CLINICAL REPORT

Desmoplakin Mutations with Palmoplantar Keratoderma, Woolly Hair and Cardiomyopathy

Manuela PIGORS1, Agnes SCHWIEGER-BRIEL1, Rodica COSGAREA2, Adriana DIACOMEASA3, Leena BRUCKNER-TUDERMAN1, Thilo FLECK4 and Cristina HAS1

1Department of Dermatology, Medical Center – University Freiburg, Freiburg, Germany, 2Department of Dermatology, University of Medicine and Pharmacy “Iuliu Hatieganu” Cluj-Napoca, 3Dermatology Ambulatory Care Center, Children’s Emergency Hospital “Grigore Alexandrescu”, Bucharest, Romania and 4Department of Congenital Heart Disease and Paediatric Cardiology, University Heart Centre, Freiburg, Germany

Mutations in genes encoding for desmosomal components are associated with a broad spectrum of phenotypes comprising skin and hair abnormalities and account for 45–50% of cases of arrhythmogenic right ventricular cardiomyopathy. Today, more than 120 dominant and recessive desmoplakin (DSP) gene mutations have been reported to be associated with skin, hair and/or heart defects. Here we report on 3 cases with yet unreported DSP mutations, c.7566_7567delAAinsC, p.R2522Sfs*39, c.7756C>T, p.R2586*, c.2131_2132delAG and c.1067C>A, p.T356K, that were associated with variable woolly hair or hypotrichosis, palmoplantar keratoderma, and cardiac manifestations. In addition, we review and summarise the clinical features and DSP mutations of the patients described in the literature, which illustrates the complexity of this group of disorders and of their genotype-phenotype correlations, which cannot be easily predicted. Early diagnosis is crucial and cardiac examinations have to be performed on a regular basis. Key words: desmoplakin; DSP; keratoderma; woolly hair; skin fragility; striate palmoplantar keratoderma.

Accepted Sep 16, 2014; Epub ahead of print Sep 17, 2014


Prof. Dr. Cristina Has, Department of Dermatology, Medical Center – University Freiburg, Hauptstrasse 7, DE-79104 Freiburg, Germany. E-mail: cristina.has@uniklinik-freiburg.de

Desmosomes are intercellular junctions that anchor intermediate filaments to the plasma membrane, providing mechanical resistance to tissues, and interacting with signalling cascades to regulate tissue homeostasis (1). Mutations in genes encoding desmosomal components, including plakophilin 1, desmoplakin, plakoglobin, desmogleins 1 and 4, desmocollins 2 and 3, and corneodesmosin are associated with a broad spectrum of phenotypes comprising skin (e.g. fragility, barrier dysfunction, palmoplantar keratoderma) and hair abnormalities, which were recently reviewed (2–5). Moreover, desmosomal gene mutations account for 45–50% of cases of arrhythmogenic right ventricular cardiomyopathy (3).

Today, more than 120 dominant and recessive desmoplakin gene (DSP) mutations have been reported to be associated with skin, hair and/or heart defects (HGMD professional 2014.2). The classification of these phenotypes and the genotype–phenotype correlations are challenging, partly because in the literature, different terms are used to designate disorders which comprise similar clinical features (see Table S1). Hence, the desmoplakin associated cutaneous phenotypes are classified as epidermolysis bullosa, as palmoplantar keratoses or as hypotrichoses, depending on the predominant features. Besides, in most cases the precise consequences of the mutations and the molecular pathology remain elusive because expression and functional studies are lacking. Absence of desmoplakin or of its tail gives rise to anacantholytic epidermolysis bullosa (AEB), which leads to early demise (6). In contrast, haploinsufficiency and various combinations of missense, loss-of-function and truncating mutations are associated with cardiocutaneous syndromes, a phenotypic spectrum including skin fragility, striate palmoplantar keratoderma, variable degrees of hair involvement ranging from complete alopecia or hypotrichosis, to woolly hair, and cardiac anomalies (2) (Table S1). Plakoglobin and desmocollin 2 gene mutations lead to overlapping cardiocutaneous phenotypes with those caused by DSP mutations (5).

Here we report on 3 cases with yet unreported DSP mutations that were associated with woolly hair or hypotrichosis, palmoplantar keratoderma, and variable cardiac manifestations.

