



The Promise and Peril of Precision Medicine: Phenotyping Still Matters Most

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Abstract

We illustrate the work necessary to reverse course after identification of a *KCNQ1* variant interpreted erroneously as causing long QT syndrome (LQTS) and to identify the true cause of a case of sudden death in the young. Surrogate genetic testing of a decedent's living brother identified a rare *KCNQ1*-V133I variant, which prompted an implantable cardioverter defibrillator and subsequent diagnosis of LQTS in other family members. Subsequently, this presumed LQT1 family came to our institution for further clinical evaluation and research-based investigations, including *KCNQ1*-V133I variant-specific analysis of the decedent, heterologous expression studies of *KCNQ1*-V133I, and a whole-exome molecular autopsy along with genomic triangulation using his unaffected parents' DNA. After evaluating several V133I-positive family members, clinical doubt was cast on the veracity of the previously levied diagnosis of LQT1, resulting in a re-opening of the case and an intense pursuit of the lethal substrate. Furthermore, the decedent tested negative for V133I, and heterologous expression studies demonstrated a normal cellular phenotype for V133I-containing Kv7.1 channels. Instead, after whole-exome molecular autopsy, a de novo pathogenic variant (p.R454W) in *DES*-encoded desmin was identified. As detailed herein, the forensic evaluation of sudden death in the young requires meticulous focus on the decedent followed by a careful and deliberate assessment of the decedent's relatives. Surrogate genetic testing can have disastrous consequences and should be avoided. Genetic test results require careful scrutiny to avoid unintended and potentially devastating repercussions. Although the root cause of the decedent's tragic death would have remained a mystery, the unintended consequences for the living relatives described herein might have been avoided based on clinical grounds alone. All family members had electrocardiograms with normal QT intervals, making the diagnosis of familial LQTS unlikely. As such, if the clinicians caring for these patients had focused solely on clinical data from the survivors, there might have been no reason to embark on a path of inappropriate treatment based on genetic testing.

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Sudden cardiac death is a major worldwide public health burden with an estimated annual incidence ranging from 180,000 to 450,000¹ in the United States and as many as 3.7 million deaths globally.² Among these sudden deaths in the United States, approximately 2000 to 5000 young people aged 1 to 35 years die suddenly.³ For many of these sudden deaths in the young (SDYs), comprehensive medicolegal investigations that include a conventional autopsy examination elucidate a clear cause of death. However, in up to 50% of these cases, gross and microscopic inspection of the heart does not reveal a definite cardiac etiology.⁴ These deaths are often termed autopsy-negative sudden unexplained death (SUD).⁵

Potentially lethal and heritable cardiac channelopathies, such as long QT syndrome (LQTS),

catecholaminergic polymorphic ventricular tachycardia (CPVT), and Brugada syndrome, are associated typically with grossly and histologically normal hearts and may account for a significant portion of SUDs. In addition, heritable cardiomyopathies, including hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy, and arrhythmogenic cardiomyopathy, can display minimal structural abnormalities deemed inconclusive.

Recently, guidelines for autopsy investigations of SDY cases stipulate procurement and retention of tissue suitable for DNA extraction as a class I recommendation and advise that postmortem genetic testing (ie, the molecular autopsy) be considered the new standard of care in the decedent's evaluation.⁶⁻⁸ Herein, we illustrate how antemortem surrogate

genetic testing can have devastating consequences and how the whole-exome molecular autopsy (WEMA) with genomic triangulation provided closure and clarity for an SDY family. In addition, the miscues in phenotypic assessment of the living and the dead along with the erroneous interpretation of the genetic test results showcase some of the challenges in making the promise of precision medicine a reality and serve as a vivid reminder that phenotyping still matters most.

MATERIALS AND METHODS

Study Participants

A Hispanic family with a previously rendered diagnosis of autosomal dominant LQT1 came to Mayo Clinic in Rochester, Minnesota, for a second opinion evaluation after the sudden death of their 13-year-old son. Importantly, a genetic evaluation of the deceased son's sample (ie, post-mortem genetic testing, also known as the molecular autopsy) was not performed before the family's second opinion evaluation. Instead, "surrogate" genetic testing of the decedent's unaffected living brother revealed *KCNQ1-V133I*, which was interpreted elsewhere as an LQT1-causative mutation. After receiving written informed consent for this Mayo Clinic Institutional Review Board-approved study, peripheral blood samples from the 3 living family members (father, mother, and brother) and a blood spot card taken at autopsy from the boy with SDY were collected for genomic DNA isolation and further genetic interrogation. This study was conducted from September 2012 through May 2016.

