centre for Cell Biology and Cutaneous Research, Blizard Institute, Queen Mary University of London and Consultant Dermatologist, Royal London Hospital

8:10 AM

Palmoplantar keratodermas in 5 steps

Eli Sprecher, MD, PhD, MBA

Chair, Division of Dermatology

Deputy Director General for R&D and Innovation

Tel Aviv Sourasky Medical Center

Frederick Reiss Professor of Dermatology and Vice Dean for Clinical Affairs

Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Chair, International Pachyonychia Congenita Consortium

The past years have witnessed dramatic advances in our understanding of the genetic basis of hereditary palmoplantar keratodermas. Despite extensive clinical and genetic heterogeneity, most PPKs seem to share a limited number of pathomechanisms, which reflect dysfunction of 5 essential components of the epidermal differentiation program. This new knowledge has not only far-reaching implications for the counseling of individuals at risk for inherited palmoplantar keratodermas, it has also recently led to the development of innovative therapeutic solutions for these often incapacitating conditions.

8:30 AM

Effects of keratin gene loss on epidermal keratinization programs

Leopold Eckhart, PhD

Associate Professor, Department of Dermatology, Medical University of Vienna, Vienna, Austria

The function of the skin as a protective organ depends on the continuous renewal and stratification of the epidermis. The differentiation of epidermal keratinocytes is controlled by alternative genetic programs characterized by the expression of specific keratins. We investigated the interdependencies and evolutionary conservation of suprabasal epidermal keratins in mammalian species. Krt1 and Krt2 are expressed together in the same keratinocytes of human skin but in a mutually exclusive manner in different regions of mouse skin. Targeted deletion of Krt2 caused aggregation of Krt10 and inflammation in mouse ear skin. The additional deletion of Krt10 suppressed aggregate formation but led to upregulation of Krt6 and Krt16 and callus formation on the soles. Fully aquatic mammals, such as dolphins and whales, have lost the evolutionarily ancient suprabasal keratins, Krt1, Krt2 and Krt10. This loss is compensated by the constitutive expression of Krt6 and Krt17 and extreme thickening of the epidermis. We propose that comparative studies of mammalian skin may provide important new insights into the control of keratin gene expression.

8:45 AM

Experience with autograft therapy using revertant keratinocytes in severe recessive epidermolysis bullosa

Akiharu Kubo, MD, PhD

Department of Dermatology, Keio University School of Medicine, Division of Dermatology, Department of Internal Related, Kobe University Graduate School of Medicine

Severe dystrophic epidermolysis bullosa (DEB) patients with biallelic loss-of-function defects in COL7A1 lack the anchoring fibrils that hold the epidermis to the dermis and develop recurrent skin erosions all over the body. By chance, somatic genetic changes can lead to the formation of revertant skin, composed of cells that spontaneously acquire functional COL7A1. A 17-year-old severe DEB patient developed ~8 cm2 of revertant skin showing positive immunostaining at the basement membrane for anti-COL7A1 antibody (LH7.2), despite completely negative LH7.2 immunostaining in the diseased skin. Genetic analysis revealed that the lesional epidermal cells, but not the dermal cells, acquired the reversion in one of the pathogenic variants to wild-type. Since the production and autologous transplantation of primary cultured keratinocyte cell sheets (JACE®), using a culture method originally developed by Howard Green, was approved for DEB and junctional epidermolysis bullosa in the national insurance system of Japan in 2019, we produced keratinocyte cell sheets from the revertant skin. Not only autografting the revertant keratinocytes onto the erosions and ulcers but also mechanical peeling of the diseased epidermis followed by autografting of the revertant keratinocytes successfully replaced the diseased epidermis with the revertant epidermis over ~60% of the body surface. Three-year follow-up showed a significant reduction in skin erosions, disappearance of fatigue, and remarkable improvement in nutritional status, e.g., body weight from 27 to ~40 kg and serum albumin from 2.2 to 3.3 g/dL. Mechanical peeling of the epidermis followed by autografting of the revertant keratinocytes may be a promising therapeutic option in severe DEB with complete loss of COL7A1.

