



# 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.

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## Double Trouble: Homozygous Dominant Mutations and Hair Loss in Pachyonychia Congenita

Alan D. Irvine<sup>1</sup>

In this issue, Wilson *et al.* report the first case of homozygous dominant negative mutations in *KRT17* in pachyonychia congenita (PC). Homozygous dominant negative mutations are a rare occurrence in keratin disorders and this is a first report in PC. These mutations cause a distinct sub-phenotype of PC that is more severe in the offspring of affected parents and has associated alopecia.

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The age of gene discovery for Mendelian genodermatoses can be said to have started in 1987 with the identification of deletions in *STS* in recessive X-linked ichthyosis (Bonifas *et al.*, 1987); there then followed more than a decade and a half of sustained, highly productive discovery, driven by several energetic groups and enabled by refined mapping techniques and the Human Genome Mapping Project (Irvine and McLean, 2003). Scien-

tific insights were plentiful as the identification of causative genes in single-gene disorders revealed previously unknown or unsuspected molecular pathways and mechanisms of disease, some of which have significant implications for common complex disorders (Chavanas *et al.*, 2000). Rare and unheralded genodermatoses, heretofore, like carefully curated museum specimens, smothered under the cumbrance of Ancient Greek and

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Latin verbiage in the less-visited recesses of larger dermatological textbooks, became fashionable to study once again. The initial gene-identification papers earned high-impact publications and a large number of citations. Gene identification had an energizing effect on investigative dermatological research in general, with many talented young researchers being attracted by the possibilities of genetic discovery.

This phase of discovery delivered direct benefits to patients, including clearer and more informative diagnostics and better-informed genetic counselling. In severe genodermatoses, DNA-based prenatal diagnosis became a clinical-service reality and, in selected cases, pre-implantation genetic diagnosis was developed. Gene correction or replacement therapy has, for many predictable and several less-predictable reasons, taken longer than initially envisioned and, like Yeats' peace, continues to 'come dropping slow' (Yeats, 1892).

For some, the golden age of gene identification had reached or nearly reached completion in the early years of the 21st century. The heft of recent efforts in genetics and dermatology has, understandably, focused on the themes of complex disease and gene correction therapy. For many there was a feeling that in the field of gene identification all the major conditions had been worked out and that greater challenges, discoveries, and insights lay elsewhere. The second-wave work that meticulously made use of these new genetic data on a broader scale and made these discoveries truly relevant to the clinician was more time consuming, more expensive, and less rewarded in academic metrics and therefore, with exceptions such as epidermolysis bullosa, less often undertaken.

However, the satisfaction derived from discovery, from making a new and accurate genetic diagnosis, from a new gene identification, or from the refinement of genotype:phenotype correlation continues. Researchers still extract valuable information that has real clinical relevance for affected families and for clinicians in genodermatology practice. Progress is now being made in two areas. Next-generation sequencing

techniques, in particular whole-exome sequencing (WES), have enabled gene identification in small families and even in individual cases that would have been too costly in consumables or in human labor to analyze using previously available tools (Blaydon *et al.*, 2011). In addition, significant lessons are being learned from analyses done by large multinational collaborations of clinicians and scientists involving many hundreds of patients. It is evident that rare or uncommon Mendelian genodermatoses are not always best served by the existing literature, vulnerable as it is to selective ascertainment and reporting bias of unusual or noteworthy cases and apparently novel or family-specific conditions. Genodermatoses are further open to misinterpretation due to potentially misleading, but relatively common phenomena such as incomplete penetrance and variable expression, as seen in many Mendelian autosomal dominant conditions. In some cases simple misdiagnosis confuses the picture. Furthermore, single-family reports have often established as holy writ, disease features that exist purely by chance in selected individuals or families and that have no genuine relationship to the underlying genetic condition. Thus, the picture an enquiring clinician might draw from the literature of any given case of genodermatosis often varies significantly from the truth.

### Clinical and genetic correlations disclosed autosomal double-dominant mutations in PC.

The best way to address and clarify these complexities—to facilitate the sorting out of what is common and uncommon in any given condition, the wheat that is worth keeping and the chaff that should not be eaten, those features that define a distinct subtype and those that define genuinely distinct conditions—is to assemble large-scale collaborative efforts. The Pachyonychia Congenita Project (PC Project; <http://www.pachyonychia.org/>) is an exemplar of such an approach. Founded in 2003, their model

of a highly motivated patient support group working together with expert clinicians and dedicated scientists has contributed greatly to the development of a clinical, genetic, and patient-oriented picture of PC that has been painted in both broader terms and in finer detail than was previously possible. The generation of patient registries, as is now happening for epidermolysis bullosa and ichthyoses, is essential not only for further understanding of disease features but also for identification of appropriate patients for future clinical trials and interventions.

With respect to nosology, old terms such as PC-3, PC-4, and PC with alopecia (van Steensel *et al.*, 2001), now recognized as Clouston syndrome (van Steensel *et al.*, 2003), can be avoided and more accurate and informative designations such as PC-17 can be utilized. The clinician who only rarely encounters these disorders now has better guidance and a more robust framework to make a firm diagnosis. Furthermore, as an illustration of the effects of, and the necessity to correct, reporting bias, previously misattributed features such as deafness, mental retardation, diabetes, bony abnormalities, early menarche, and cataracts can be safely excluded from the canon of PC disease manifestations. Inaccurate associations add unnecessarily to the burden that families with these conditions carry; clarity around these issues does everyone a service. Given the known genetic heterogeneity in PC, accurate clinical classification facilitates a more directed and efficient molecular diagnostic approach.

Illustrating the substantial merit of this type of consortium endeavor and the requirement for careful second-phase work after a disease gene is identified, the PC Project continues to uncover new phenotypic subtleties and genotype:phenotype correlations nearly 17 years after the initial identification of the first causal genes in PC. A PC Project-supported work earlier this year reported a new clinical subtype of PC with transgressions features (Harris *et al.*, 2012). In this issue, Wilson *et al.* (2012) again show the benefit of careful clinical and genetic correlation by disclosing the first autosomal double-dominant mutations in PC. In this work, two families

(one from the Middle East and another of Hispanic origin) were identified through the PC consortium. In each family both parents had, or were anamnestically inferred to have, classical PC. Their offspring had more severe than normal PC and the additional feature of scalp alopecia. The phenotypic similarity between these two unrelated families from different parts of the world strongly suggests that this represents a genuine disease subtype. This must be a rare occurrence in keratin diseases given that these conditions have been well studied for 20 years and only a small number of epidermolysis bullosa simplex cases with double-dominant mutations been reported. It is important that clinicians practicing genodermatology be aware of these cases; experience suggests that first reports are often followed by further recognition of similar cases. The implications for genetic counselling are important in that affected individuals will have a 100% chance of transmitting the condition.

This work reminds us that even familiar and well-studied conditions can yield further insight into a detailed and thoughtful clinical and genetic study.

#### CONFLICT OF INTEREST

The author states no conflict of interest.

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