KCNQ1-V133I Variant-Specific Analysis of the Decedent's Sample

After genomic DNA isolation from the decedent's autopsy specimen, *KCNQ1-V133I* variant-specific analysis was performed using standard DNA dye terminator cycle sequencing protocols as described previously.⁹

Heterologous Expression Studies of *KCNQ1-V133I*

The *KCNQ1-V133I* variant was engineered into wild-type (WT)-*KCNQ1* (Kv7.1) complementary DNA as previously described.¹⁰ The integrity of the construct was verified by DNA sequencing

(Advanced Genetic Technologies Center, University of Kentucky).

Human embryonic kidney (HEK293) cells were transfected transiently with WT (3 μ g), V133I (3 μ g), or WT (1.5 μ g) plus V133I (1.5 μ g) plasmid DNA using the SuperFect reagent (Qiagen) as previously described.¹⁰ *KCNE1* (3 μ g) and green fluorescent protein (0.3 μ g) plasmid DNA were co-transfected for all experiments. *KCNE1* is required to generate I_{K_S} -like current in heterologous expression systems.¹¹ The cells were cultured in minimum essential medium supplemented with 10% fetal bovine serum at 37°C and were analyzed 24 to 30 hours after transfection.

The standard whole-cell patch clamp procedure was performed on green fluorescent protein-positive HEK293 cells as previously described.¹⁰

Statistics for Cellular Electrophysiology Studies

Electrophysiologic data are reported as the mean \pm SE. A paired or unpaired *t* test was performed when appropriate to determine whether values were different from one another. For comparison of 3 or more groups, a 1-way analysis of variance was performed. If the analysis of variance showed a $P < .05$, then a post hoc Tukey multiple comparison test was used to identify which data sets were significantly different at $P < .05$.

WEMA and Genomic Triangulation

Whole-exome sequencing (WES) and subsequent variant annotation (Advance Genomics Technology Center and Bioinformatics Core Facilities, Mayo Clinic) were performed on genomic DNA derived from the deceased child, the unaffected father, and the unaffected mother as previously described.¹²

After WES, single nucleotide variants and insertion/deletions (INDELs) were filtered to identify variants that followed a sporadic, autosomal dominant, or autosomal recessive inheritance pattern using VarSeq software (Golden Helix Inc). All variants were first filtered for a call quality score of at least 20 and a read depth of at least 10. To be considered a candidate pathogenic variant, the variant identified in the child had to be nonsynonymous (ie, amino acid altering; missense,

nonsense, splice-error, frameshift INDEL, or in-frame INDEL).

For the sporadic and autosomal dominant models, only rare variants (minor allele frequency [MAF] <0.00005 in the Exome Aggregation Consortium [ExAC] database) that were absent in the exomes of both parents (sporadic) or present in either the mother (autosomal dominant, maternally derived) or father (autosomal dominant, paternally derived) were considered. For the recessive inheritance model, only rare variants (MAF <0.005 in the ExAC database) present as either homozygotes (same mutation inherited from each parent) or compound heterozygotes (2 unique mutations in the same gene each inherited from a different parent) were considered.

The remaining filtered variants then underwent gene-specific surveillance for all known channelopathy- and cardiomyopathy-susceptibility genes (N=100).¹³ The American College of Medical Genetics and Genomics (ACMG) standards and guidelines for the interpretation of sequence variants was used to assist in assessment of the genetic findings.¹⁴

Candidate disease-causing variants identified through WES were confirmed in the decedent and his parents' genomic DNA samples using standard polymerase chain reaction and Sanger sequencing methods. The polymerase chain reaction primers, conditions, and sequencing methods are available on request.

RESULTS

Initial Case Description

The index case was a previously healthy 13-year-old Hispanic boy (weight, 72.6 kg) who died suddenly during sleep. Significant findings from his autopsy included a heart weight of 430 g, a left ventricular wall thickness of 17 mm, mild fiber disarray noted throughout the left ventricle, diffuse areas of firm gray white fibrosis in the papillary muscles, and marked endocardial fibrosis in the left atrium. Despite these stated necropsy findings, the medical examiner deemed the autopsy inconclusive for a specific cardiomyopathy. No second opinion from a cardiac pathologist was sought.

After the adolescent's death, his parents and brother were evaluated clinically elsewhere. Although the results of initial cardiologic testing were normal for all, the brother's 21-day event monitor captured a brief episode of paroxysmal supraventricular tachycardia that was interpreted as nonsustained ventricular tachycardia. The brother's death (perceived to be inadequately explained after autopsy) and now this ambulatory electrocardiographic (ECG) finding prompted their physician to render a diagnosis of familial LQTS and to implant a prophylactic defibrillator. Thus far, 2 inappropriate shocks have been delivered.