9:00 AM

Neuronal control of sweat gland stem cells in the palmoplantar skin

Catherine Pei-ju Lu, PhD

Assistant Professor, Hansjörg Wyss Department of Plastic Surgery, New York University Grossman School of Medicine

Sympathetic nerves co-develop with their target organs and release neurotransmitters to stimulate their functions after maturation. Here, we provide the molecular mechanism that during sweat gland morphogenesis, neurotransmitters released from sympathetic nerves act first to promote sweat duct elongation via norepinephrine and followed by acetylcholine to specify sweat gland stem cell fate, which matches with the sequence of neurotransmitter switch. Without neuronal signals during development, the basal cells switch to exhibit suprabasal (luminal) cell features. Sarcolipin (SLN), a key regulator of sarcoendoplasmic reticulum (SR) Ca2+-ATPase (SERCA) expression is down-regulated in the sweat gland myoepithelial cells upon denervation. Our work highlights that neuronal signaling not only acts transiently for mature sweat glands to function, but also exert long-term impact on stem cell specification during development through regulating intracellular Ca2+ dynamics.

9:15 AM

Molecular mechanisms of intermediate filament tetramerization

Christopher G. Bunick, MD, PhD

Associate Professor of Dermatology, Program in Translational Biomedicine, Yale University

During the assembly process, intermediate filaments form a tetramer species. A unique "knob-pocket" interaction at both ends of the 1B sub-domain within the helical rod plays a critical role in forming and stabilizing the tetramer. We characterized the molecular function of the knob-pocket mechanism of assembly at single-residue resolution, and examined the effect in cells of directly inhibiting this mechanism.

9:30 AM

Connecting skin inflammation and morphogenesis through desmosomes

Kathleen J. Green, PhD

Joseph L. Mayberry Professor, Departments of Pathology and Dermatology, Northwestern University Feinberg School of Medicine

While classic cadherin-actin connections have ancient origins, desmosomal cadherins and their connections with intermediate filaments (IF) appeared much later in evolution, reaching the height of complexity in terrestrial vertebrates. These connections, which occur at intercellular junctions called desmosomes, provided opportunities create more complex tissues such as the epidermis with barrier functions that allowed us to meet the challenges of life on land. One of the desmosomal cadherins expressed only in complex tissues of mammalian vertebrates is the desmosomal cadherin Dsg1, which is first expressed in basal cells committing to differentiate and stratify. Upon expression, Dsg1 dials down EGFR signaling while working with classic cadherins to remodel cortical actin cytoskeleton necessary for promoting cell delamination, a critical contributor to epidermal stratification. Beyond its role in epidermal formation, Dsg1 also keeps a damper on keratinocyte-dependent inflammatory signaling. Genetic loss of function mutations in human SAM syndrome patients lead to IL-17/23 signaling associated with psoriatic-like skin inflammation. Our most recent data have identified SH2/SH3 adaptor family as molecules that link Dsg1-mediated actin polymerization required for stratification with suppression of IL-23 expression in keratinocytes, highlighting the mechanistic links between Dsg1's diverse functions in the epidermis. Collectively, our studies promise not only to elucidate how cytoarchitectural systems are structurally and functionally integrated within a complex tissue, but also how disabling specific nodes in the network contributes to human disease.

9:45 AM

Pachyonychia congenita keratin isoforms modulate motility signals during wound healing

Benjamin A. Nanes, MD, PhD

Instructor of Dermatology, University of Texas Southwestern Medical Center

Keratin intermediate filaments form strong mechanical scaffolds that confer structural stability to the epidermis. Fifty-four different keratin isoforms are expressed in an intricate pattern depending on tissue, anatomic site, and differentiation state, but why this family of structural proteins is so large is not understood. In pachyonychia congenita and other inherited skin diseases, keratin gene mutations disrupt epidermal architecture where the affected isoforms are expressed. Expression of pachyonychia congenita associated keratin isoforms also increases during wound healing, altering the composition of keratin filaments. How this change modulates cell function remains unclear. We report an unexpected effect of keratin isoform variation on signal transduction. Increased expression of pachyonychia congenita and wound-associated keratin 6A, but not of steady-state keratin 5, potentiates keratinocyte migration without compromising epidermal stability. Elevated keratin 6A expression promotes actomyosin contractility, aiding the progression of wound closure. This pathway depends on differential interaction between unstructured keratin head domains and non-filamentous vimentin shuttling myosin-activating kinases. These results substantially expand the functional repertoire of keratin filaments from their canonical role as mechanical scaffolds to include roles as signaling scaffolds that spatiotemporally organize signal transduction cascades depending on keratin isoform composition.

