Editorial

Surviving Sudden Death

Where Does Next-Generation Sequencing Fit in the Assessment of Sudden Death Victims and Their Families

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The investigation of sudden death is one of the few enduring responsibilities of the coronial system that had its origins in 11th century Britain and was formally established by the articles of Eyre in 1194.[1] People finding a body from a sudden or unnatural death were required to raise a hue and cry and notify the coroner.

See Article by Lin et al

Although the familial nature of sudden death, including structural and electric cardiomyopathies, has been recognized for many decades, British pathologist MJ Davies[2] in 1999 may have been the first to suggest that the family might be approached in the evaluation of sudden cardiac death (SCD). In the same year, Ackerman et al[3] used molecular diagnosis to identify the cause of SCD in a 19-year-old who died after near-drowning, heralding the era of what would be called the molecular autopsy. (Of note, the decedent's mother had a definitely prolonged QT interval) Shortly thereafter, clinical genetic testing for inherited arrhythmia conditions became increasingly available.

Potential approaches to identifying heritable causes of SCD include family assessment, molecular assessment, or a combined approach (see Table).

Behr et al[4] clinically evaluated 147 first-degree relatives of 32 sudden arrhythmia death syndrome victims with a 22% diagnostic yield for the cause of SCD, whereas more recently, in a larger cohort of victims, a 13.5% yield was identified.[5] Recent studies of the molecular autopsy approach using gene panels of varying sizes[6,7,9] or whole-exome sequencing[8] have identified varying diagnostic yields averaging of 13%. Large studies using a combined approach of family assessment combined with molecular diagnosis of decedent or family members provided larger diagnostic yields than family or molecular assessment alone, with an averaged combined diagnostic yield of 31%.[11,13,16–18]

In the current study, Lin et al[14] have performed an evaluation of 89 cardiac channelopathy and cardiomyopathy genes in a sudden unexpected death cohort of 296 decedents, applying a statistical framework to filter candidate causal variants based on factors that include prevalence and penetrance of the diseases related to those variants[15] and reporting the results according to the recent American College of Medical Genetics and Genomics and Association for Molecular Pathology (ACMG) framework.[19] Using these stringent guidelines, they identified 17 pathogenic or likely pathogenic variants in 16 subjects or 5.4% of their cohort.

However, the authors also identify 46 novel variants and 130 variants with allele counts lower than that expected on the basis of their related disease. This finding demonstrates the high stringency of ACMG guidelines, for which novelty or rarity represents only a single moderate criterion for pathogenicity. In the absence of family data (identifying a *de novo* or segregating status for the variant) or a well-established functional assay, such variants will not fulfill pathogenic or likely pathogenic status.

A specific comparison to the recent study of Lahrouchi et al[11] is warranted as that study also applied ACMG criteria. Lin et al[14] used GNOMAD instead of ExAC, and this may have given rise to different minor allele frequencies that may have altered yield in the Lahrouchi article. There is lack of data on frequent rare variants or disease-associated variants in non-white ethnic groups. The Lahrouchi study was predominantly white compared with 50% black in the current study. The lack of available family data limited the ability to upgrade variants of uncertain significance to pathogenic or likely pathogenic. This was helpful in supporting pathogenicity for several novel variants using family segregation or confirmation of de novo variants in the Lahrouchi article.

In parallel with SCD investigation, a system for investigation of survivors of sudden cardiac arrest and their family members is becoming increasingly important. Assessment of sudden cardiac arrest survivors (and their family members) may provide an even higher diagnostic yield than SCD victims[18] because the proband demonstrating the clearest disease penetrance is thus available for both detailed clinical and genetic assessments. In the assessment of such cardiac arrest survivors, clinical assessment again seems to provide a higher diagnostic yield[10] than genetic assessment alone.[12]

The authors are somewhat unique as a large medical examiner's office performing their own sequencing and variant interpretation as opposed to most coroner/medical examiner systems that use commercial laboratories for this work. Although part of the rationale for this is the wide variation of reporting from commercial laboratories, representatives from

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Table. Selected studies of clinical and/or genetic assessment of sudden cardiac death or arrest victims and their families

