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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A new type of pachyonychia congenita

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Summary

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Summary : We describe two patients with an apparently unique autosomal dominant ectodermal dysplasia. Symptoms consist of thickening of all nails as seen in pachyonychia congenita and severe generalized hypotrichosis. No other abnormalities were present. Histopathological examination of scalp skin showed a reduction in the number of hair follicles, but other abnormalities were not found. Direct sequencing of the keratins known to be associated with pachyonychia congenita, Krt 6a, 6b, 16 and 17, failed to detect mutations. This suggests that this may be a new type of pachyonychia caused by a mutation in a so-called hard keratin.

Keywords : pachyonychia, hypotrichosis, keratin genes, baldness.

Pictures

ARTICLE

Pachyonychia congenita (PC) is a group of disorders characterized by symmetrical nail changes affecting all nails. The base of the nails appears normal but there is subungual hyperkeratosis, raising the free edge of the nail. The lateral borders of the nail often angulate towards the center. McKusick recognizes two subtypes, the Jadassohn-Lewandowsky and Jackson-Lawler syndromes [1]. These are caused by mutations in keratin genes *Krt* 6b/17 and 6a/16, respectively [2-4]. Both show associated symptoms of skin and mucosa and sometimes of other ectodermal derivatives [5]. Autosomal dominant as well as recessive modes of inheritance have been described. Here we describe two Dutch patients with an apparently new type of pachyonychia congenita, not associated with mutations in *Krt* 6a/b, 16 or 17 and consisting of thickening of the nails with severe generalized hypotrichosis in the absence of any other symptoms.

Case report

The proband, a 65 year old male, had been suffering since birth from baldness and thickening of the nails. Body hair was scant. During puberty, some growth of axillary and pubic hair occurred. Pubertal development was otherwise normal. The nails progressively thickened up to the point where they had to be filed and trimmed regularly in order to obtain an acceptable shape. No natal teeth had been present and dentition had always been normal. Sweating was normal, eyesight was described as excellent. The patient enjoyed excellent general health. His father and two each of his brothers and sisters had been similarly affected, as are five other living relatives *(Fig. 1)*. The paternal grandmother (I-2) was said to have lacked eyelashes and eyebrows. Whether she had suffered from thickened nails could not be ascertained.

Upon examination, the patient showed atrichia of the scalp, except for a few terminal hairs in the temporo-parietal region that could easily be removed *(Fig. 2)*. Eyelashes and eyebrows were absent. Axillary and pubic hair was nearly absent. Finger- and toenails exhibited subungual hyperkeratosis with hypercurvature of the nails *(Fig. 3)*. Dentition was normal for age; oral leukokeratoses were absent. His sister (III-9) was examined as well and showed identical abnormalities. Other affected family members could not be contacted.

Histopathology

Histopathological examination of a scalp biopsy showed a normal epidermis. The number of follicles was reduced and a mild inflammatory infiltrate was present around some of these *(Fig. 4)*. Microscopic examination of hair shafts failed to reveal any specific abnormalities.

Mutation analysis

Blood was drawn from the proband and DNA isolated from lymphocytes using the Qiagen DNA isolation kit. The keratin genes 6a, 6b, 16 and 17 were directly sequenced using methods described elsewhere [2, 3]. No mutations were found in the coding regions of these genes (data not shown).

Discussion

Here we describe two patients with an apparently unique autosomal dominant ectodermal dysplasia group 1-3 [6]. Pinheiro and Freire-Maia have described an ectodermal dysplasia belonging to the same group, which they called hair-nail dysplasia. However, their patients had thin and fragile nails [7]. Hypotrichosis and nail abnormalities are also seen in other ectodermal dysplasias, but these are associated with tooth and other abnormalities not seen in our patients *(Table I)*.

The different types of pachyonychia congenita (PC), the group of disorders that most resemble the phenotype we describe, are characterized by thickening of the nails as seen in our patients. McKusick recognizes two major subtypes of PC. In the Jadassohn-Lewandowsky form (MIM #167,200), pachyonychia occurs together with palmoplantar hyperkeratosis, hyperhidrosis and follicular keratosis. This form of PC has been shown to be caused by mutations in the *Krt* 16 and 6a genes [2-4]. The Jackson-Lawler syndrome (MIM #162,710), the other subtype, is characterized by the appearance of multiple epidermal cysts (steatocystoma multiplex). Hair abnormalities, hoarseness and natal teeth also occur in this disorder. It is caused by mutations in *Krt* 6b or 17. Alopecia and hypotrichosis have been described in this variant of PC, but universal hypotrichosis has not. Chang *et al.* and Price *et al.* have described patients with thickening of the nails in the absence of other syndrome abnormalities [8, 9]. No hair abnormalities were described. To our knowledge therefore, hypotrichosis as the only accompanying abnormality has not been described before.

CONCLUSION

In conclusion, both clinical and molecular data rule out a diagnosis of PC type 1 or type 2. The results of mutation analysis and the phenotype suggest that this may be a new type of PC caused by mutations in keratins specific to hair and nails. Different keratins are expressed by human epidermis and its appendages in a body-site and differentiation-specific manner [10]. Human nails contain both skin and hair differentiation-specific (or trichocyte) keratins, both expressed in the nail bed. The skin-specific keratins in the nail bed are K16 with its partner K6a and K17 with its partner K6b. Hair follicles show variable expression of *Krt* 6a/b and 16/17 and express mainly trichocyte, or hard, keratins [11]. Considering these expression patterns, *Krt* 6a/b, 16 and 17 as well as the hard keratins are excellent candidate genes for this type of pachyonychia congenita. Since we failed to find any mutations in the former group of genes, mutations in one of the trichocyte keratins may be causing this new PC variant. The hair disorder monilethrix was found to be due to mutations in the hair keratin genes *hHb1* and *hHb6* [12, 13], which proves that hard keratins can be associated with hair abnormalities in humans. The finding of a mutation in a hard keratin in our patient would be of considerable interest, as this would be the first demonstration of the involvement of structural hair proteins in non-scarring baldness.

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