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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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