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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.
Homozygous Dominant Missense Mutation in Keratin 17 Leads to Alopecia in Addition to Severe Pachyonychia Congenita

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TO THE EDITOR

Homozygosity for dominant mutations in keratin genes is rare and has only been reported for epidermolysis bullosa simplex (EBS; Stephens et al., 1995; Hu et al., 1997; Oldak et al., 2011). The majority of pathogenic variants reported in 23 keratin genes are heterozygous missense or small in-frame insertion/deletion mutations inherited in an autosomal dominant manner (http://www.interfil.org; Szeverenyi et al., 2008). A small number of recessive cases have been reported, mostly due to nonsense mutations (Yiasemides et al., 2008). Here, we report homozygosity for dominant missense mutations in keratin 17 that modify the pachyonychia congenita (PC) phenotype. PC is an autosomal dominant skin disorder caused by heterozygous mutations in any one of the genes encoding keratins K6a, K6b, K16, or K17 (McLean et al., 2011). The main characteristics are palmoplantar keratoderma, plantar pain, and nail dystrophy. Additionally, oral leukokeratosis, follicular keratoses, and epidermal cysts often occur. PC due to mutations in K17 (termed PC-17) is more frequently associated with neonatal teeth and widespread pilosebaceous cysts in adults.

Family 1, of Hispanic ancestry, showed autosomal dominant inheritance (Figure 1a). A consanguineous marriage between affected individuals resulted in three affected (one homozygous [proband] and two heterozygous) and one unaffected offspring. Both parents had some characteristics of PC. The father had thickened nails, mild plantar hyperkeratosis and steatocysts; the mother had steatocysts but reported neither nail changes nor keratoderma. The 10-year-old proband had features typical of PC but was much more severely affected than other family members and had additional features (Figure 1b-g). Unusually, all nails were thickened at birth. He also had several neonatal teeth. At 4 months he developed leukokeratosis, and by 7 months had blistering on his hands and feet, and thickening of palmar plantar skin that is now localized to pressure points (Figure 1b, c, e, and f). He continues to have painful blisters and has follicular keratosis (Figure 1g). He has no steatocysts to date, although these generally develop at puberty. The most unusual feature, not previously associated with PC, was hair loss, first noted at 7 months and has continued during his lifetime (Figure 1d). On examination he had a circumscribed area in the occipital region where the hairs were much shorter and thinner. Eyebrows were normal. His affected brother (25 years old) and sister (13 years old) had thickened toenails, slight thickening of fingernails with splinter hemorrhages and widespread steatocysts. Neither sibling had keratoderma, blistering, neonatal teeth nor alopecia (Figure 1h–j). The brother’s 1-year-old daughter had nail involvement and a neonatal tooth.

Genomic DNA was obtained with informed consent and appropriate ethical approval that complies with the Declaration of Helsinki Principles (Western IRB study no. 20040468). DNA extraction and mutation detection were performed according to the published protocols that avoid pseudogene contamination (Wilson et al., 2011). Two primer sets were used for each mutation hotspot exon to ensure against polymorphism. By DNA sequencing of KRT17, a homozygous dominant missense mutation was identified, designated p.Asn92Ser (protein), c.275A>G (DNA), in the proband of Family 1. The mildly affected parents and siblings were heterozygous (Figure 1k–n). Mutation p.Asn92Ser is the most commonly reported mutation in KRT17, occurring in 36% of PC-17 families (Wilson et al., 2011).

Family 2 was of Middle Eastern ancestry. The proband, a 32-year-old male, had thickened finger and toenails by 2 years of age (Figure 2a and b). Painful blisters, calluses, fissures, and ulcerations were present on hands and feet (Figure 2c and e), and he had follicular hyperkeratosis (Figure 2f and g) but no oral leukokeratosis. He developed generalized alopecia at the age of 3 years and now has almost total alopecia (Figure 2d, at age 8). At the age of 7, the patient received oral etretinate (Tigason; 1 mg·kg⁻¹ per day) for 3 months, which reduced the follicular hyperkeratosis but did not improve the plantar blisters, alopecia, or pachyonychia. His parents were reportedly unrelated but unfortunately were not available for examination or DNA sampling. The father was reported to have steatocysts. The proband of Family 2 was homozygous for dominant missense mutation p.Arg94Cys, c.280C>T in KRT17 (Figure 2h and i). The proband was homozygous for microsatellite markers spanning type I keratin locus. Mutation p.Arg94Cys has been reported in several cases of dominant PC-17 (http://www.interfil.org).

