Keratin 17 (KRT17) is well known to be involved in a variety of skin conditions across the spectrum from common to rare and benign to malignant. In the interest of Pachyonychia Congenita (PC) specifically, KRT17 has been on the radar since McLean and colleagues established its role in PC twenty years ago in *Nature Genetics*.

Today, great progress continues towards improved understanding of the pathogenesis of disorders involving KRT17 as we elaborate on the relationship between KRT17 and the autoimmune regulator (Aire), a transcriptional regulator with an established role mediating immunologic tolerance in the medullary thymus.

Initially, the physical connection between KRT17 and Aire was described by Kumar and colleagues in the *American Journal of Pathology* in 2011 and identified in the cytoplasm via coimmunoprecipitation and *in situ* colocalization in keratinocytes. This discovery was hardly surprising given that a mutation in Aire was already known to cause Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED), a syndrome presenting commonly with alopecia, nail dystrophy, vitiligo, and enamel hypoplasia. The ectodermal anomalies exhibited in APECED syndrome considered in combination with the KRT17 mutation in PC suggested that the KRT17-Aire bond may also be of pathophysiologic relevance.

Hobbs and colleagues continued to pursue the relationship between KRT17 and Aire and recently in the July 2015 publication of *Nature Genetics*, exciting new discoveries were revealed. In both human and mouse tumor-prone keratinocyte cell lines, they identified a nucleus-localized form of KRT17, previously thought to solely localize in the cytoplasm, and recognized its role regulating gene expression at the transcriptional level. Furthermore, an extrathymic role for Aire during the acute inflammatory process and tumorigenesis was established in the skin to require a physical and functional association with KRT17.

This newfound relationship between KRT17 and AIRE confirm yet another strong thread connecting the skin and immune system, providing completely new insight relating to the pathomechanisms underlying KRT17 involvement in inflammatory processes and immune responses in affected skin. Ultimately, these new findings contribute to our knowledge relating to some of the complex mechanisms involving KRT17 so that understanding may no longer be “up in the AIRE”.

**References**


INT’L PC RESEARCH REGISTRY (IPCRR)

The IPCRR continues as one of 17 registries selected to participate in Phase 2 of the NIH/NCATS GRDR® Program. Our registry was one of 12 patient advocacy groups in the GRDR pilot project and also participated in Phase 1 of the GRDR. The pilot project involved validating and implementing Common Data Elements (CDEs) and gauging general interest from the rare diseases community. Under the direction of Yaffa Rubenstein (NIH/NCATS), the GRDR is beginning the next phase of development of this important resource for rare disease research.

For more about the NIH/NCATS GRDR® Program see https://ncats.nih.gov/grdr

Data from the IPCRR often provide the basis for publications, clinical studies and research studies. We welcome researchers and authors who wish to publish IPCRR data.

In this Newsletter, we include
(1) Findings from a recent clinical study in which patients were recruited from the IPCRR
(2) Graphs showing IPCRR data and statistics

To access IPCRR data, please contact info@pachyonychia.org.

RECENT PUBLICATIONS ON PACHYONYCHIA CONGENITA


Our website at www.pachyonychia.org hosts IPCRR registry forms which can be completed online.
Topical Rapa (Sirolimus)
Since the trial data is now locked, and the post-trial data collected, we are pleased to be able to publicly report some findings from the study.

Post-trial Questionnaire
Thinking about your PC while in the study, which PC feature was your MOST bothersome feature?
PAIN 11/11

While you were in the study, did you notice improvement in your most bothersome feature?
YES—8/11 NO—3/11

Did you notice improvement in any other PC feature?
YES—9/11 NO—2/11

After you stopped using the drug, did you notice any changes?
YES—7/11 NO—4/11

When you were in the study did you feel that the cream on your feet was helping?
YES—9/11 NO—2/11

If the TD201 study drug were available to you now, would you use it?
YES—11/11 NO—0/11

The following graphs show the individual responses.
**IPCRR STATUS REPORT July 2015**

Questionnaire, Photos & Physician Notes in IPCRR

817 individuals in 494 families

641 (79%) have confirmed PC

176 (21%) have other disorders not PC

(2) AAGAB
(1) APS Type 1
(1) CAST
(2) COL7A1
(12) Connexin 30
(5) Desmoglein1
(2) Desmplakin
(6) FZD6
(3) K1
(6) K9
(1) Kawasaki
(1) Rabson-Mendenhall
(8) TRPV3

### Distribution of PC genes in 641 individuals in 494 families with genetically confirmed Pachyonychia Congenita

<table>
<thead>
<tr>
<th>PC- K6a</th>
<th>PC-K6b</th>
<th>PC-K6c</th>
<th>PC-K16</th>
<th>PC-K17</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=253</td>
<td>N=58</td>
<td>N=21</td>
<td>N=197</td>
<td>N=100</td>
<td>N=641</td>
</tr>
</tbody>
</table>

- **# Individuals**: 257 (21), 59 (6), 21 (2)
- **in # Families**: 160 (21), 22 (6), 7 (2)
- **Female**: 146 (21), 23 (6), 11 (2)
- **Male**: 111 (21), 36 (6), 10 (2)
- **In USA**: 108 (21), 20 (6), 11 (2)
- **Outside USA**: 149 (21), 39 (6), 10 (2)
- **Spontaneous**: 109 (21), 8 (6), 0 (2)
- **Familial**: 148 (21), 51 (6), 21 (2)

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**Interactive Map**

An interactive map showing location of all genetically confirmed patients with Pachyonychia Congenita is available on the website at:

[www.pachyonychia.org/pc_data.php](http://www.pachyonychia.org/pc_data.php)