

**Editorial**

Translational medicine in genetic familial diseases: from the autopsy room to the molecular bench and vice versa

Significant improvements in the treatment and prevention of cardiac diseases have led to declining morbidity and mortality over the past 3 decades [1]. However, because of our lack of knowledge of the molecular basis of diseases, we predominantly treat the crisis instead of preventing patients from acquiring heart disease. The discovery of genes involved in familial cardiac diseases might prepare the way to better select patients at risk and to establish targeted therapies that can prevent hospitalizations and even death.

Genetic familial disorders of the heart are found in a variety of diseases such as cardiomyopathies, arrhythmogenic disorders, conduction disturbances, and cardiac malformations and are sometimes accompanied by defects of other organs [2]. Moreover, several genetic neurological and muscular syndromes such as Friedreich ataxia or Duchenne muscular dystrophy are associated with cardiac diseases. In 1961, a familial accumulation of dilated cardiomyopathy, one of the leading causes of heart failure, accounting for about 36 cases per 100 000 population and for 10 000 deaths annually in the United States, was first described by Battersby and Glenner [3,4]. A systemic analysis done by Michels et al [5] exhibited that the genetic background is involved in approximately 25% of all dilated cardiomyopathies. The importance of genetic familial defects is also substantiated by the fact that the hypertrophic cardiomyopathy (HCM) is the most common cause of death among the young, especially athletes [6,7]. Another familial cardiomyopathy, the arrhythmogenic right ventricular cardiomyopathy (ARVC), is also established as a major cause of sudden death in the young [8]. This disease is characterized by a gradual loss of myocytes and replacement by fatty and fibrous tissue, leading to dilatation of the right ventricle and decreased cardiac function. Notably, the penetrance of most genetic cardiac diseases is highly variable and age-dependent, and many relatives of patients with genetic cardiac diseases show only minor cardiac abnormalities. Therefore, it is a major clinical challenge to identify carriers, and genotyping will provide a useful

tool to screen patients. Fortunately, the identification of genes responsible for cardiac diseases increases dramatically. Because of newly developed linkage analysis, the first gene (β -myosin heavy chain) for familial HCM was mapped in 1990 [9]. In the meantime, 7 genes with more than 100 mutations have been identified as responsible for familial HCM [2].

In long QT syndrome, which can be acquired or congenital, the first locus was mapped in 1991, and today, 6 loci and 5 genes have been identified [10]. All of the genes encode proteins that function as ion channels [11]. Patients are identified by a prolongation of the QT interval in the electrocardiograph, and the typical ventricular arrhythmia is torsade de pointes. The syndrome of Brugada [12], first described in 1992, leads to fast polymorphic ventricular tachycardia because of fast inactivation of a sodium channel and is recently linked to an abnormal incidence of sudden death in some countries in Southeast Asia.

In the current issue of HUMAN PATHOLOGY, the findings reported by D'Amati et al [13] underscore the importance of precise autopsy in sudden cardiac death and exemplify the complementary interplay of basic science, clinical examination, and autopsy in genetic familial diseases. Based on a case of a 17-year-old boy who died of sudden cardiac death, the authors' persistent investigation brought forward a novel missense mutation of the ryanodine receptor (*RyR2*) gene, a cardiac calcium-release channel in the sarcoplasmic reticulum (SR). *RyR2*-mediated calcium release during systole activates the contractile proteins responsible for cardiac contraction [14]. However, during diastole, *RyR2* must shut tightly or calcium will leak uncontrollably from the SR into the cytoplasm. Importantly, the novel *RyR2* mutation reported in this issue was mapped to a domain interacting with the FK506 binding protein 12.6 (FKBP12.6) binding domain. Binding of FKBP12.6 to *RyR2* was found to prevent subconductance states and aberrant activation during diastole [15]. Because FKBP12.6-targeted gene deletion in mice caused "leaky"

SR calcium channels in response to both exercise-induced stress and protein kinase A-mediated phosphorylation, defective *RyR2* function is linked to exercise-induced sudden cardiac death [16]. Therefore, the *RyR2* might become a therapeutic target itself, and the calcium-sensing protein S100A1 has recently been shown to modulate *RyR2* function, thus decreasing the SR calcium leakage in failing cardiomyocytes and restoring normal function in heart failure [17].

Histological analysis of the heart of the 17-year-old boy revealed fatty and fibrofatty replacement in the right ventricular myocardium, and the authors linked the case to the diagnosis of ARVC. Because ARVC is a major cause of sudden death, clinical examination and DNA analysis were arranged for all relatives, and catecholaminergic polymorphic ventricular tachycardia was diagnosed in the mother and the sister of the index case. Oral administration of β -adrenergic receptor blockers are proven to reduce *RyR2*-mediated calcium leakage from the SR via restoration of protein kinase A hyperphosphorylation and FKBP12.6 stoichiometry in failing hearts [18]. In this context, it is intriguing that the stress test-triggered onset of polymorphic ventricular arrhythmia in the mother and the sister disappeared under oral β -blocker therapy. Because ARVC is accompanied by structural abnormalities, which are absent in catecholaminergic polymorphic ventricular tachycardia, this case also highlights the great variability of genetic cardiac familial diseases even within the same family and suggests the importance of the genetic background and modifier genes.

Advances in molecular biology techniques and growing knowledge of molecular defects will provide targeted and clinically applicable treatment strategies for genetic familial diseases. To successfully translate these approaches into clinical work and to further reduce the mortality and morbidity in cardiovascular diseases, the clinical ability to screen patients and a competent and ambitious autopsy will be crucial. Overall, this report demonstrates the potential of pathological examination and the complementary role of basic science, clinical examination, and autopsy to fight against familial genetic diseases.

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