10:00 AM **BREAK**

開花 Kaika (Therapies session)

Chair: Roger Kaspar, PhD

Ayni Therapeutics, California USA

10:15 AM **Towards an in vitro model of Pachyonychia Congenita**

Laura Ramos, PhD

Postdoctoral Researcher, Blizard Institute, Queen Mary University of London

Palmoplantar skin found on palms and soles is uniquely adapted to withstand high levels of mechanical stress whilst contributing to epidermal barrier function. A range of skin conditions, including Pachyonychia Congenita, have been shown to display a preferential manifestation in palms and soles. Nevertheless, there is still very limited understanding regarding the distinct molecular characteristics of this specific skin site.

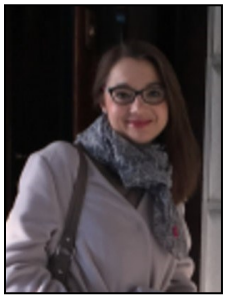
Using publicly available single-cell RNA-sequencing data, we have identified key gene expression differences between human-derived palmoplantar and body skin. We are employing this data to validate and characterize an in vitro 3D organotypic model of human palm skin. Our goal is to incorporate a genetically engineered pachyonychia congenita palm cell line into our characterized 3D organotypic model, with the purpose of investigating the molecular drivers of the disease in a physiologically relevant in vitro environment.

In addition, given the high levels of exposure of palms and soles to mechanical stress, we are working towards the generation of a model for mechanical stress dynamic response using the Flexcell FX5000 Tension system. Although we are initially looking at cytoskeletal differences between stretched interfollicular and palm keratinocytes, we aim to further investigate the contribution of mechanical stress to the phenotype of the Pachyonychia congenita palm cell lines.

By investigating the differences between palmoplantar and body skin and generating suitable human in vitro skin models, we will therefore be able to further our molecular understanding of Pachyonychia congenita.

10:25 AM

Innovations in CRISPR gene editing for epidermolysis bullosa



Joanna Jacków, PhD

Lecturer in Molecular Dermatology and Therapeutics, St. John's Institute of Dermatology, School of Basic and Medical Biosciences, Faculty of Life Sciences and Medicine, King's College London

Base and prime editors are novel CRISPR variants that reduce the risk of off-target effects by avoiding double-stranded DNA cleavage, bypassing the need for homology-directed repair. These tools offer therapeutic potential for inherited diseases like recessive dystrophic epidermolysis bullosa (RDEB). Bi-allelic loss-of-function mutations in COL7A1 cause RDEB, resulting from loss of functional type VII collagen (C7) in the basement membrane zone. We have established a highly efficient pipeline for gene correction using adenine base editor in primary fibroblasts with a favourable safety profile. This work lays a foundation for therapies for RDEB patients using ex vivo or in vivo base editing strategies. Next, we are exploring prime editing which introduces single stranded breaks and uses reverse transcriptase to encode any small, desired edit into the genome with lower risk of indels than base editors.

10:40 AM

Personalized preclinical gene editing protocols for in vivo correction of pachyonychia congenita

Marta Garcia Diez, PhD

Bioengineering Department, Universidad Carlos III de Madrid (UC3M); Biomedical Innovation Unit, Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT); Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER-ISCIII); Instituto de Investigación Sanitaria Fundación Jiménez Díaz (IIS-FJD), Madrid, Spain

Pachyonychia congenita (PC) is a rare skin disease that is inherited in an autosomal dominant pattern. PC is associated with mutations in the genes encoding keratins K6, K16 or K17, related to epidermal hyperproliferation. Patients with pachyonychia present with severe and painful palmoplantar keratoderma accompanied by blistering that is very disabling, as it greatly impairs ambulation. There is currently no curative treatment, so therapy focuses on pain control using emollients to reduce hyperkeratosis and measures to limit friction and trauma to the feet. Gene therapy approaches to restore the function of the gene associated with this pathology should focus on inactivating the pathogenic allele, as it exerts a dominant negative effect on the healthy allele. The recent development of gene editing technology allows us to contemplate gene therapy protocols for pachyonychia patients using CRISPR tools. We have previously developed a model of pachyonychia in bioengineered human skin in immunodeficient mice. We have also demonstrated restoration of the keratin cytoskeleton in patient cell cultures after CRISPR/Cas12 treatment. We are now working on the possible development of tools to introduce the CRISPR/Cas12 system into the skin of patients, and on testing these systems in the experimental model previously established in our laboratory to evaluate their efficacy in correcting the hyperkeratinization phenotype characteristic of this disease.

