Founder Mutation Genotyping and Sudden Cardiac Arrest
The Promise of Precision Medicine Fulfilled or the Next Step Into Precise Uncertainty

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After the Human Genome Project, a resulting explosion of genetic information has led to the identification of thousands of new disease-susceptibility genes. This has created the dream of genetic medicine, where the identification of pathogenic mutations would lead to the early diagnosis, treatment, and prevention of disease. This ideal has no more important implications than with respect to sudden cardiac arrest (SCA) and subsequent sudden cardiac death (SCD). SCD stemming from ventricular arrhythmias accounts for \( \approx 300,000 \) deaths annually within the United States alone and is a leading cause of death worldwide. Although the vast majority of these SCDs involve the elderly, thousands of SCDs involve young people and result in a significant number of lost-life-years in general and lost-tax paying-life-years in particular. Furthermore, the unexpected nature of these youthful SCDs has a devastating impact on surviving family members and communities as a whole, leaving many wondering "why did this happen?" and "could it happen to other family members?". Therefore, the ability to identify pathogenic mutations as SCA-predisposing biomarkers holds great promise to save lives and provide answers for these families.

Over the past 15 years, over a hundred genes have been implicated in cardiomyopathies and channelopathies associated with SCA/SCD. The maturation of genetic testing in many of these disorders has now resulted in routine phenotype-driven genetic testing because of the genetic test result’s clear diagnostic, prognostic, and therapeutic impact. Although hundreds of putative pathogenic mutations have been identified in numerous SCA-associated genes, a reduction in sequencing costs has allowed for the sequencing of tens of thousands of individuals, revealing a startling burden of rare genetic variation. This background rate of rare, benign variation in the SCA-associated genes presents a profoundly difficult interpretative conundrum for the referring physician: Is an identified rare variant, the true pathogenic cause of the SCA or is it rare, just there, just because? Even within a specific disease, variant interpretation is not as clear-cut as the dream of precision medicine would entice. These interpretative difficulties within a specific disorder are further compounded in SCA, where a potential lack of phenotypic guidance makes the quagmire of variant interpretation turn the dream of precision medicine into a nightmare.

These difficulties have led to current guidelines that recommend genetic testing for SCA be based on results of a medical evaluation or, in the case of SCA-caused demise, be limited to those cases under the age of 40 where the burden of cardiomyopathies and channelopathies is much higher. Although most of the variants identified in these disorders are rare, novel, and limited to a single individual/family, making interpretation difficult, a handful of clearly pathogenic founder mutations, which could be easily interpreted as biomarkers for those at risk of disease progression or tragically SCA, exist in each disorder.

To that end, Milano et al examined the potential of definitively pathogenic mutations as contributors to SCA in the Dutch community. In this study, the authors compared the frequency of 6 well-vascularized Dutch founder mutations (MYBPC3-p.Trp792fsX17, MYBPC3-p.Arg943X, MYBPC3-p.Pro955fsX95, PKP2-p.Arg79X, PLN-p.Arm14del and the Chr7q36 idiopathic ventricular fibrillation-risk haplotype) among 1440 unselected cases of SCA from the North Holland province of the Netherlands versus ethnically/geographically matched controls. Supporting the role of these founder mutations as biomarkers of SCA in this Dutch community, these mutations were 2.5× more common in the SCA cases than in the controls. Still, however, only a touch over 1% (1.1%) of these cases could be attributed potentially to one of these 6 founder mutations. Similarly, a study recently identified 10 Finnish founder mutations in 1% of an unselected SCD cohort from Finland. The identification of an over-representation in SCA/SCD provides proof-of-principle that these definitive mutations contribute to SCA in the Dutch community.

Although the potential benefit of post-SCA screening for these mutations in homogeneous populations like the Netherlands or Finland seems apparent, such SCA biomarker testing will not be generalizable to a more heterogeneous population, like the United States. In the Dutch population, these 6 founder mutations alone account for as much as 15%
of the particular cardiac disease. Similarly within Finland, 2 founder mutations account for as much as 18% of all hypertrophic cardiomyopathy in that population. In contrast, the heterogeneity of the United States populations causes no single mutation to contribute to >2% of any of the genetic SCA-predisposing disorders. Additionally, an identification rate of only 1 in 200,000 (0.005%) for the 6 Dutch founder mutations in the Exome Aggregate Consortium, a database of over 60,000 exomes drawn from large international cohorts, is dramatically lower than the Dutch prevalence (0.07%–0.4%). Although small pockets of the United States may have a large Dutch population, there will be no clinical utility in genotyping for these founder mutations in the majority of the United States. For so-called precision medicine to work, such SCA biomarker testing must be constrained precisely to the appropriate population. In this example, although it might work in the Netherlands and Finland, it will not in the United States.

