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Disease classification using clinical and molecular features

Dear Editor,

We read with great interest the report by Guo *et al.*[1] on a patient displaying nail thickening, palmoplantar keratoderma, corneal hyperemia and alopecia, which they refer to as pachyonychia (PC) unknown.

As mentioned by the authors of this report, the phenotypical features displayed by their patient do not fit the clinical manifestations usually observed in PC.[2,3] Alopecia is highly unusual[4] and corneal involvement has never been reported to date in conjunction with a mutation in any of the five genes known to be associated with PC.[2,3]

We believe that the mere occurrence of palmoplantar keratoderma and nail thickening is not sufficient to pose a diagnosis of PC, especially in the face of highly unusual clinical features, and that it may in fact be misleading. Indeed, the constellation of signs demonstrated in their patient may possibly be due to mutations in another gene, associated with another mode of inheritance than PC, which in turn may result in ill-founded genetic counseling. As an example, the combination of signs displayed by the case under study may reflect a mild form of follicularis, alopecia and photophobia (IFAP) due to mutations in *MBTPS2*.[5] IFAP is inherited as an X-linked recessive trait whereas PC is inherited in a dominant fashion which obviously carries serious implications in terms of genetic counseling. In addition, in the era of next-generation sequencing, many such unusual phenotypes are in fact found to be the result of the unfortunate co-occurrence of two mutations in two genes, a possibility that cannot be excluded here either.

In conclusion, disease classification should nowadays be based whenever possible on a combination of clinical and molecular features, which is why we would recommend thorough molecular analysis of the present case using advanced sequencing technologies prior to assigning it to a given clinical entity.

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