

Sudden Cardiac Death Syndrome: Age, Gender, Ethnicity, and Genetics

Ruey J Sung,^{1,7} Chi-Tai Kuo,² Shan-Nan Wu,³ Wen-Ter Lai,⁴ Nazar Luqman⁵ and Ngai-Yin Chan⁶

Prevention of sudden cardiac death (SCD) is an important issue in clinical practice. Causes of SCD depend on age, gender, ethnicity, and genetics. It can not be overstated that an accurate clinical judgment along with a diligent diagnostic work-up is essential. A history of prior syncope especially more than once, a family history of premature death (e.g., < 60 years of age), a critical lesion in the coronary artery, poor left ventricular function (e.g., EF < 35%), and abnormal ECG findings (e.g., QTc > 450 msec) should alert a physician about the risk of SCD. As a rule, physical exertion is prohibited in any patient with active myocardial ischemia associated with atherosclerotic coronary heart disease (ASHD), and total revascularization as early as possible is mandatory for the prevention of SCD. Special consideration should be given to women with ASHD as they often present with atypical symptomatology associated with a worse prognosis. Other cardiac diseases such as various forms of cardiomyopathies, valvular heart disease, congenital heart disease, and electrical disorders such as congenital long QT syndrome and Brugada syndrome, particularly in the young, can often be suspected. According to the each individual disease condition, the diagnostic and therapeutic strategies should be individually tailored. Life style adjustment and/or modification, medical therapy, catheter ablation, device implantation (e.g., pacemaker or implantable cardioverter/defibrillator) or surgical intervention should be appropriately advised. Molecular genetic analysis in autopsy-negative cases (molecular autopsy) is indicated for identifying the likely cause of SCD and this should be extended to the surviving relatives of the SCD victim for risk stratification, for reproductive counseling, and for taking preventive measures in the surviving family members.

Key Words: Sudden cardiac death • Atherosclerotic coronary heart disease • Molecular genetics • Hypertrophic cardiomyopathy • Long QT syndrome

Sudden cardiac death (SCD) is a major public problem accounting for approximately 20% of all mortality in the western world.¹ In the USA alone, SCD afflicts

450,000 people each year. The causes of SCD differ greatly among various age groups.^{2,3} Studies investigating the causes of SCD have emanated predominantly from North American and Europe. In individual subjects ≥ 40 years old, atherosclerotic coronary heart disease (ASHD) is the most common cause. Between one and 40 years of age, the causes of SCD are commonly hypertrophic cardiomyopathy (HCM), unexplained left ventricular hypertrophy, myocarditis, congenital heart disease and other less common entities such as aortic dissection, valvular heart disease and arrhythmogenic right ventricular dysplasia/ cardiomyopathy (ARVDC).³⁻⁷ In a series of 107 sudden death cases with ages ranging between 1 and 35 years gathered from a northern county of Spain from 1991 to 1998, the mortality rate was calculated to be 2.4/100,000/ year.⁷ Men were found to be three-fold

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¹Institute of Life Science, National Central University, Taoyuan; ²Department of Cardiology, Chang Gung University, Taoyuan; ³Institute of Basic Science Research, National Cheng Kung University, Tainan; ⁴Kaohsiung Medical Center, Kaohsiung Medical University, Kaohsiung, Taiwan; ⁵Princess Margaret Hospital, 2-10 Princess Margaret Hospital Road, Lai Chi Kok, Kowloon, Hong Kong; ⁶Department of Cardiology, RIPAS Hospital, Brunei, Darussalam; ⁷Department of Medicine, Stanford University School of Medicine, Stanford, California, USA.

