## Sudden unexplained death due to cardiac arrest

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**Summary.** Sudden unexplained death due to cardiac arrest refers to a group of heterogeneous heart disorders characterized by sudden cessation of cardiac activity followed by hemodynamic collapse. It may be associated with structural heart disease or may occur in the absence of structural abnormalities. These inherited conditions increase the risk of sudden unexplained death in living relatives when there is a family history of sudden death. It is recommended to screen other family members of sudden unexplained death victims, as studies have revealed affected individuals in 40% of families. (www.actabiomedica.it)

Key words: sudden unexplained death, cardiac arrest, arrhythmia

Sudden unexplained death (SUD) due to cardiac arrest refers to a group of heterogeneous heart disorders characterized by sudden cessation of cardiac activity followed by hemodynamic collapse. In the elderly, it is a relatively common cause of death, mostly due to structural heart disease. In the non-elderly it is less frequent and can be called sudden unexplained death syndrome, which includes all sudden autopsy-negative deaths occurring after the first year of life and involving previously healthy children, adolescents and young adults (1). The world incidence of SUD due to cardiac arrest is 4-5 million cases per year (4).

Sudden unexplained death may be associated with structural heart disease, such as hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic cardiomyopathy and arrhythmogenic syndromes, or may occur in the absence of structural abnormalities, as in the case of long or short QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, early repolarization syndrome, idiopathic ventricular fibrillation, primary arrhythmogenic disorders, Wolff-Parkison-White syndrome or SUD in epilepsy (2,3). Approximately 80% of cases are ascribed to coronary artery disease, 10-15% are associated with non-ischemic cardiomyopathy and 5% are caused by arrhythmic disorders (4). These inherited conditions increase the risk of SUD in living relatives when there is a family history of sudden death. It is recommended to screen other family members of SUD victims, as studies have revealed affected individuals in 40% of families (5). First and second-degree relatives of the deceased should undergo comprehensive cardiovascular evaluation, physical examination, 12-lead electrocardiogram, treadmill stress test, 24-h Holter monitoring and echocardiogram, and full personal and family medical histories should be recorded (6).

Genetic testing is useful for confirming diagnosis of SUD and for differential diagnosis, recurrence risk evalutation and prenatal diagnosis in families with a known mutation. Pathogenic variants may be sequence missense, nonsense, splicing and small indels, as well as large deletions/duplications (Supplementary Table 1). A multi-gene NGS panel is used by MAGI to detect nucleotide variations in coding exons and flanking introns of the above genes. Tests comprehensive of all genes associated with disorders that may lead to sudden unexplained death are not currently listed in Orphanet, but are offered by 16 accredited medical genetic laboratories in the US, listed in the GTR database. The guidelines for clinical use of genetic testing are described by the American Heart Association (7).

## Conclusions

We created a NGS panel to detect nucleotide variations in coding exons and flanking regions of all the genes associated with cardiac disorders. When a family with a previous case of sudden unexplained death comes to our attention we perform the analysis of all the associated genes.

In order to have a high diagnostic yield, we developed a NGS test that reaches an analytical sensitivity (proportion of true positives) and an analytical specificity (proportion of true negatives) of  $\geq$ 99% (coverage depth  $\geq$ 10x).

**Conflict of interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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