No Evidence of Skin Blisters with Human Desmocollin-3 Gene Mutation

To the editor: Ayub et al.[1] recently reported that a homozygous nonsense mutation (c.2129T>G [p.Leu710X]) in the human desmocollin-3 (*DSC3*) gene underlies hereditary hypotrichosis and recurrent skin vesicles. The publication is of great interest, because this is potentially the first pathophysiologic role for desmocollin-3 in human genetic disease. However, there is no clinical or histologic data shown to document the presence of skin vesicles in affected patients. The clinical photograph (Figure 2C in Ayub et al.[1]) does not show skin vesicles but instead appears consistent with a different skin disorder known as keratosis pilaris, which is associated with follicular plugging on histology. In support of this diagnosis, the scalp-skin biopsy (Figure 2D in Ayub et al.[1]) shows follicular plugging, but no evidence of blistering. Because keratosis pilaris is a common disorder (affecting up to 40% of the adult population), further studies would be necessary to conclude that *DSC3* gene mutations cause an epidermal phenotype in affected patients.

The nonsense mutation in *DSC3* is predicted to occur at the junction of the transmembrane and cytoplasmic domains, which the authors predict will lead to nonsense-mediated decay of the truncated protein. It remains unknown, however, whether truncated desmocollin-3 protein is expressed in patient skin. Previous studies in mice have shown that targeted deletion of desmocollin-1 causes superficial blistering and abnormal differentiation,[2] whereas a truncated desmocollin-1 protein lacking most of the cytoplasmic domain incorporates into desmosomes but does not cause an epidermal phenotype.[3] If truncated protein is expressed in human skin, this may identify a pathologic role for the mutant protein in hair follicle development, perhaps distinct from its role in epidermal adhesion.

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Response to Payne

To the Editor: This is with reference to the letter by Dr. Aimee Payne and colleagues in which they have pointed out some reservations about clinical features of the patients and expression of truncated desmocollin-3 (DSC3) protein in patient's skin, discussed in our recently published article.[1] Regarding the presence or absence of vesicles filled with watery fluid on skin, we have absolutely no doubt that the features of the skin we have discussed in the article are correct. The family that we have reported in the article belongs to Afghanistan, a country bordering Pakistan. Presently, hundreds of families from Afghanistan live in different regions of Pakistan. We have studied a large number of families (>200 individuals) from Afghanistan with different genetic disorders and have not found any such lesions on skin of any other individual. Additionally, such lesions were not observed on any unaffected member of the family. We agree with the second observation of Dr. Aimee Payne and colleagues about the expression of truncated DSC3 protein in patient's skin. We were unable to perform such studies because of the nonavailability of the material.

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