10:55 AM **Gene therapy for epidermolysis bullosa**

M. Peter Marinkovich, MD

Associate Professor Stanford University

Dystrophic epidermolysis bullosa (DEB) is a rare genetic disorder due to mutations in COL7A1 gene encoding type VII collagen (C7). DEB is characterized by skin fragility, painful wounds, and various cutaneous and systemic comorbidities. Currently there is no specific treatment for DEB. In this talk, we present preclinical to phase 3 development of three genetic therapies for DEB. The first involves retroviral COL7A1 over expression of primary autologous patient keratinocytes, which are then arranged into monolayer grafts which are then placed on patient wounds. This therapy has completed phase 3 and a BLA is expected to be submitted soon. The second approach involves lentiviral mediated COL7A1 over expression of autologous patient fibroblasts followed by injection of modified fibroblasts into patient wounds. This therapy is currently at the phase 3 stage. Finally we discuss a third therapy beremagene geperpavec (B-VEC)which is an investigational herpes simplex virus type 1 (HSV-1)-based vector designed to restore C7 by delivering COL7A1 topically after application to patient wounds on a weekly basis. This therapy has completed phase 3 and is expected to be approved by the FDA in May 2023.

11:10 AM **BREAK**

満開 Mankai (Clinical insights and disease modeling session)

Chair: Alain Hovnanian, MD, PhD
INSERM U1163, Imagine Institute, Paris, France

11:25 AM

Mouse models for Pachyonychia Congenita

Pierre A. Coulombe, PhD
G. Carl Huber Professor and Chair, Department of Cell and Developmental Biology, University of Michigan Medical School

Amanda Orosco, PhD Candidate
Cellular and Molecular Biology Program, University of Michigan Medical School

Pachyonychia congenita (PC) is a rare disorder that features palmoplantar keratoderma (PPK) as its most significant symptom. PPK are thick calluses arising in palmar and plantar skin that are painful to the point of debilitation in PC and related disorders. PC is caused by dominantly-acting small mutations that affect the coding sequence of *KRT6A, KRT6B, KRT6C, KRT16* or *KRT17*. Unlike the case for many other keratinopathies, cell fragility is not a key driver of the genesis of PPK lesions in PC. There currently is no effective treatment for this disorder.

We previously generated a mouse strain, *Krt16* null, that develops PC-like PPK in footpad skin (J. Invest. Dermatol. 132:1384-91, 2012). The study of these mice has yielded novel insight into the pathophysiology of PC. However, given that most cases of PC involve dominantly-acting missense alleles in *KRT16* and other PC genes, *Krt16* null mice are not genetically relevant to PC nor are they amenable to developing or testing mutant allele-specific therapies. To address this deficiency, we used CRISPR-Cas9 to introduce a R123C point mutation in the *Krt16* gene of mice. This allele accounts for 21% of the *KRT16*-based cases of PC (33/158 families) and is associated with a classic PC presentation. We will be reporting on our preliminary characterization of the newly generated *Krt16* R123C mutant mouse strain.

11:40 AM

Lessons learned from pachyonychia congenita may provide clues to the pathogenesis of hidradenitis suppurativa

Michelle Lynn Kerns, MD, MS

Assistant Professor of Dermatology at Cleveland Clinic, Department of Dermatology, Johns Hopkins University School of Medicine, Baltimore, MD