Address correspondence and reprint requests to: Dr. Ruey J Sung, Institute of Life Science, National Central University, No. 300, Jhongta Rd, Taoyuan, Taiwan. Tel: 886-3-422-7151 ext. 65050; Fax: 886-3-422-8482; E-mail: rsung@cvmed.stanford.edu

at risk of sudden death than women. About 43 % of sudden death cases in this series were due to SCD. ASHD was the most frequently found in those over 30 years of age. Myocardial diseases and conduction system abnormalities were common between 15 and 30 years of age. Of all sudden death cases, 39% were related to extra-cardiac causes with infections being frequently noted in children, and epilepsy, asthma and intracranial hemorrhage in those between 15 and 30 years of age. Notably, 18% of cases, especially children, had a negative postmortem, that is, the cause of sudden death remained unexplained despite a detailed histological examination.⁷ Under one year of age, SCD can be part of sudden infant death syndrome (SIDS)⁸ which is often associated with a negative postmortem. Sudden death with a negative postmortem is referred to as “autopsy-negative sudden unexplained death (SUD)”, the cause of which is most likely a primary arrhythmogenic event.⁹

MOLECULAR GENETIC STUDY

Advances in molecular genetics research in the past decade have extended our knowledge about a variety of inherited structural cardiovascular diseases and malignant arrhythmogenic disorders related to SCD.^{10,11} In the former, mutations in genes encoding developmental components of organs/systems and in the latter, mutations in genes encoding functional units of ion channels and/or their membrane components are often the underlying etiologies of these illnesses.^{10,11} Consequently, better understanding of pathophysiological mechanisms of these illnesses has enabled cardiologists and electrophysiologists to be able to provide more rational and effective strategies in the management of SCD. The inherited structural cardiovascular diseases causing SCD are most frequently HCM,^{12,13} ARVD/C,^{14,15} and dilated cardiomyopathy.^{16,17} On the other hand, the most likely encountered inherited arrhythmogenic disorders that may cause SCD are congenital long QT syndrome (LQTS),¹⁸ Brugada syndrome,¹⁹ catecholaminergic polymorphic ventricular tachycardia (CPVT),²⁰ and short QT syndrome (SQTS).²¹

In an inclusive epidemiologic study, it has been noted that over 30% of SCD cases in the young are autopsy-negative SUD.²² Postmortem molecular diagnos-

tic studies, referred to as “molecular autopsy”, have identified pathogenic mutations in LQTS, Brugada syndrome, CPVT and SQTS-related genes in over one-third of SCD victims.²² Collectively, these inherited arrhythmogenic disorders are called “ion channelopathies”. Even in a large population-based cohort of SIDS, molecular autopsy has elucidated genetic mutations in 5-10% SUD cases.²² Further, molecular genetic analysis can also be applied to surviving relatives of SUD cases for attempting to define the likely causes of death.²³ In a cohort of 43 consecutive families with 1 SUD victim who died at ≤ 40 years of age, cardiological evaluation (e.g., resting/ exercise ECG and Doppler echocardiography) along with the use of molecular genetic analysis, could identify an inherited disease and the likely cause of death in 17 families (40%).²³ Of these, twelve families were found to have inherited arrhythmogenic disorders: 5 CPVT, 4 LQTS, 2 BrS, 1 LQTS/Brugada syndrome, and 4 families inherited structural cardiac diseases: 3 ARVD/C and 1 HCM. Molecular genetic analysis provided confirmation in 10 families. Taken all together, the clinical and genetic approach generated an impressively high diagnostic yield, unmasking 151 presymptomatic disease carriers in the survivors of SCD victims.²³

GENDER

In an analysis of USA Vital Statistics data gathered between 1989 to 1998, SCD death rates increased 12.4% (from 56.3% to 63.9%) and age-adjusted SCD rates declined 11.7% in men and 5.8% in women but the age-specific SCD death rates increased 21% among women aged 35 to 44 years.² It was suggested that women might have received less aggressive and more delayed treatment for heart disease because of their often atypical clinical presentation of chest pain that often got unrecognized.²⁴ Women were also noted to have a high risk of death after myocardial infarction.²⁴ Pathophysiological studies had shown that young women with SCD were more likely to be smoker and elder women tended to have higher prevalence of diabetes, hypertension and hypercholesterolemia.^{25,26} Further, it was noted that SCD in younger women was more commonly associated with plaque erosion leading to acute coronary thrombosis

whereas SCD in elder women were more likely to be linked to plaque rupture or healed myocardial infarction.²⁵