To our knowledge, homozygous dominant missense mutations have not

Abbreviations: EBS, epidermolysis bullosa simplex; PC, pachyonychia congenita
Homozygous Missense Mutation in Keratin 17

Normal K17, exon 1

K17 p.Asn92Ser

Homozygous (proband)

K17 p.Asn92Ser

Heterozygous (mother)

K17 p.Asn92Ser

Heterozygous (father)
Figure 1. Pedigree, clinical features, and mutational analysis of KRT17 in Family 1. (a) Pedigree of Family 1. Clinical pictures of proband (IV-5) of Family 1 showing: (b) blistering and keratoderma on the soles of the feet; (c) thickened toenails; (d) region of the scalp showing loss of hair; (e) follicular hyperkeratosis on the knees; and (g) follicular hyperkeratosis on the elbow. Molecular genetic analysis of KRT17. (h) Normal KRT17 sequence in exon 1, showing nucleotides 271–285. (i) The equivalent region as in (h) from the proband showing homozygous missense transition mutation c.275A>T (arrow) leading to amino-acid substitution p.Asn92Ser. (m) The equivalent region as in (k) from the mother showing heterozygous mutation c.275A>G (arrow) leading to amino-acid substitution p.Asn92Ser.

Figure 2. Clinical features and mutational analysis of KRT17 in Family 2. Clinical pictures of proband of Family 2, at age 8, showing (a) thickened toenails and (b) finger nails; (c) painful blisters on the feet; (d) generalized alopecia; (e) plantar keratoderma and blisters; (f) follicular hyperkeratosis on the knees; and (g) follicular hyperkeratosis on the elbow. Molecular genetic analysis of KRT17. (h) Normal KRT17 sequence in exon 1, showing nucleotides 271–285. (i) The equivalent region as in (h) from the proband showing homozygous transition mutation c.280C>T (arrow) leading to amino-acid substitution p.Arg94Cys.
been previously reported in PC. However, both these mutations are commonly seen as heterozygous mutations, with p.As92Ser being the most commonly reported mutation in KRT17. Interestingly, both mutations, p.As92Ser and p.Arg44Cys, have been reported to show phenotypic variation; most commonly giving rise to PC-17 (http://www.interfil.org) but occasionally steatocystoma multiplex (Covello et al., 1998; Wang et al., 2009). Intra-familial phenotypic variation, as seen here between affected homozygous members of Family 1, has previously been reported (Smith et al., 1997).

Of the three reported cases of homozygosity for a dominant mutation in another keratin disorder, EBS, two mutations were described as partially dominant (or semidominant)—homozygous individuals were more severely affected than heterozygotes (Hu et al., 1997; Oldak et al., 2011). However, in a third EBS family, homozygosity for a mutation in KRT15 did not alter clinical severity (Stephens et al., 1995).

In the families studied here, the features typical of PC were more severe in the homozygous cases than heterozygotes, again indicating a gene dosage effect. The additional feature of hair loss, seen in both cases, is particularly interesting as alopecia has not been previously reported in the cases of mutation-confirmed PC. K17 is expressed in the hair follicle (Moll et al., 2008), and we hypothesize that the increased dosage of mutant K17 in the homozygotes crosses a threshold where hair abnormalities become evident. K17-null mice develop hair fragility during the first week after birth resulting in severe alopecia (McGowan et al., 2002), showing that this protein is critically important for hair follicle function.

Individuals homozygous or compound heterozygous for dominant mutations have a much greater risk of having affected offspring (essentially 100%), compared with heterozygous carriers of a dominant mutation (50%). Therefore, in terms of genetic testing, homozygous or compound heterozygous mutations should be especially sought in PC patients who present with alopecia. As four keratin genes are involved in dominant PC, bigenic inheritance is also a possibility in unusually severe cases resembling those reported here.

CONFlict of Interest
The authors state no conflict of interest.

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