Subsequently, the commercial genetic test performed on a sample from the living brother identified the presence of the variant *KCNQ1-V133I*, which was annotated by the commercial gene test company as a "probable deleterious mutation." Accordingly, it was concluded that there was now clinical and genetic evidence of LQT1. The medical examiner's office was updated with this information, and the autopsy report was amended, concluding that the cause and manner of death was a lethal LQT1-triggered ventricular arrhythmia. Believing that the genetic test result had provided closure and clarity, variant-specific cascade genetic testing was performed throughout the father's side of the family, leading to the eventual diagnosis of LQT1 in more than 2 dozen family members (data not shown).

Second Opinion Clinical Evaluation in Living Relatives With *KCNQ1-V133I*

Subsequently, the surviving brother, both parents, and several other V133I-positive distant relatives sought a second opinion evaluation at Mayo Clinic. None of them had personal symptoms suggestive of an LQTS-triggered cardiac event, and none had ECG evidence, at rest or with treadmill stress testing, to generate an index of suspicion for LQTS in general or LQT1 in particular.

Specifically, the V133I-positive, defibrillator-implanted brother had resting QTc values of 408 and 431 milliseconds on 2 consecutive days (Figure 1). In addition, his QT and QTc values were normal at rest (405, 409, and 384 milliseconds while sitting, lying, and standing, respectively), during

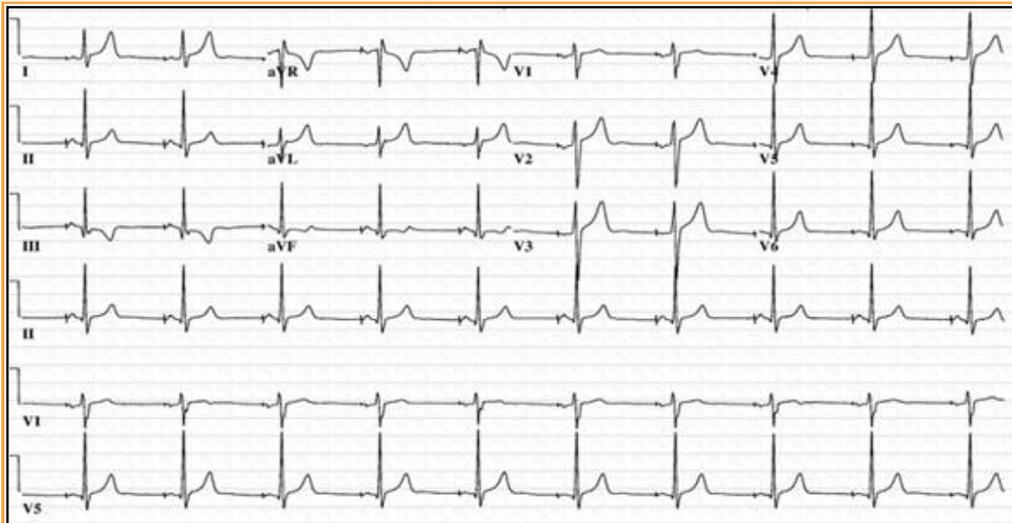


FIGURE 1. Representative 12-lead electrocardiogram for the *KCNQ1*-V133I-positive living brother of the boy with sudden death in the young. Note the normal QTc and normal T wave architecture, as well as an atrial-paced rhythm associated with the implanted pacemaker-defibrillator.

exercise (416 milliseconds at 1 minute and 443 milliseconds at his peak heart rate of 151 bpm), and, most importantly, during the recovery phase of his stress test, where his recovery phase QTc values were 417, 455, and 436 milliseconds at 1, 3, and 5 minutes, respectively (data not shown).

Postmortem *KCNQ1*-V133I Genetic Testing and Subsequent Heterologous Expression Studies of *KCNQ1*-V133I

