Clinical and genetic studies reveal cutaneous phenotypes linked to desmoplakin haploinsufficiency in arrhythmogenic cardiomyopathy

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Desmosomes are cell-cell adhesion complexes that maintain the integrity of the skin and electromechanical coupling in cardiomyocytes. Mutations in desmosomal proteins can be associated with cardiocutaneous syndromes; eg. recessive desmoplakin (DSP) mutations underlie Carvajal Disease (a combination of arrhythmogenic cardiomyopathy (ACM), woolly hair, and palmoplantar keratoderma (PPK)). Dominant mutations in desmosomal proteins account for up to 50% of "non-syndromic" ACM cases. Here, we performed deep clinical and molecular phenotyping of both cardiac and cutaneous features in a cohort of 6 ACM families with dominant truncating or frame-shift mutations in DSP, and identified a penetrant clinical phenotype of curly hair and to a lesser extent PPK. Of the 38 mutation carriers examined, 28 (74%) had curly and 4 (10%) had wavy hair, almost five times the incidence in the general population. This phenotype perfectly co-segregated with DSP mutation carrier status in 5 of the 6 families studied. Sanger sequencing of nonlesional skin cDNA suggested degradation of the mutant allele on the mRNA level. Immunohistochemical staining also revealed dysregulation of DSP and other junctional proteins in the skin. Interestingly, in one family (p.E1493X), 6 of 7 mutation carriers had straight hair and no PPK, while DSP localisation was comparable to control skin. This mutation affects the DSPI isoform-specific rod domain of the protein, which supports our previous studies where DSPII not DSPI is the major isoform regulating keratinocyte adhesion. Taken together, we found that heterozygous DSP truncating mutations lead to a form of cardiocutaneous syndrome. The underlying mechanism is haploinsufficiency that also affects expression of other junctional proteins. ACM poses a significant diagnostic challenge due to the frequent lack of early onset symptoms; our study provides evidence for additional cutaneous clues that may aid the timely diagnosis.