Compared to men, women are less frequent to suffer from SCD and notably women who present with SCD are less likely to have a prior history of heart disease (37% versus 56%).²⁶ In a retrospective study involving 355 consecutive survivors of out-of-hospital cardiac arrests (84 women and 271 men), women were noted to be less likely to have ASHD than men (45% versus 80%) but more likely to have other forms of heart disease or structurally normal heart.²⁷ Moreover, while left ventricular ejection fraction of $\leq 40\%$ was the most important predictor in men, the presence of ASHD is the most important predictor of total and cardiac mortality in women.²⁷ In a prospective study in which a large cohort of 121,701 women aged 30 to 55 years were enrolled, 244 SCD victims were identified between 1976 and 1998 in USA.²⁸ Similarly, most (69%) of these SCD victims had no prior history of cardiac disease before death but most (94%) of them had at least one ASHD risk factor such as smoking, hypertension, and diabetes (2.5 to 4.0-fold increased risk for SCD). Of note, the underlying mechanism of SCD was determined to arrhythmia in the majority (88%) of cases.²⁸

In searching for genetic factors predisposing to arrhythmias in the presence of myocardial ischemia/infarction in 113 SCD cases from two large cohorts of women and men, no mutations were found in any of 53 men (96% white, age 65.5).²⁹ However, five rare missense variants in SCN5A that either had been associated with long QT syndrome (A572D and G615E), had been reported to alter sodium channel function (F2004L) or had never been previously described in control populations (A572D and A572F) were identified in 6 (10%) of 60 women (100% white, age 60.8).²⁹ Mutations in SCN5A have been shown to be associated with several distinct phenotypes, many of which manifest malignant ventricular arrhythmias, most notably LQTS,³⁰ Brugada syndrome¹⁹ and SIDS.³¹ It was inferred that these functional significant mutations and rare variants might contribute to the risk of SCD among women, in particular the white, with myocardial ischemia/infarction.²⁹

The female gender may also exhibit a distinctly different clinical course from that of the male gender. Taking congenital LQTS for example, cardiac events tend to occur more frequently during childhood. However, LQTS boys tend to have a significantly high rate of fatal and

near fatal cardiac events than girls.³² While male gender carries an increased risk of events during preadolescence, female gender has higher events rates in adolescence and thereafter.^{33,34} Also female gender with events before age 18 tends to have an increase in event recurrence between age 18 and 40.³⁵ In particular, the female gender with QT interval near 500 ms and interim syncope episode is associated with a significantly high risk of life-threatening events in adulthood.³⁵ After age of 40, LQTS continues to pose a threat of life-threatening cardiac events in both men and women.³⁶ The history of recent syncope (< 2 years in the past) has been identified as the predominant risk factor in affected LQTS patients and the LQTS3 genotype as the most powerful predictor of outcome.³⁶

Women are known to be more prone to adverse drug reaction than men as two-thirds of cases of drug-induced torsade de pointes (acquired LQTS) occur in women.³⁷ The causes of gender-related differences in drug responses are multifactorial. The female gender, particularly the young, is associated with a longer QT interval at baseline presumably because of effects of sex steroids.³⁷ There are also gender-associated differences in drug exposure, the number of drug prescribed, and drug pharmacokinetics and pharmacodynamics.³⁷ Many classes of drugs such as antiarrhythmics, antibiotics, antihistamines, antipsychotics, and gastrokinetics possess a common property that inhibits the voltage-gated potassium channels, especially the rapid component (I_{Kr}) of the delayed rectifier. As such these drugs may further prolong the process of repolarization, thereby provoking torsade de pointes arrhythmia leading to syncope and cardiac arrest.³⁷

