

Letter to the editor

# R298Q mutation of *p63* gene in autosomal dominant ectodermal dysplasia associated with arrhythmogenic right ventricular cardiomyopathy

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## Abstract

Mutations in the *p63* gene have been identified in five types of syndromic ectodermal dysplasias (EDs) with overlapping phenotypes: Ectrodactyly–Ectodermal dysplasia–Clefting (EEC syndrome, MIM 604292), Ankyloblepharon–Ectodermal dysplasia–Clefting (AEC syndrome, MIM 106260) [3], Acro-Dermato-Ungueal-Lacrimal-Tooth (ADULT syndrome, MIM 103285), Rapp–Hodgkin (RHS syndrome, MIM 129400) and Limb–Mammary (LMS syndrome, MIM 603543) [2].

In all those conditions congenital heart defects have been only occasionally found and to date, arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVC) has never been observed in patients affected by *p63*-related ectodermal dysplasia [9]. Here we describe for the first time this association.

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## 1. Case report

A 17-year-old boy was referred to medical attention because of asthenia, dyspnea and cardiopalm. At clinical examination he had normal growth parameters. Ectodermal signs such as hypodontia with enamel and dentine dysplasia, persistence of four deciduous teeth, dystrophic nails, sparse, fragile and wiry hair, decreased sweating and right atelia were seen (Figs. 1 and 2).

Microscopic hair examination showed trichorrhexis nodosa. He did not have significant skin changes such as dry skin, freckling or photosensitivity. Hands and feet were clinically normal and nor radiographic anomalies were seen. Ocular abnormalities included lacrimal duct aplasia and recurrent blepharitis. In the first months of life this boy had suffered from many episodes of hyperpyrexia during summer probably due to reduced sweating.



Fig. 1. Hypodontia with enamel and dentine dysplasia, persistence of deciduous teeth.

Cardiological findings were consistent with the diagnosis of ARVC by morphological, functional, ECG and histologic features. Following amiodarone therapy he developed hypothyroidism and L-tiroxine treatment was started. A cardioverter defibrillator was implanted one year after diagnosis.

His mother had atelia, hypodontia and currently she wears dentures but she had no heart defects or arrhythmias. Mother's echocardiography and EKG were negative; the maternal family history was negative for sudden death, rhythm disturbances and dilated cardiomyopathy.

## 2. Discussion

ARVC is most often an autosomal dominantly inherited cardiomyopathy with primarily right ventricular involvement. The clinical presentation is highly variable but common findings are ventricular arrhythmias, syncope, and sudden death. Diagnosis is based on internationally



Fig. 2. Atelia.

accepted clinical criteria [6]. Four causative genes encoding plakoglobin, desmoplakin, transforming growth factor- $\beta$ 3, and cardiac ryanodine receptor have been suggested as disease-genes in isolated ARVC, but only a small subset of patients has been found to have mutations. Plakophilin 1, a member of the plakoglobin/beta catenin family, is mutated in one of the “dermatologic” types of EDs, the ectodermal dysplasia/skin fragility syndrome, however, in this dermatologic ED arrhythmias and/or congenital heart defects are not observed [7].

The association of ARVD/C with dermatologic signs such as woolly hair and palmoplantar keratoderma has been reported in Carvajal and Naxos syndromes [8,11]. Our cases, however, do not have hyperkeratosis or skin fragility but rather major ectodermal derivatives involvement suggesting an autosomal dominant ED. We performed *p63* gene mutation analysis in both the proband and his mother and we found a R298Q mutation. Interestingly, this mutation, that affects the DNA binding domain of *p63* [1], has been identified in 16 patients belonging to five families affected by ADULT syndrome. One of those ADULT cases had paroxysmal supraventricular tachycardia as well [10]. The patients we describe did not have the skin and limb characteristics of the ADULT cases although they share its typical mutation.

Our findings further underline not only the clinical overlapping of *p63*-related ectodermal dysplasias but also the difficulty of establishing unequivocal genotype–phenotype correlations [2,3]. The rhythm disturbances in ARVC are ventricular arrhythmias. Paroxysmal supraventricular tachycardia, reported in one ADULT patient, could represent a consequence of right atrio-megalia and it could be the expression of inadequate cell adherence mediated by desmosomes disease as in ARVC.

To date, no occurrences of ARVC have been reported in *p63*–Ectodermal dysplasias and cardiac involvement is occasionally seen [9]. Our proband raises the suggestion of a yet unrecognized role of *p63* in the development of the heart. *P63* might implement subprograms fundamental to stratified epithelial development and integrity. *Perp* is a key effector in the *p63* developmental program as it is highly expressed in the skin, tongue, palate, and hair follicles; it is well known that it plays an essential role in promoting the stable assembly of desmosomal adhesive complexes and in enhancing the ability of tissues, including cardiac tissue, to resist mechanical stress. *Perp*'s role in desmosomal integrity has significant implications for understanding of human syndromes affecting the ectoderm and its derivatives [4,5]. Because mutations of desmosomal components (plakoglobin, plakophilin, and desmoplakin) are responsible of ARVC we think that there is a molecular link between *p63* and genes that have been linked to ARVC. Although our report concerns only one case we think that this may be a true association and not merely coincidence. Careful search for minor ectodermal signs and screening for *p63* mutations might be suggested in cases of ARVC without mutation in already known genes.

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