Year	Author	Jurisdiction	Date Range	Subjects	Number	Genes	Genetic Yield	Clinical Yield	Combined Yield
Family assessment only									
2003	Behr et al[4]	England	2002	Sudden arrhythmic death syndrome (SADS)	32 (147 first-degree relatives)			22% (7/32)	
2014	Giudici et al[5]	London and Milan	2003–2013	Autopsy-negative SUD (1–50 y)	52 families			13.5% (7/52)	
Genetic assessment only									
2017	Dewar et al[6]	Manitoba	1998–2013	Autopsy-negative child SUD ≤5 y	191	71	6.3%		
2014	Wang et al[7]	New York City	2008–2012	Autopsy-negative SUD (0–58 y)	274 (141<1 y)	6	13.5%–19.8%		
2014	Bagnall et al[8]	Sydney	2005–2009	SUD age 1–40 y	28	Exome	10%–31%		
2015	Farrugia et al[9]	Strasbourg		Autopsy-negative SUD age <35 y	16	22	18.8%		
Genetic and family assessment									
2005	Tan et al[13]	Amsterdam	1996–2003	Sudden unexpected death age <40 y	43 families	Targeted based on phenotype	23% (10/43)	40% (17/43)	40% (17/43)
2017	Lahrouchi et al[11]	Multiple	2000–2015 overlapping cohorts	Autopsy-negative SUD age 1–68 y	302	77	13% (40/302) 22% 18/82	26% (21/82)	39% (32/82)
2008	Behr et al[16]	St. George's Hospital, London		Autopsy-negative SUD age 4 to 64 y	57 families	12 Targeted based on phenotype	14% (8/57)	51% (29/57)	53% (30/57)
2013	Hofman et al[17]	Amsterdam	1996–2011	Sudden unexpected death age <45 y	372 families	Targeted based on phenotype	18% (67/372)	25% (93/372)	29% (108/372)
2013	Kumar et al[18]	Melbourne	2007–2012	SUD	109	Targeted based on phenotype			18% (19/109)
Cardiac arrest survivors									
2013	Kumar et al[18]	Melbourne	2007–2012	SCA survivor	52	Targeted based on phenotype			62% (32/52)
2016	Herman et al[10]	Canada	2004–2013	SCA survivor age 18–88 y	200			34%–41%	
2017	Mellor et al[12]	Canada	2006–2015	SCA survivor	174	Targeted based on phenotype	17% (29/174)		

SCA indicates sudden cardiac arrest; and SUD, sudden cardiac death.

such laboratories did contribute to ACMG guidelines and most are now using the ACMG framework for reporting. It seems infeasible for small to moderate coroner/medical examiner programs to reproduce the described system. It would be of interest to know how the variant identification and interpretation process reported compares to that within heritable heart disease clinics in the New York City region and whether hospital-based clinics have to repeat or reinterpret this process once a patient is sent for consultation (a potential problem if systems are not integrated).

Although coroners and medical examiners should provide an opinion about what cardiac disease was or might have been present after a detailed examination and death investigation, this should be seen as only the beginning of the assessment. The evaluation of the family (in which genetic contribution is suspected to have played a role) in subspecialty clinics provides another layer of information that is complementary to death investigation and aligns the responsibility of identifying a familial cardiac condition with those who will care for that family going forward.

Beyond sequencing and variant interpretation, coroner and medical examiner offices and pathologists aim to improve recognition of appropriate pathological entities by integrating investigations with pathological examinations (ensuring identification of the correct phenotype), keeping the needs of inherited arrhythmia clinics in mind and maximizing information transfer, communicating with families, and encouraging families to attend those clinics.

It is equally critical that geneticists and cardiologists embrace the efforts of death investigation systems to assist with these cases. A fruitful approach for the clinical community may involve guiding the efforts of death investigators through education, highlighting examples of appropriately integrated systems, and actively reaching out to pathologists and coroners to improve collaboration and integration of their activities into clinical practice guidelines to establish a standard of care. The cardiac pathology community is a great bridge in this endeavor.

It may be neither appropriate nor rewarding to wait for a molecular autopsy result. After an appropriate mourning period, family evaluation as advised by guidelines[20] yields important clinical diagnoses.[4,13,16] The overall yield of clinical diagnoses in sudden arrhythmia death syndrome families is ≈30% when summarizing currently known studies.[21] Lahrouchi et al[11] found that in 82 families, diagnoses were made in 29% with clinical evaluation and 22% with molecular autopsy. Combined, this yielded 39% of families with clinical and molecular diagnoses, with 8% to 9% sharing clinical and molecular diagnoses. Ideal management, therefore, requires both molecular autopsy and family evaluation to achieve the optimal findings.

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