Hidradenitis suppurativa (HS) presents as recurrent nodules and abscesses resulting in sinus tracts and scarring affecting intertriginous sites. HS is an inflammatory disorder of the hair follicle unit wherein follicular occlusion secondary to infundibular hyperkeratinization and hyperplasia of the follicular epithelium results in follicular dilation and rupture. The coexistence of HS and pachonychia congenita (PC), an autosomal dominant disorder caused by mutations in stress inducible keratin genes (KRT16, KRT17, and KRT6A/B/C), has been described. PC presents with ectodermal abnormalities, e.g. follicular hyperkeratosis, steatocystoma multiplex, and painful palmoplantar keratosis. Herein, we report indirect immunofluorescence (IF) studies that demonstrate an upregulation of both K16 and its binding partner K6 in the hyperplastic outer root sheath of HS hair follicles and sinus tracts. Nrf2 signaling, a key regulator of the cellular stress response and a target of K16, has been shown to be dysfunctional in PC. Thus, we assessed levels of both total and phosphorylated (active form) Nrf2 and its inhibitor Keap1 in HS lesional skin. There is a striking decrease of IF signal for all three targets in HS hair follicles compared with controls. These preliminary findings suggest that impaired Nrf2 signaling, possibly by virtue of its bidirectional regulatory relationship with K16, may contribute to HS pathogenesis. Michelle L. Kerns, Xianying Xing, Johann E. Gudjonsson, Sewon Kang

11:55 AM

Erythromelalgia: A newly identified feature of pachyonychia congenita

Rebecca McCarthy, BMBS(Hons) BSc(Hons)

Blizard Institute, Queen Mary University of London, England UK

Pachyonychia congenita (PC) is a rare autosomal dominant genodermatosis characterised by focal keratoderma of the palms and soles, severe plantar pain and hypertrophic nail dystrophy. Other recognised features of PC include oral leukokeratosis, epidermoid and steatocystoma cysts, natal teeth, splinter haemorrhages, follicular hyperkeratosis, itch and neurovascular structures. Erythromelalgia is a rare neuropathic disorder characterised by episodic burning pain, redness and warmth of the extremities. Features required for clinical diagnosis were first described as the presence of erythema, increased temperature of the affected skin and burning extremity pain which is aggravated by warming and relieved by cooling. The primary aim of this study is to identify the prevalence of erythromelalgia in a cohort of patients with PC. Our data supports that a subgroup of patients with pachyonychia congenita appear to have symptoms and signs suggestive of secondary erythromelalgia. Understanding the role of erythromelalgia in PC is important both for providing insight into the disease process and for development of treatments for pain in PC.

12:05 PM

Palmoplantar keratodermas in The Netherlands, a continued learning experience

Antoni Gostynski, MD, PhD

Dermatologist, Maastricht University Medical Center

Maastricht UMC+ is an expert center for genodermatoses (PPK) providing diagnostic and treatment services to patients from the Netherlands. The center's goal is to improve patient care, raise awareness among practitioners about the importance of molecular diagnosis, and contribute to the understanding of PPK. Recent data shows that variants in AAGAB are the second most common cause of keratoderma in the PPK population, after FLG gene variants. Of the 22 patients with FLG gene variants, there were no other known molecular causes for keratoderma. Clinical severity varied among patients, with associated symptoms including erythema, hyper linearity, and transgrediens. We also identified several PPKs caused by variants in DSG1, including missense, nonsense, splice-site, small deletion/duplication, and gross deletion. Clinical variability was observed with striate, focal, or diffuse PPK. The center has also recently identified two patients with PPK caused by a potential variant in FAM83G gene. One patient had a homozygous deletion of FAM83G, while the other had a homozygous missense variant. The missense variant showed reduced binding capacity to CK1a, similar to all other known variants.

12:20 PM

Complicated genetic background of palmoplantar keratoderma in Japanese: A heterozygous SERPINB7 variant is a possible modifying factor for clinical features

Masashi Akiyama, MD, PhD

Vice Dean, Nagoya University Graduate School of Medicine, Nagoya, Japan,

Professor and Chairman, Department of Dermatology

Nagashima-type palmoplantar keratoderma (NPPK) is an autosomal recessive genodermatosis caused by homozygous or compound heterozygous pathogenic variants in SERPINB7 encoding a member of the serine protease inhibitor superfamily, serpin family B member 7 (SERPINB7). NPPK is one of the most common types of palmoplantar keratoderma (PPK) in the East Asian populations including Japanese. The carrier rate of pathogenic SERPINB7 variants in Japanese is thought to be high, greater than 2%. We identified SERPINB7 heterozygous variants in a Japanese striate PPK case with a DSG1 variant and a Japanese epidermolytic PPK case with a KRT9 variant. Our findings suggest that heterozygous SERPINB7 variants might be a possible modifying factor for Japanese PPK patients.