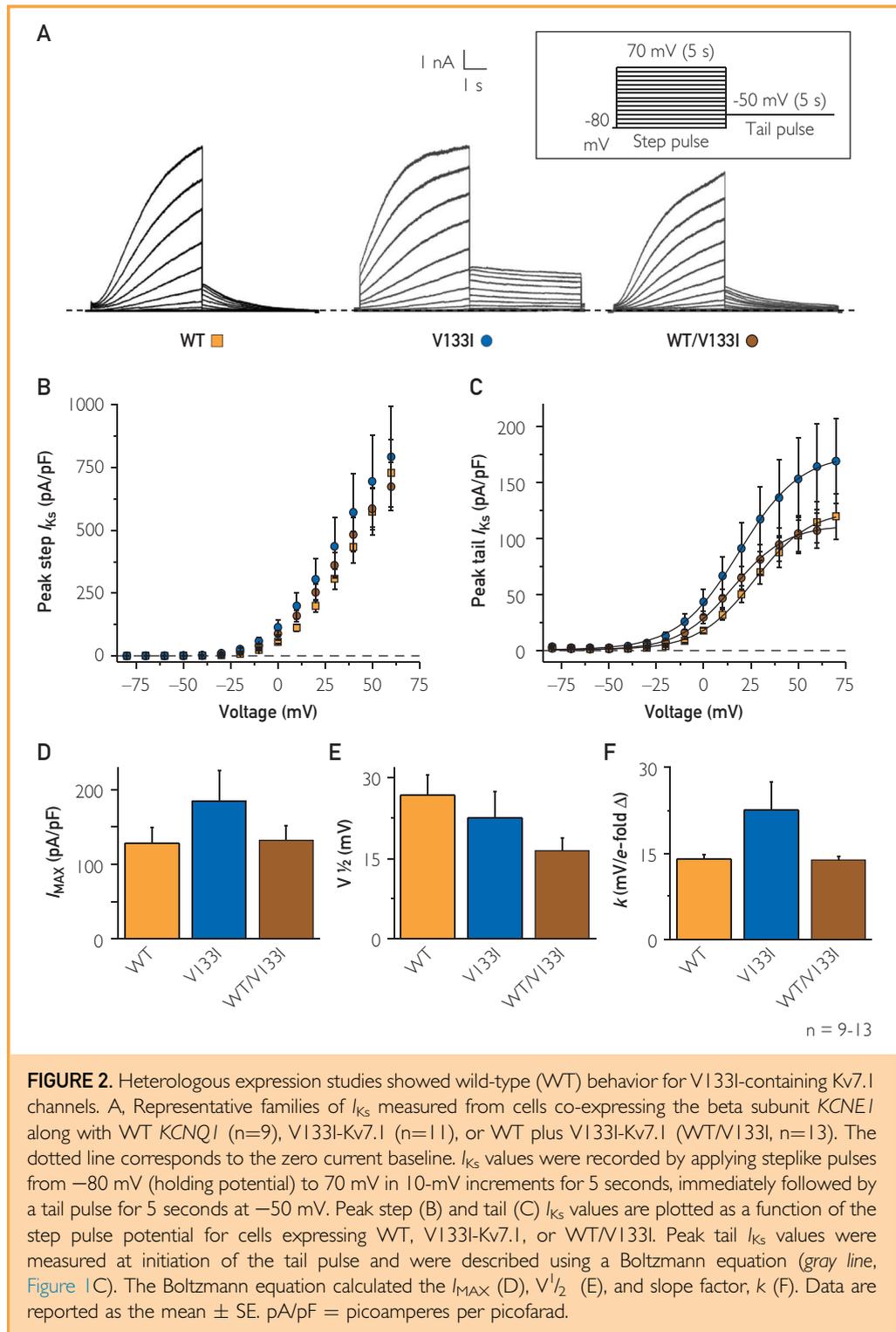
After receiving a blood spot card from the deceased individual, variant-specific testing was performed, and the only heretofore symptomatic individual (ie, the boy with SDY) tested negative for *KCNQ1*-V133I. Although the lack of clinical evidence for LQT1 in the living relatives and now the absence of V133I in the decedent made the case for causality weak, we nevertheless functionally characterized this variant because it localized to the S1 transmembrane domain of the *KCNQ1*-encoded Kv7.1 potassium channel and was rare, being observed in only 1 of 33,355 white individuals (MAF=0.00001499) in the ExAC database. Heterologous expression studies elicited no evidence of a loss-of-function biophysical phenotype typically seen for LQT1-causative mutations (Figure 2).

WEMA and Genomic Triangulation Reveal a Sporadic Mutation, R454W, in *DES*-Encoded Desmin

After dismissing *KCNQ1*-V133I as rare but irrelevant to this family, a WEMA was performed to find the root cause. Specifically, the decedent's DNA and both unaffected parents' DNA underwent WES. The genetic results were first filtered considering either a sporadic recessive (homozygous or compound heterozygous) or autosomal dominant inheritance pattern (Figure 3).

After WES, 137,728 total variants were identified for this family trio. Of these, 71,066 variants had a call quality score of at least 20 and a read depth of at least 10. To be conservative in the sporadic approach, we limited these variants to those with an MAF of 0.00005 or less in the ExAC database, yielding 31,057 variants, of which 216 represented nonsynonymous variants. Parental exome subtraction from the index case's exome yielded 8 sporadic variants (identified in the case and absent in both parents) in 8 different genes.

