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Genotype-phenotype correlation in arrhythmogenic cardiomyopathies

Introduction: Arrhythmogenic Cardiomyopathies (ACM) are inherited cardiomyopathies histologically caracterized by fibro-fatty myocardial alteration, and clinically by ventricular arrhythmias starting at an early disease stage, usually later followed by identifiable structural and hemodynamic disorder. Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C) is in its typical form a subcategory of ACM with primarily RV involvement. However, ACM also includes predominant left ventricular disease. ACM is associated with pathogenic mutations encoding desmosomal and non-desmosomal proteins.

Aim: Analysis of genotype-phenotype correlation in a large transatlantic ACM patient cohort.

Results: In 577 well-phenotyped patients (230 probands, 347 relatives) pathogenic mutations were found in 5 desmosomal (*JUP, PKP2, DSG2, DSC2, DSP*) and 2 non-desmosomal genes (*TMEM43, PLN*). Mutations in *PKP2* were found in 80% of individuals. 36 Patients presented with sudden cardiac death, particularly in 4/19 (21%) with *DSP*, versus only 29/463 (6%) with PKP2.Those presenting alive were followed during 6±7 years. Arrhythmic outcome in males was worse compared to females, and >1 mutation did worse compared to a single mutation. *PLN* and *DSP* were significantly more associated with left ventricular dysfunction than *PKP2*. Premature truncating, splice site, and missense mutations were associated with a similar arrhythmic and hemodynamic outcome.

Conclusion: Genotype-phenotype correlation shows clinically relevant differences. Because of frequent predominant left ventricular involvement in DSP and PLN, fulfilment of ARVD/C Task Force Criteria may be absent, although these subcategories have an unfavorable outcome.

Biography

Hauer was born in 1947 in Amsterdam. He obtained MD graduation in 1974 at Leiden University and in 1980 Board Certification in Cardiology at Amsterdam University (mentor prof. Durrer). His mentors in Clinical Electrophysiology were Prystowsky and Zipes at Indiana University. In 1987 Hauer obtained his PhD degree with a thesis on ventricular arrhythmias and catheter ablation. In the years 1996-2012 he was full professor in Clinical Electrophysiology at the University Medical Center in Utrecht, Netherlands. Hauer is author or co-author of 190 publications in the field of cardiac arrhythmias in peer-reviewed international journals and member of the editorial board of Journal of Cardiovascular Electrophysiology. He was mentor of 15 PhD students. Since 2005 Hauer is project leader of the Netherlands Heart Institute project on Arrhythmogenic Cardiomyopathy with focus on diagnosis, genotype-phenotype correlation, and long-term risk assessment. This project is in collaboration with Johns Hopkins University in Baltimore (Dr. Calkins).

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