12:35 PM **LUNCH & Symposium Adjourns**

花吹雪 Hanafubuki – The grand finale: a brighter, glorious future for PC patients and all who suffer from painful PPKs

Konohana Sakuya Hime, or the Cherry Blossom Princess, is a deity revered in Japanese mythology as the spirit of the sacred Mount Fuji, and the goddess of the cherry blossoms.

In this dream-like painting on silk by Insho Domoto (1892-1975), the princess reclines on a spring meadow with wild flowers at her feet, and Sakura tree branches heavy with flowers bowing down to greet her.

Please notice her beautiful, perfect feet.

(References: https://japanobjects.com/features/cherry-blossom-art; https://www.hirosakipark.jp/florescent.html)

IPCC Working Committees

Steering Committee: Eli Sprecher (lead), David Hansen, Edel O'Toole, Robyn Hickerson, Pierre Coulombe, Alain Hovnanian, Roger Kaspar
Responsibilities: Decision-making body for "all things PC", budget oversight, partnership with the PC Medical and Scientific Advisory Board and the Board of Trustees

Research Committee: Pierre Coulombe (lead), Alain Hovnanian, David Kelsell, Robyn Hickerson
Responsibilities: Review grants and requests for funding, define priorities, oversee data sharing; look for sources for outside research funding both in and outside of US, oversee final completion of PC Research Agenda

Patient Committee/Genetics Team: David Hansen (head), Eli Sprecher, Edel O'Toole, Alain Hovnanian, Antoni Gostynski
Responsibilities: Monthly meetings reviewing patient registry submissions, genetic testing, counseling

Membership Committee: Edel O'Toole (lead), Roger Kaspar, Pierre Coulombe
Responsibilities: Recruit patients, physicians, scientists, philanthropists to PC Project.

Communications Committee: Robyn Hickerson (lead), Michael Conneely, Peter Steijlen
Responsibilities: Chart and implement strategy for PC website, newsletters for PC social media platforms

AVAILABLE GRANTS FOR 2023

Two Catalyst Research Grants – up to $50,000
Designed to support talented early-career scientists on the path toward becoming the next generation of PC thought leaders by supporting hypothesis-driven research projects.

PC Champion Research Grant – up to $100,000
Encourages established researchers to pursue research on ongoing or emerging challenges in PC or to bring their expertise to the field of PC.

Important Dates:
May 10, 2023 – Application Portal Opens
August 31, 2023 – Application Portal Closes
November 1, 2023 – Awards Announced

Learn more at https://www.pachyonychia.org/apply-for-a-grant/

About Pachyonychia Congenita Project

PC Project is the only patient advocacy organization in the world dedicated to patients with Pachyonychia Congenita, a painful and debilitating skin disorder.

PC Project unites patients, researchers, physicians, and industry partners on a global level to **advance research and drug development for meaningful treatments and ultimately, a cure for PC.**

PC Project's mission is accomplished by sponsoring two powerful programs**:**

1. **International Pachyonychia Congenita Research Registry** (**IPCRR),** a free online IRB approved registry that gathers data from patients with clinical signs of PC. Registrants are offered genetic testing, individualized support, and notified of studies for PC treatments, advances in research, and activities (online forums, patient support meetings, etc.). Currently, more than 2700 patients have been included in the registry. And while most of the patients have PC mutations in *KRT6A*, *KRT6B*, *KRT6C*, *KRT16* or *KRT17*, the registry also collects data from patients with other rare skin diseases with painful plantar keratoderma.

2. **International PC Consortium (IPCC)**, a group founded by experts in PC and fueled by dedication to patients impacted with PC. The IPCC facilitates collaboration among scientists, physicians, and industry partners interested in advancing research and translational therapeutics for PC. De-identified data from the registry are available for research purposes and genetically diagnosed registry patients continue to participate in studies.

PC Project encourages all interested professionals to join our collaborative community to help achieve our **Vision**: a day when those who suffer from PC will live without excruciating pain, isolation, and embarrassment.

Just Calluses? Think Again.

THIS IS PACHYONYCHIA CONGENITA (PC)

"I don't know what a painless day is."
— PC Patient

Pachyonychia.org
Patient Advocacy and International Pachyonychia Congenita Research Registry

Your efforts lift patients all over the world.

PC Project

Pachyonychia Congenita
Research & Patient Support Project

www.pachyonychia.org