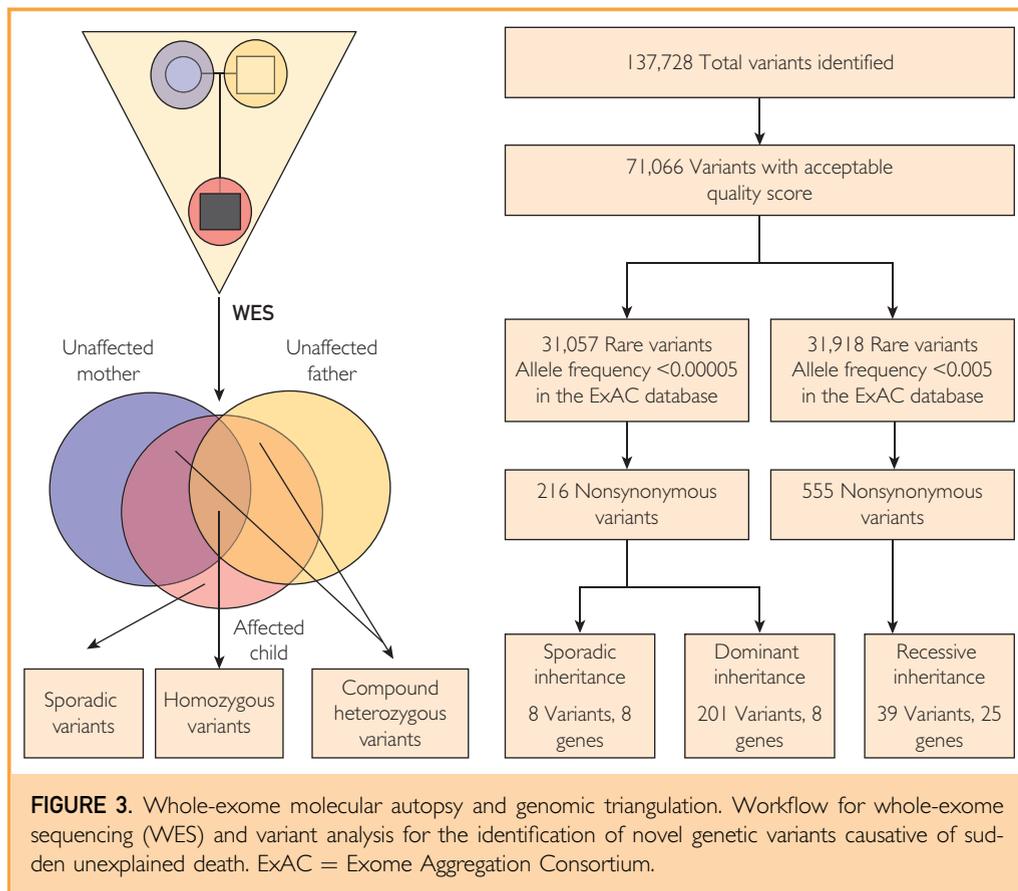
For the recessive model, we first limited the 71,066 variants to include only rare variants with an MAF of 0.005 or less in the ExAC database. This resulted in 31,918 variants, of which 555 were nonsynonymous.



After index case—parent exome subtraction/inclusion criteria fitting a recessive inheritance pattern, there were 35 compound heterozygous variants in 21 genes and 4 autosomal

homozygous recessive variants in the 4 genes that remained.

In addition, we considered an autosomal dominant inheritance pattern with the



possibility of incomplete penetrance. Using the same initial filtering method as was applied for the sporadic model but then accounting for autosomal dominant inheritance yielded 201 variants: 110 derived paternally and 91 derived maternally.

After rare variant and specific inheritance pattern filtering, the 8 sporadic variants, 4 recessive homozygous variants, 35 recessive compound heterozygous variants, and 201 autosomal dominant variants were scrutinized with respect to the 100-sudden death gene panel that comprises all genes currently known to cause LQTS, CPVT, Brugada syndrome, HCM, dilated cardiomyopathy, or arrhythmogenic cardiomyopathy. This sudden death gene panel surveillance yielded 2 rare nonsynonymous variants (*DES-R454W* and *RYR2-Y3891F*) as potential candidates responsible for the sudden death. Both variants were confirmed by Sanger sequencing as present in the person with SDY. Whereas the *RYR2-Y3891F* variant

was derived paternally, the *DES-R454W* variant was absent in both parents and, thus, was confirmed to be a sporadic de novo variant in the boy with SDY (Figure 4A).