CASE REPORTS

The male index case 1 presented at the age of 5 years with hypotrichosis (Fig. 1a), striate and focal keratoderma on palms and soles (Fig. 1b, c), and keratotic papules on the dorsal aspects of the hands, arms and lower legs (Fig. 1d). A cardiac ultrasound at the age of 6 years revealed no signs of cardiac involvement. His parents are of Romanian origin, healthy and not consanguineous by report and there was no other affected member in the family.

1https://doi.org/10.2340/00015555-1974
Case 2 was a 14-year-old male born without any abnormalities after an uneventful pregnancy. Initially, his hair appeared normal. However, after the shedding of neonatal hair, new hair grew extremely slowly and scarce, with a woolly appearance. At age 13, the patient suffered a sudden episode of acute heart failure with need of resuscitation and implantation of an extracorporeal life support device. He was diagnosed with dilated cardiomyopathy with severe left ventricular insufficiency. Recently, a cardiac transplant was successfully performed. On clinical examination, woolly hair and mild focal palmoplantar keratosis were noted (Fig. 1e–g).

Case 3 was the 10-year-old sister of case 2. She had no scalp hair at birth, and later, hair grew sparse. Because of the severe cardiac disease in her brother, she was carefully examined and found to have a dilated cardiomyopathy with an ejection fraction of 35–40%. Clinical examination revealed mild focal plantar keratoses and hypotrichosis. The family history of the siblings revealed curly hair in many members of the maternal family. The mother also had very curly hair and suffered from mild bradycardia. She had suffered 2 miscarriages early in the course of the pregnancy. The patients’ father had suffered a myocardial infarction as a young man and had passed away from a malignant gastrointestinal carcinoma in his thirties.

Following written informed consent, genomic DNA was extracted from EDTA–blood and amplification and sequencing of DSP (NM_004415.2) was performed, as described in (7). The study was approved by the ethics committee of the University of Freiburg and was conducted according to the Declaration of Helsinki Principles.

In case 1, a deletion-insertion mutation, c.7566_7567delAAinsC, p.R2522Sfs*39 and a nonsense mutation, c.7756C>T, p.R2586*, in exon 24 of DSP, both in a heterozygous state were disclosed (Fig. S1a1). The father was found to be a heterozygous carrier of the deletion-insertion mutation while the nonsense mutation was found in a heterozygous manner in the mother’s DNA. In cases 2 and 3, c.1067C>A, p.T356K in exon 9 and c.2131_2132delAG, p.S711Cfs*4 at the acceptor splice site of exon 16 of DSP were found in a heterozygous state (Fig. S1b1). The mother was a heterozygous carrier of the deletion.

To the best of our knowledge, all these variants have
The curly hair and cardiac problems in the mother might suggest a link to his putative mutation, p.T356K. While hypotrichosis and palmoplantar keratoderma were early features in case 1, there were no signs of cardiac disease at this point in time. The absence of skin fragility strongly suggests that residual expression of truncated desmoplakin accounts for a partial function of desmosomes. Since both mutations, p.R2522Sfs*39 and p.R2586* are located within the C-terminus of desmoplakin, it is highly probable that they will lead to the formation of truncated polypeptides. The same effect was shown for the deletion c.7623delG, p.K2542Sfs*19 (8) that is in close proximity to the mutations reported in this study, whereas the mutation, c.7248delT was associated with AEB (9). The C-terminus of desmoplakin is crucial for its interaction with the keratin intermediate filaments (10), but since both variants in the patient will only affect the last of the 3 desmoplakin functional C-terminal domains, namely subdomain C, the coherence of desmoplakin and keratin filaments will probably only be weakened but not completely interrupted.

Prediction of the consequences of the mutations c.1067C>A, p.T356K and c.2131_2132delAG found in cases 2 and 3 is challenging. Intriguingly, compared with the patient reported by Whittick et al. (11), who had a comparable mutation constellation, our cases had no skin fragility. The palmoplantar keratoses were minor and remained initially unrecongised, while hair involvement was variable, with the sister being more severely affected than her brother. DNA of the deceased father or of his relatives was not available for analysis, but myocardial infarction at a young age in the father began in most cases at a young age and determines the prognosis. Therefore, early diagnosis is crucial and cardiac examinations must be performed on a regular basis.

ACKNOWLEDGEMENTS
We are very grateful to the patients and their families who participated in this study.

REFERENCES
8. Norgett EE, Hatsell SJ, Carvajal-Huerta L, Cabezas JC,