ETHNICITY

Based on the United States Vital Statistics data, SCD occurred in 456,076 (63%) of 719,456 cardiac deaths aged ≥ 35 years in 1998.² ASHD was the most frequent underlying disease associated with SCD (58.9%-62.9%) followed by cardiomyopathy and arrhythmia (8.8%-11.6%), hypertension (4.6%-7.7%) and congestive heart failure (2.0%-7.7%).² Of note, the black people (503 per 100,000) had higher SCD death rates compared to white (407 per 100,000), American Indian/Alaskan native (259 per 100,000) and Asian/Pacific Islander (213 per 100,000) populations. Among various causes of SCD, Af-

rican Americans had notably higher proportions of primary cardiomyopathy and hypertensive heart disease, but lower proportions of ASHD and congenital heart disease.³

Between 1985 and 2000, a total of 584 young athletes aged ≤ 35 years who died suddenly were reported to the registry.³⁸ Of these 584 subjects, 298 were ultimately excluded from the SCD count because other non-cardiovascular causes of death had been identified (e.g., drug abuse, complications of asthma, heat stroke, drowning, head trauma, ruptured cerebral artery, blunt chest trauma, etc.). The remaining 286 athlete deaths were documented to be SCD with ages ranging from 9 to 40 (mean 17 ± 3) years. 156 (55%) were white and 120 (42%) were African American. Most were male (90%) and 67% occurred while playing basketball and football. Among identifiable causes of SCD, HCM was most common (36%) followed by anomalous coronary artery of wrong sinus origin (13%), indeterminate form of cardiomyopathy (probable HCM) (10%), myocarditis (7%), ruptured aortic aneurysm (4%), ARVD/C (4%), tunneled coronary artery (4%), aortic stenosis (3%), ASHD (3%), idiopathic dilated cardiomyopathy (3%), and mitral valve prolapse (3%). Of the athletes with SCD related to HCM, 42 (41%) were white and 56 (55%) were African American. This latter finding was in contrast to the data showing that only 158 (8%) of the 1,986 clinically diagnosed HCM patients were African American.³⁸ The discrepancy suggested that many HCM cases had gone unrecognized in the African American community probably because of relatively lower socioeconomic status compared to the white, but in addition, there may be underlying genetic factors making the black to predispose to a higher risk of SCD and cardiovascular mortality. For example, a variant of SCN5A, Y1102, noted to accelerate sodium channel activation, thereby increasing the likelihood of abnormal cardiac repolarization, was first noted to be present in about 13.2% of African Americans.³⁹ Subsequently, in studies attempting to define the spectrum and prevalence of cardiac sodium and potassium channel variants among blacks, white, Asian, and Hispanic individuals, nineteen (49%) of total 39 distinct variants in SCN5A and more than half of 49 distinct variants in LQTS-causing potassium channel genes (KCNQ1, KCNH2, KCNE1, and KCNE2) were found exclusively in the black cohort.^{40,41} These genetic variants may alter the repolarization prop-

erties of cardiac tissues, thereby mediating an increased susceptibility to arrhythmias in the settings of diseases or drug ingestion.

Also of interest, in the State of Hawaii, it was observed that full and part Hawaiians had the highest age-adjusted cardiovascular mortality rates among the 4 main ethnic groups comprising the population in 1980 and 1990.⁴² Additionally, Asian ancestry groups (e.g., Filipino and Japanese) had much lower cardiovascular mortality rates compared to Hawaiians and Caucasians despite having similar cardiovascular risk factors (e.g., diabetes, hypertension, hyperlipidemia, etc.). The reason accounting for Hawaiians to have higher cardiovascular mortality rates than other ethnic groups remains elusive. Nevertheless, some investigators have suggested that it can in part be attributed to Hawaiians' intrinsically having a longer baseline QTc interval⁴³ presumably due to the angiotensin-converting enzyme gene with insertion/deletion polymorphism.⁴⁴ Further more detailed molecular genetic research work is required to clarify the issue.

