Autosomal dominant Carvajal plus syndrome due to the novel desmoplakin mutation c.1678A > T (p.Ile560Phe)

Josef Finsterer ⁊, Claudia Stöllberger b, Eva Wollmann b, Susanne Dertinger c, Franco Laccone d

ABSTRACT

Background: Carvajal syndrome is an autosomal dominant or autosomal recessive disorder, manifesting with dilated cardiomyopathy, woolly hair, and palmoplantar keratoma. Additional manifestations can be occasionally found. Carvajal syndrome may be due to mutations in the desmocollin-2, desmoplakin, or plakophilin-2 gene.

Methods and results: We report a family with Carvajal syndrome which additionally presented with hypoacusis, noncompaction, recurrent pharyngeal infections, oligodontia, and recurrent diarrhoea. Father and brother were also affected and had died suddenly, the father despite implantation of a cardioverter defibrillator (ICD). Genetic studies revealed the novel pathogenic mutation c.1678A > T in the desmoplakin gene resulting in the amino acid change Ile to Phe at position 560 in the index case and her brother. The index case underwent ICD implantation recently.

Conclusion: Phenotypic manifestations of Carvajal syndrome are even broader than so far anticipated, the number of mutations in the desmoplakin gene responsible for Carvajal syndrome is still increasing, and these patients require implantation of an ICD as soon as their diagnosis is established.

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Much more frequent due to other causes.

Desmoplakin consists of a keratin-binding domain, a plakin domain, a N-terminal head domain, and a desmoplakin specific rod-domain [8]. The effect of the mutation on the function of the protein remains speculative since the detailed function of desmoplakin is still insufficiently understood. The mutation detected in the present case results in an amino acid change in the plakin domain of the protein. In this domain at least two further missense mutations have been described leading to Carvajal/Naxos syndrome with leukonychia and oligodontia [3] and to a right ventricular arrhythmogenic cardiomyopathy [9]. The mutation may result in a structural change of the spectrin 4 repeat leading to an insufficient recruitment of desmoplakin into desmosomes or may have a dominant-negative effect on the recruitment of other desmosomal proteins [7]. This scenario is conceivable since desmoplakin binds plakoglobin and plakphilins via its N-terminal domain. Desmoplakin mutations may not only cause Carvajal syndrome but also cutaneous and cardiac syndromes such as non-syndromic, isolated striate palmoplantar keratoderma, and non-syndromic ARVD [7]. Altogether 24 patients with Carvajal syndrome due to a desmoplakin mutation have been reported (Table 1). The phenotypic variability among our patients was higher than so far anticipated. Additional phenotypic features found in previously reported cases include oligodontia (n = 6), ARVD (n = 4), nail abnormalities (n = 4), LVHT (n = 2), alopecia (n = 1), bisepidial aortic valves (n = 1), and mucosal blistering (n = 1) (Table 1).

In conclusion, this study of a family with Carvajal syndrome shows that the phenotypic manifestations of this syndrome are possibly broader than so far anticipated, that the number of mutations in the desmoplakin gene responsible for Carvajal syndrome is still increasing, and that these patients require implantation of an ICD as soon as their diagnosis is established. Future studies must focus on the genotype-phenotype correlation more extensively since it remains unclear if certain mutations are more prone to be at risk of severe complications than others.

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