Genetic Variant Interpretation

The paternally derived variant (c.11672A>T) annotated as p.Y3891F in the *RYR2*-encoded cardiac ryanodine receptor/calcium release channel was also present in the decedent's brother. Pathogenic *RYR2* variants represent the most common cause of autosomal dominant CPVT.¹⁵ However, neither the living brother nor the father displayed any clinical evidence of CPVT; specifically, they both had normal treadmill stress test results. Furthermore, *RYR2-Y3891F* localizes to one of *RYR2*'s uninterpretable exons (exon 87), where variants identified in this region only have an estimated predictive value of 35%, and that is in the setting of a high index of suspicion for CPVT.¹⁶ Based on the current

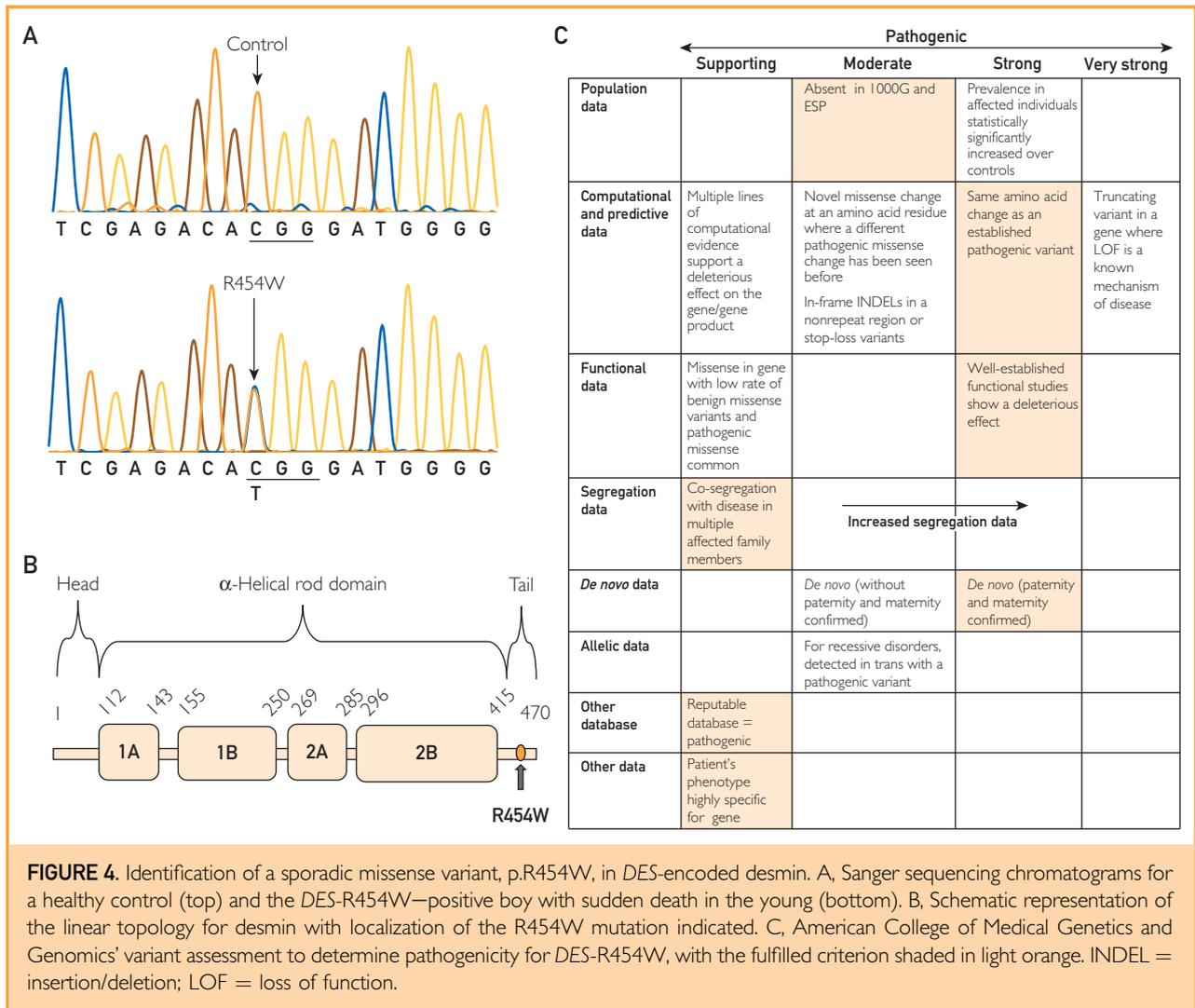


FIGURE 4. Identification of a sporadic missense variant, p.R454W, in *DES*-encoded desmin. **A**, Sanger sequencing chromatograms for a healthy control (top) and the *DES*-R454W–positive boy with sudden death in the young (bottom). **B**, Schematic representation of the linear topology for desmin with localization of the R454W mutation indicated. **C**, American College of Medical Genetics and Genomics' variant assessment to determine pathogenicity for *DES*-R454W, with the fulfilled criterion shaded in light orange. INDEL = insertion/deletion; LOF = loss of function.

knowledge and the ACMG guidelines for variant adjudication, RYR2-Y3891F would be classified as a variant of uncertain significance.