SPECIFIC DISEASES

Hypertrophic cardiomyopathy

HCM appears to be a global disease because it has affected populations from North America, Western Europe, Far East, the Middle East, South Africa, and Australia with a world wide prevalence of approximately 0.2% (1:500).¹² HCM bears a broad clinical spectrum and genetic etiology, and is strongly associated SCD in the young and the athletes. It is primarily transmitted by an autosomal dominant fashion. At present, at least 12 genes with most of them encoding for cardiac sarcomeric proteins have been identified.¹³ In a series of 197 index cases of European origin, disease-causing mutations were identified in 124 patients (63%). Cardiac myosin binding protein C (MYBP3) and beta-myosin heavy chain (MYH7) are most frequently found, 42% and 40%, respectively, while others were noted in only $< 10\%$ of cases.⁴⁵ Of note, in 22 index cases with a malignant course, MYH7 was the most prevalent gene (45%) followed by MYBPC3 (18%), cardiac troponin I (TNNT3) (14%), myosin ventricular regulatory light chain2 (MYL2) (14%) and cardiac troponin T (TNNT2) (9%). In each

protein, "hot spots" associated with malignant prognosis have been identified, e.g. R403, R719 and R663 in MYH7, R502, D778 in MYBP3, R162 in TNNT3 and R58 in MYL2.⁴⁵ Of note, mutations in the TNNT2 gene have been reported to be associated with no or mild left ventricular hypertrophy with a high risk of SCD.⁴⁶ Moreover, a subset of HCM patients may exhibit a restrictive phenotype associated with mutations in MYH7 and TNNT3.⁴⁷ The restrictive phenotype is characterized by restrictive hemodynamics with minimal or no hypertrophy. Clinically, this subset entity connotes a rather poor prognosis because of severe limitations, diastolic heart failure and high rates of atrial fibrillation/flutter and stroke.⁴⁷

In a population-based echocardiographic analysis of 8080 Chinese adults, the prevalence of HCM was estimated to 0.16% comparable to those of the western world.⁴⁸ Moreover, in a 30-year follow-up study of 118 Chinese patients with HCM, certain distinctive features different from those of Caucasian patients had emerged.⁴⁹ Specifically, there was a high incidence of atrial fibrillation (35% vs. 20% in most other studies) and there was also high percentage of patients showing phenotypic expression of non-obstructive apical hypertrophy in the most distal portion of the left ventricle (41% vs. 3% in non-Asians and 15% in Japanese)^{12,49,50} along with a relatively low annual mortality rate (1.6% vs. 5.6% in the literature).¹² Furthermore, in contrast to the experience of non-Asian patients,⁵¹ HCM appeared to be more severe in Chinese women with HCM as the female sex was the only independent predictor of mortality noted in that study.⁴⁹ In analyzing mutation profiles of 34 Chinese HCM patients, MYH7 and MYBPC3 were also found to be the predominant genes similar to those reported in the western world.⁵² However, the most common hot and malignant mutation R403Q in MYH7 identified in Caucasians could not be documented in Chinese HCM patients.⁵²

Pediatric cardiomyopathy

Epidemiologically in a series of 314 new cases of pediatric cardiomyopathy in Australia representing an annual incidence of 1.24 cases per 100,000 children younger than 10 years of age, dilated cardiomyopathy constituted up to 58.6% of cases, HCM 25.5%, restrictive cardiomyopathy 2.5%, and left ventricular non-compaction 9.2%.¹⁶ There was a male predominance among cases with HCM and unclassified cardiomyopathy, and indigenous

children had a higher incidence of dilated cardiomyopathy than non-indigenous children. Lymphocytic myocarditis was found in 43.3% of cases with dilated cardiomyopathy. Of note, SCD was the first presenting symptom in 11 patients (3.5%), of which 9 had dilated cardiomyopathy, 2 had unclassified cardiomyopathy and none had HCM. The estimated incidence of pediatric cardiomyopathy in New England and the Central Southwest region of the United States was similar to that of Australia (1.13 cases per 100,000 children).¹⁷ About half (41%) of the cases were diagnosed within the first 12 months of life. The annual incidence was higher among black than among white children (1.47 vs. 1.03 per 100,000) and higher among boys than among girls (1.32 vs. 0.92 per 100,000). Likewise, when categorized according to type, dilated cardiomyopathy was the most common (51%), HCM was the second (42%) and restrictive and others are rare.

