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LETTER

An Xp11.23 deletion containing *PORCN* may also cause angioma serpiginosum, a cosmetic skin disease associated with extreme skewing of X-inactivation

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In the May 2007 issue of *European Journal of Human Genetics*, a three-generation family with an X-linked dominant form of a rare skin condition called angioma serpiginosum (OMIM no. 300652) was described.[1] The presence of very mild nail dystrophy, with affection of no more than 1–4 nails per patient, and concomitant non-symptomatic oesophageal papillomatosis, led to the suggestion that angioma serpiginosum might be allelic to focal dermal hypoplasia (FDH).[1] The affected females' only complaint was cosmetic due to the emergence of vascular streaks along Blaschko's lines. The rash progressed from childhood to adulthood. Growth was normal, and no bodily asymmetry was present. None of the individuals had hand, eye, skeletal or other malformations commonly found in FDH patients.

The genetic cause of FDH, also called Goltz-Gorlin syndrome, was recently published.[2,3] Deletions or mutations affecting *PORCN*, a regulator of Wnt signaling, was found in both sporadic and rare familial cases. Now, we have found that all affected females in the above-mentioned Norwegian family also had a deletion containing the *PORCN* gene. This deletion was 112 kb (from 48 198 to 48 310 kb from Xpter) and removed *PORCN* and four other genes, i.e., just 25 kb smaller than a deletion previously found in FDH patients (Supplementary Figure 1).[2]

We suspect that it is not the minor difference in deletion size but different efficacy of protective X-inactivation that causes the phenotypic difference. In both angioma serpiginosum females and in FDH females with deletions, the X-inactivation pattern was extremely skewed.[1–3] All these deletions contained at least four genes in addition to *PORCN*. In contrast, only one of the patients with a mutation in the *PORCN* gene was extremely skewed.[3] This variability of disease expression may depend on the timing and extent of counter-selection against cells randomly inactivating the normal X-chromosome during embryogenesis. If a deletion is inherited, the extra deleted genes (ie *SLC38A5*, *FTSJ1*, *EBP*, *OATL1*, and more variably the centromeric *RBM3*, *WDR13* and the telomeric *SSX* genes) could make such counter-selection even more efficient. In a few tissues, e.g. striated epithelia (skin, oesophagus), this cell fitness-based X-selection may be less efficient, allowing escape of a few mutated cell lines. The lack of Wnt expression from these epithelial streaks may be the cause of gradual connective tissue changes with angioid malformations in the underlying mesodermal tissue. Unlike the situation in microdeletion patients, embryonic cells lacking only *PORCN* may not be counter-selected as efficiently. This could result in malformations due to defective Wnt-dependent morphogenesis later in development. Alternatively, most of the *PORCN* mutation-only patients may be somatic mosaics because the mutations are post-zygotic, and it is the mosaicism that makes embryonic survival possible. Evidence for such mosaicism has already been found.[2,3]

There are no good explanations for why the FDH-family with a 137 kb microdeletion[2] and the angioma serpiginosum family with a 112 kb microdeletion affecting the same five genes except *RBM3* have such a difference in phenotypic severity (Supplementary Figure 1). Patient GG1 from the FDH family had pronounced skin lesions and nail dysplasia, and in addition unilateral breast hypoplasia.[2] In the angioma serpiginosum family, the skin texture was normal, and no breast hypoplasia or other signs of asymmetry have been seen. Possibly, modifying genes affecting the timing of X-inactivation during embryogenesis may have caused this difference.

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Supplementary Information accompanies the paper on European Journal of Human Genetics website (http://www.nature.com/ejhg)