In contrast, the decedent's sporadic de novo variant (c.1360 C>T) annotated as p.R454W in the *DES*-encoded desmin protein would be classified as a pathogenic variant. In fact, desmin has been implicated previously in HCM and is a muscle-specific, type III intermediate filament that integrates the sarcolemma, Z disk, and nuclear membrane in sarcomeres and regulates sarcomere architecture.¹⁷⁻¹⁹ This variant, p.R454W, resides in a highly conserved B-turn structural motif (Thr-Arg-Asp-Gly) in desmin's tail domain, and the substitution of an arginine (R) for a bulky aromatic tryptophan (W) residue is

most likely responsible for pronounced filament instability (Figure 4B). In vivo and in vitro studies of p.R454W have shown a dramatic effect on filament formation.^{20,21} Furthermore, this precise variant (p.R454W) was described previously as a sporadic pathogenic mutation in a 15-year-old boy who developed exercise intolerance and HCM, leading to cardiac transplantation at age 25 years; he subsequently developed slowly progressive muscle weakness.²⁰ This pathogenic variant was also described in a small autosomal dominant pedigree characterized with cardiomyopathy, heart failure, and death by age 31 years in an affected father and both of his affected children, who died after heart failure at ages 27 and 28 years.²²

Based on this information, the ACMG guidelines would classify *DES-R454W* as a pathogenic variant (Figure 4C).¹⁴ Considering the normal comprehensive cardiovascular evaluation in both parents and recalling the original autopsy findings of an enlarged heart and microscopic myocyte disarray in the deceased child, the case for causality of sporadic *DES-R454W* is strong.

DISCUSSION

The profound tragedy of an SDY was compounded further by a subsequent journey that resulted in the misdiagnosis of familial LQT1 secondary to *KCNQ1-V133I* in more than 20 relatives and treatment with an implantable defibrillator, which has delivered 2 inappropriate shocks, in the decedent's otherwise healthy and asymptomatic brother. Only after seeking further evaluation was final closure and clarity achieved, namely, a tragic sudden death stemming from a sporadic, desmin-mediated cardiomyopathy with no evidence of a discernible channelopathy/cardiomyopathy in the living. This case highlights several critical issues that must be adhered to and respected for the promise of so-called precision medicine to be fulfilled.

First, surrogate genetic testing of the living is a dangerous and potentially misleading substitute for genetic testing of the dead.²³ Recently, several expert consensus guidelines have called for practice standardization of autopsies in young sudden unexpected deaths and have recommended postmortem genetic analysis in structural and nonstructural genetically determined heart disease.⁶⁻⁸ One of the most important recommendations is that appropriate "DNA-friendly" biological material, such as blood in EDTA, blood spot on a filter card, or frozen heart tissue, is retained at autopsy for future genetic testing. Importantly, in SUD cases where no DNA-friendly material was collected, genetic testing should not be initiated in any living family relatives unless a clear disease phenotype is present.²⁴ Although a blood spot card was retained in this case, surrogate genetic testing was chosen instead of the molecular autopsy, precipitating an undesirable chain reaction.

Second, although not yet mandated as standard of care, this case supports the notion that a decedent-centric WEMA may be a far

more accurate and cost-effective approach for the investigation of not only individuals with SDY but also their next of kin. The current standard of care is for the surviving first-degree relatives to undergo some sort of cardiologic investigation after their family member's sudden death. Periodic cardiologic tests depend on the results of the primary evaluation. As illustrated herein, the present approach resulted in not only misdiagnosis and overtreatment but also costs that were 20-fold greater than what would have been incurred had a molecular autopsy been performed instead. Although formal cost-effectiveness studies need to be performed, it seems obvious that an initial decedent-focused investigation, including molecular autopsy, followed by a secondary clinical and genetic evaluation of the living guided by the test results from the dead will be more precise and will save money.