Arrhythmogenic right ventricular dysplasia/cardiomyopathy

ARVD/C is primarily characterized by an autosomal mode of inheritance with a family history being present in 30~70% of cases.¹⁴ Up to date, six chromosomal loci have been found.^{15,53} Of these, five are desmosomal genes and the remaining the cardiac ryanodine receptor (RyR2) gene. Notably, mutations in the RyR2 gene on the 1q42-q43 locus (e.g., R176Q, L433P, N2386I&T 2504M) cause a distinct clinical entity referred to as ARVD2, characterized by effort-induced polymorphic ventricular tachycardia and juvenile SCD.^{54,55} Reportedly, ARVD/C accounts for 20% of SCD in the young.⁵⁶ However, there are significant ethnic and geographical variations. ARVD/C is frequently identified in Northern Italy (especially the Veneto and the Emilia Romagna regions), France, Germany, Greece and Japan, but rarely in the North American Indian population.⁵⁵ A small series (11 patients) of Chinese patients with ARVD/C have also been recognized.⁵⁷ Reportedly, two patients (18%) have a positive family history of ARVD/C or premature SCD and left ventricular involvement in affected individuals are uncommon.⁵⁷

Congenital long QT syndrome

The incidence of congenital LQTS is estimated to be at one in 10,000-15,000 live births.⁵⁸ Congenital LQTS is caused by mutations that encode ion channel proteins that regulate the flux of sodium, potassium and calcium

ions across the cell membrane of the cardiac myocyte. At least 10 subtypes of congenital LQTS mostly due to mutations in genes encoding cardiac potassium, sodium and calcium channels have been identified.⁵⁹ In congenital LQTS, cardiac events related to arrhythmias mostly occur before reaching the adulthood.^{20,34} Physical exertion and emotional stress are common triggers of syncope and SCD, although occasionally these events can occur at rest and be instigated by loud noise. Among patients with clinical evidence of LQTS, the yield of genetic testing is about 75% with LQT1 (KCNQ1, 30-35%), LQT2 (KCNH2, 25-30%), and LQT3 (SCN5A, 5-10%) constituting the majority of the cases. The rate of cardiac events appears to be genotype-related: 30% in LQT1, 46% in LQT2, and 42% in LQT3 calculated from birth to the age of 40 years with a mortality of approximately 13%.²⁰ It should be noted that LQT7 (KCNJ2) and LQT8 (CACNA1C), also known as Andersen-Tawil syndrome and Timothy syndrome, respectively, are each a multisystem disease. LQT7 is caused by mutations in KCNJ2 which encodes the cardiac and skeletal muscle inward rectifier K⁺ channel Kir2.1, and clinically is characterized by periodic paralysis, ventricular arrhythmias and dysmorphic features.⁶⁰ LQT8 is due to mutations (G406R and G402S) in CACNA1C that encodes the pore-forming α -subunit of the cardiac L-type Ca²⁺ channel⁶¹ and clinically exhibits extensive involvement of various organ systems (e.g., syndactyly, dysmorphic facial features, myopia, autism, congenital heart disease, recurrent infection, intermittent hypoglycemia, hypothermia, etc.). LQT8 is the most malignant congenital LQTS as patients with LQT8 seldom survive beyond 3 years of age.⁶¹ In Japan, the genotypes of LQTS are mainly LQT1 and LQT2 (about 20% each). Incidences of LQT3 and others are rare but many of them have not been well screened. Mutations found in Japanese LQTS families are mostly novel compared to those reported in other countries and in different ethnicities.⁶² Female gender tends to manifest more severe symptoms than males (31.7% versus 11.6%). During a follow-up evaluation of 131 cases for 7.2 years, the SCD rate is estimated as 3.8%.⁶²

