LETTERS

Angioma serpiginosum is not caused by *PORCN* mutations

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In 2007, Blinkenberg *et al*¹ described ‘angioma serpiginosum’ in a four-generation family and assigned the underlying gene locus to Xp11.3–Xq12. Subsequently, Houge *et al*² documented a deletion containing *PORCN* gene in the affected individuals and argued that this gene ‘may also cause angioma serpiginosum’. With regard to this diagnosis, however, I would like to raise my voice of polite dissent.

My diagnosis is focal dermal hypoplasia (FDH). On higher magnification the erythematous skin lesions, as photographically documented by Blinkenberg *et al*,¹ are found to be intermingled with small patches of dermal hypoplasia or atrophy. This feature is not compatible with angioma serpiginosum (AS), but is highly suggestive of FDH. A biopsy obtained from such areas would certainly have shown a rather thin dermis and thus would have helped to distinguish this skin disorder from AS. On the other hand, dilated capillaries located in the papillae and in the uppermost part of the dermis, as noted by Blinkenberg *et al*,¹ cannot be taken as a distinguishing feature of AS, because such signs of telangiectasia do likewise occur in FDH.^{3–6}

The proposed diagnosis would imply that no member of this family had AS. In contrast to FDH, AS is not associated, according to the present knowledge, with major extracutaneous anomalies. AS is often arranged in an asymmetric or otherwise segmental distribution, which, on rare occasions, may even be reminiscent of Blaschko’s lines, but such cases have so far always been sporadic.⁷ In familial cases of AS, the involvement is rather symmetric and nonsegmental.⁷ So far, there is not the slightest indication that AS can be inherited as an X-linked trait.

For the following reasons I propose to exclude the diagnosis of AS in the family described by Blinkenberg *et al*:¹ (i) Some patients had nail dysplasia and bald patches involving the scalp, which are characteristic signs of FDH but unknown in AS.⁸ (ii) Esophageal or hypopharyngeal

papillomatosis is a typical feature of FDH,^{9–11} but absent in AS. (iii) An X-linked transmission limited to females is characteristic of FDH but not compatible with AS that is most likely caused by an autosomal gene.⁷ (iv) When AS shows a mosaic arrangement, a familial occurrence has so far never been reported.⁷

Therefore, the statement of Houge *et al*² that their patients had ‘angioma serpiginosum, a cosmetic skin disease’ does not seem to be correct. In my view, AS cannot be considered as ‘a mild variant of Goltz–Gorlin syndrome’, as suggested by Blinkenberg *et al*.¹ On the contrary, skin lesions, as documented in this family, were part of a potentially serious multisystem birth defect in the form of FDH. Perhaps, a thorough examination of the bones by imaging techniques would have revealed additional features of this syndrome. This is not merely a theoretical issue because in this family genetic counseling may be affected by an incorrect diagnosis of AS. After all, one cannot predict the severity of the manifestation of FDH in the next generation.

In conclusion, I fear that according to the present knowledge, a search for *PORCN* mutations in patients with AS would yield completely negative results.

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Reply to Happle

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We are honoured by the attention given by Professor Happle to our recent papers on angioma serpiginosum (AS) and *PORCN* mutations.^{1,2} Surely the issue here is whether the clinical diagnosis AS is right, or whether the phenotype in the family we described should be regarded as a mild form of focal dermal hypoplasia (FDH, also known as Goltz–Gorlin syndrome). We published detailed clinical data in the first paper in 2007. Contrary to Professor Happle, we have not observed focal hypoplasia of the skin by personal investigations of any of the probands. Two skin biopsies of affected areas have been taken and carefully examined by experienced pathologists. Again no dermal hypoplasia was observed. Also contrary to the statement by Professor Happle, none of the patient had bald patches involving the scalp, only sparse and thin hair occurred. Indeed these signs were so mild that they remained unnoticed until the idea arose in one of us (RCMH) that AS and FDH could be allelic entities. The chance discovery of concomitant non-symptomatic esophageal papillomatosis was a major additional clue for this. There were many features common in FDH that were missing in the family, patients did not have ophthalmological signs or symptoms, they had no papillomas around orifices, no clefting, not the thin and anteverted pinnae that are very frequent in FDH, no prominent coccyx, and missed even any limb anomaly. However, we agree with Professor Happle that a patient may still have FDH without these additional features. This made us state that the patients have AS and only resemble FDH, and that the two entities are allelic.

Professor Happle mentions in his letter that there is 'not the slightest indication' that AS is an X-linked condition.

However, it is known that the vast majority of cases with AS are females.³ Furthermore, in several patients affected skin following Blaschko lines has been described,⁴ and no male to male transmission has been reported. Indeed, OMIM mentions that the few male cases with AS that have been described 'may actually represent somatic mosaicism of an X-linked gene'. There are very rare families reported in which AS seems to segregate in an autosomal dominant manner, although in one of these families X-linked inheritance can be excluded. It may be that AS is a genetically heterogeneous condition. Professor Happle suggests that AS can be explained as a somatic mosaicism for an autosomal dominant acting gene. We agree that sporadic AS may well be explained by somatic mosaicism, but the gene involved can be both X-linked and autosomal dominant. Biopsies of affected areas in a large series of patients with AS may be needed to investigate this in more detail.

We conclude that there is overwhelming evidence that AS is an X-linked disorder, and that the features in the family we described would be well in agreement with the diagnosis of AS and only resemble FDH as not only FDH itself is absent, but all the other common features of FDH are also missing. Owing to this we favour studying the rare familial AS occurrence for *PORCN* mutations.

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