The Milano et al study suggests that screening for these clearly pathogenic founder mutations may have merit in SCA in selected populations; however, limiting the genetic analysis to only these variants will miss a substantial genetic component, leaving many cases and families without answers. In previous studies, the rate of genetic discovery in SCA/SCD cases has varied from 11% to 45%, which is at least 10-fold higher than the 1.1% accounted for by the 6 Dutch founder mutations. Furthermore, the role of the clinical evaluation/autopsy cannot be underevaluated because clinical or pathological evidence pointing to a particular disease drastically increases the yield of genetic testing and decreases the confounding background noise by limiting the genetic interrogation to a particular disease gene panel. This reduction in yield for unscreened cohorts of SCA/SCD resulted in current expert guidelines restricting the recommendations for genetic testing to particular clinical phenotypes or in only younger cases of SCD. In fact, in the Milano et al study, a subanalysis by age identified that the overrepresentation of the 6 founder mutations in SCA was driven by cases <50 years of age, where the yield of these mutations was 7-fold higher than in the controls. The lack of overrepresentation in the older cases, from the Milano et al study, suggests that adherence to the existing guidelines would have yielded the majority of cases hosting these founder mutations.

Given the clear genetic predisposition for the development of either MYPBC3-mediated hypertrophic cardiomyopathy, PKP2-mediated arrhythmogenic cardiomyopathy, PLN-mediated arrhythmogenic cardiomyopathy, or Chr7q36-mediated idiopathic ventricular fibrillation that has been established with these 6 founder mutations, it is at first glance disconcerting that as many as 1 in 250 (0.4%) of the ethnically/geographically matched controls hosted one of these founder mutations: a frequency surpassing the prevalence of most diseases that are already included on many newborn screening panels. Again, the Finnish study also identified that as many as 0.8% of the Finnish population hosted one of the 10 Finnish founder mutations. Based on these frequencies, it is tempting to consider the merits of not only a founder mutation-specific molecular autopsy in these countries but also universal, premortem SCA screening for these founder mutations in these respective countries to enable the early identification of individuals shown to be at increased relative risk for the tragic end point of premature SCA and SCD.

However, before succumbing to this temptation to screen for these particular genetic heart disease- and SCA-predisposing founder mutations in either SCA cases or even universal screening in these founder mutation-prone countries, what precisely is going to be the drill for the 1:100 to 250 members of the Dutch population who will be founder mutation positive. Will they be the beneficiary of precision medicine or will they be stuck precisely in incomplete penetrance oblivion? Yes, the owner of one of these founder mutations can be given the prognostic forecast that he/she may be at 2.5-fold greater odds of SCA compared with his/her founder mutation negative neighbor. But, will the patient understand also that he/she has a good chance (with the exact forecast being precisely uncertain) of never expressing the disease phenotype for which that founder mutation confers susceptibility. Even among the clearly pathogenic founder mutations, the penetrance may be only as high as 60%, and for many mutations, this may be drastically lower. Nevertheless, because we now know who you are, we will be duty bound to do some level of cardiac testing (ie, the drill) periodically to see if/when you declare yourself as not only founder mutation genotype positive, but also disease phenotype positive.

Despite the recent renaissance of genetic medicine, the difficulties toward achieving genetic results that can warrant decisive clinical action has been limited by an increasingly recognized genetic background noise. The authors of this study should be applauded for their effort to address the often difficult nature of genetic testing in SCA by showing the potential advantage for screening of founder mutations within these homogeneous source populations. However, this screening approach is limited in heterogeneous populations and may severely underestimate the genetic burden for SCA when clinical/pathological evidence is evaluated in conjunction with genetic testing. Although founder mutation screening for not only the sudden dead but the still living is appealing at first blush, it is clear that even in this set up that seemingly enhances the potential for precision medicine, the way forward remains precisely unclear.

Disclosures

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References


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