Risk stratification of congenital LQTS is based on not only the gender and degree of QT prolongation but also the location and biophysical property of the mutation. It has been suggested that mutations located at the C-terminal region (e.g., KCNQ1-R555C, and KCNQ1-G589D mutation)

are associated with a relatively less severe clinical phenotype^{63,64} whereas mutations located in the transmembrane region have a significant increase in risk of serious cardiac currents.^{34,65} It has also been pointed out that LQT2 patients with mutations in the pore region (amino acid residues 550-650) of the HERG protein have a markedly increased risk for arrhythmia-related cardiac events compared to those with non-pore mutations.⁶⁶ Indeed, a missense mutation (G604S) in the S5/pore region of HERG has caused LQT2 in a large Chinese with 100% penetrance and a high incidence of SCD.⁶⁷ Additionally, in LQT1 patients, the KCNQ1-A341V mutation at the pore region has also been shown to confer unusually severe clinical manifestations independent of the ethnic origin.⁶⁸

Brugada syndrome

Brugada syndrome is an endemic disorder found in east and southeast Asia, particularly Thailand, Japan, Philippines and Cambodia with mortality rates as high as 38 per 100,000.⁶⁹ It is the most common cause of SCD that occurs during sleep in the young and is also referred to as "sudden unexplained nocturnal death syndrome" (SUNDS).⁶⁹⁻⁷¹ The clinical features are characterized by the presence of a right bundle branch block pattern and ST-segment elevation in the electrocardiographic leads V1-V3 associated with a propensity to ventricular fibrillation and SCD.²³ Brugada syndrome has been linked to mutations in the SCN5A gene that encode the α -subunit of the sodium channel³⁰ and those in the CACNA and CNCNB genes that encode the α - and β -subunits of the calcium channel, respectively,⁷² and the gene that encodes glycerol-3-phosphate dehydrogenase 1-like enzyme GPD-L.^{73,74} However, more than 70% of cases remain unaccounted for by the genotype.⁷⁵ In Japan, the incidence of SCN5A mutations varies from 2% to 27% (mean 12%) which is much lower than that reported in Europe (20%).⁶² Of note, Brugada phenotype is 8 to 10 times more prevalent in men than in women. This gender distinction is attributed to the presence of a more prominent Ito giving rise to a more prominent notch in the action potential of right ventricular epicardial cells in males versus females.⁷⁶ Mutations in GPD1-L is a pathogenic cause for a small subset of SIDS as they may precipitate a marked decrease in the peak I_{Na} , thereby creating a potential lethal Brugada syndrome-like proarrhythmic substrate referred to as Brugada syndrome

2.^{73,74} In Japan, Brugada syndrome is estimated to be 0.12 to 0.14%.⁷⁷ Interestingly, a recent study has revealed that sequencing of SCN5A promoter identifies a haplotype variant consisting of 6 polymorphisms in near-complete linkage disequilibrium occurring commonly at an allelic frequency of 22% in Asians, which was absent in white and black patients.⁷⁸ It is speculated that these findings could account for the relatively high prevalence of Brugada syndrome noted in the Asian population.

Sudden infant death syndrome

SIDS is the leading cause of death for infants aged between 1 month and 1 year.⁸ SIDS is etiologically heterogeneous comprising more than one entity and potentially involving several genetic alterations.^{79,80} In general, there is a strong association between SIDS and proxies for socioeconomic status.⁸¹ In USA, it has demonstrated that there is a significant relationship between the degree of poverty in the metropolitan counties and the risk of SIDS for non-Hispanic blacks and whites.⁸² With regard to genetic alterations, they can be either (A) mutations that cause genetic disorders directly leading to SIDS or (B) polymorphisms that predispose SIDS under critical circumstances. Based on clinical, epidemiological, and neuropathological observations in SIDS victims, candidate genes of at least 5 categories have been pursued: (a) genes for ion channel proteins such as KVLQT1 and SCN5A causing congenital long QT syndrome and Brugada syndrome, (b) genes for serotonin transport causing decreased serotonergic receptor binding in the brain stem (c) genes pertinent to the early embryology of the autonomic nervous system (with a link to the 5-HT system) leading to its dysregulation (d) genes for nicotine metabolizing enzymes (e) genes regulating inflammation, energy production, hypoglycemia and thermal regulation.

Recently, in a large-scale collaborative genetic screen, functionally significant genetic variants in LQTS genes have been identified in 9.5% of a Norwegian SIDS cohort of 201 cases, of which 50% are in SCN5A.^{31,83} Of note, S1103Y, a common variant in SCN5A, has been shown to confer susceptibility to acidosis-induced arrhythmia (a gene-environmental interaction), thereby increasing the risk of SIDS in African Americans.⁸⁴ Recently, a CPVT-like phenotype due to mutation in RyR2 has also been

reported to a rare cause of SIDS.⁸⁵

CLINICAL IMPLICATIONS

SCD continues to pose a clinical challenge to practicing physicians. Causes of SCD depend on age, gender, ethnicity and genetics. Preventive medicine is the ultimate goal of medical practice. From a clinical standpoint, various structural heart diseases and arrhythmogenic disorders as described above are potential candidates that can cause SCD. Identification of patients at high risk of SCD can be accomplished by a thorough diagnostic work-up including a detailed history, a complete physical examination along with confirmatory ECG, Chest X-ray, and laboratory tests. In selected cases, further testing with stress exercise with or without thallium scan and/or coronary angiography and magnetic resonance imaging are necessary. Nevertheless, it can not be overstated that an accurate clinical judgment along with a diligent diagnostic work-up is essential. For example, a history of prior syncope especially more than once, a family history of premature death (e.g., < 60 years of age), a critical lesion in the coronary artery (e.g., left main stenotic disease), poor left ventricular function (e.g., EF < 35%) and abnormal ECG findings (e.g., QTc > 450 msec) should alert a physician about the risk of SCD. As a rule, physical exertion is prohibited in any patient with active myocardial ischemia associated with ASHD, and total revascularization with either percutaneous coronary angioplasty or aorto-coronary bypass grafting as early as possible is mandatory for the prevention of SCD. Special consideration should be given to women with ASHD as they often present with atypical symptomatology associated with a worse prognosis.²⁴⁻²⁶ Other cardiac diseases such as HCM, dilated cardiomyopathy, ARVD/C, aortic stenosis, congenital heart disease, anomalous origin of coronary artery, Wolff-Parkinson-White syndrome, congenital LQTS, CPVT, Brugada syndrome, etc. can often be suspected. According to the each individual disease condition, the diagnostic and therapeutic strategies should be individually tailored. Life style adjustment and/or modification, medical therapy, catheter ablation, device implantation (e.g., pacemaker or implantable cardioverter/ defibrillator) or surgical intervention should be appropriately advised.

As it has been advocated molecular genetic analysis in autopsy-negative cases (molecular autopsy)²² is useful

for identifying the likely cause of SCD and this should be extended to the surviving relatives of the SCD victim.²³ Information so obtained can then be applied for risk stratification, for reproductive counseling and for taking preventive measures in the surviving family members. At present, because of cost-effectiveness, it is not advisable to perform molecular genetic analysis in the public.^{10,11,86} However, in selected groups of subjects such as those with strong family history of SCD or premature death, extensive clinical work-up along with molecular genetic analysis for common genetic mutations and/or variants (a clinical and genetic approach)²³ may be justified. Lastly, it is refreshing to learn that a more causative therapy to correct a culprit mutant gene and its products may come to light in the future.^{87,88}

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In the wake of recent demise of the Interior Minister of Taiwan to be, late Mr. Hoong Te Liao (廖風德先生), who died suddenly at the age of 57, this review on the issue of sudden cardiac death can not be more timely appropriate and will serve the purpose of calling physicians, especially cardiologists, to take heed of reinforcing preventive medicine for this tragic complication in their daily practice.

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