Third, even when a genetic test company renders an interpretation of "probable deleterious mutation," do your own homework. Just as it would be frowned on to rely on an ECG company's automated interpretation rather than to study the ECG yourself and render your own interpretation, the same expectation must be applied to genetic test reports. However, we often neglect this responsibility because the current genetics understanding and interpretation skills of the practicing physician in general or the cardiologist in particular ranks far below his or her ability to interpret other tests, such as an ECG. At minimum, make sure that there is concordance with both the genotypic and phenotypic data. Remember the mantra that "phenotype is king, genotype is queen," and if the subjectively and objectively ascertained phenotype is not matching the alleged genotype, stop and reassess.²³ In other words, phenotyping still matters most.

In this case, there was complete discordance between the alleged genotype, *KCNQ1-V133I*, and the phenotype. Not only did the only relative with a phenotype of concern (ie, sudden death) test negative for this variant, those who tested positive for this variant did not exhibit the ECG stigmata associated with LQT1. Unfortunately, there was no corroboration of the ascertained phenotype and the elucidated genotype. In

the absence of any phenotypic data, the genetic test company adjudicated the variant as being a pathogenic/deleterious *KCNQ1* variant based on its own internal variant calling algorithm. As recently demonstrated for the other two canonical LQTS-susceptibility genes, *KCNH2* and *SCN5A*, there is total heterogeneity among the various genetic test companies as to how they prosecute a variant and whether they deem it as guilty as charged (pathogenic), innocent (benign), or insufficient evidence (variant of unknown/uncertain significance).²⁵

On the other hand, the ordering physician did not perform his or her due diligence to see whether he or she concurred with the genetic test company's verdict. Even in the absence of the heterologous expression data that were obtained showing WT behavior for the *KCNQ1*-encoded Kv7.1 channels containing this variant, a healthy dose of skepticism should have been raised by the absence of any discernible phenotype for either LQTS in general or LQT1 in particular for those hosting this *KCNQ1* variant. More than a decade ago, we sounded the alarm after discovering that approximately 3% to 5% of seemingly healthy white people and 4% to 8% of nonwhite people hosted a rare nonsynonymous single nucleotide substitution (ie, missense variant) in 1 of the 3 major LQTS-susceptibility genes, debunking the incorrect notion that such critical genes would not be host to rare, amino acid-altering genetic variations.^{26,27}

Before this revelation, because seeming rarity was equated with pathogenicity, we and the collective scientific community of mutation finders had a low hurdle to jump over to assert that a new variant of interest in an established bona fide disease-susceptibility gene was, in fact, a disease-associated variant (ie, a pathogenic mutation). Back then (just 10-15 years ago), the industry standard was to probe 50 controls to ensure that the variant of interest was not present in 100 alleles. If not, another new disease-associated variant was declared. Then, the stringency was increased to 100 controls (ie, 200 alleles) and then to 400 controls (ie, 800 alleles) to make a statistical declaration that if a case-associated variant of interest was absent among those 400 controls, then there was 95% confidence that the variant's true MAF

was less than 0.005, making it below the polymorphism threshold.

So, the mere presence of a rare variant in a bona fide LQTS-susceptibility gene should not compel a pathogenic, probably deleterious variant rendering. Furthermore, secondary to the aforementioned flaw in the variant case-control studies of the past, just because a variant has been sanctioned in the published literature as a disease-associated variant, this does not guarantee that variant's pathogenicity. We and others have estimated that at least 10% of the variants published as LQTS-associated mutations (including those published by our research team) may have been classified erroneously.^{28,29} Moreover, beyond the field of cardiology, a recent study indicated that as many as 30% of all disease-causing genetic variations cited in the literature may be misinterpreted variants.³⁰ Indeed, the human "incidentalome" is far more expansive than originally contemplated.³¹

Herein, the ordering physician accepted the conclusion of the genetic test company's report rather than weighing the evidence in the balance and finding it wanting. Given the circumstances, this should have been viewed at most as an incidental finding and recognizing that approximately 1 in 6000 individuals have *KCNQ1*-mediated LQTS (ie, LQT1) and at least 1% of healthy individuals host rare *KCNQ1* variants, there would have been 60 to 1 odds of predicting it to be benign. Then, with the correct clinical realization that there were no phenotypic stigmata to implicate LQT1 in the first place, any residual possibility or probability of pathogenicity should have vanished completely.

Although perhaps a bit tangential to this illustrative family study, the findings do exemplify the clear and present danger associated with the ACMG's 56-gene "hit list" whereby variants adjudicated as potentially or probably deleterious are to be reported back as "incidental findings" when detected in the context of WES or whole-genome sequencing diagnostic odyssey cases, for example.³² All 3 canonical LQTS-susceptibility genes (*KCNQ1*, *KCNH2*, and *SCN5A*) reside on this hit list. Somewhat akin to this study, the senior author (M.J.A.) is already aware of more than 1 patient on a diagnostic odyssey who became the recipient of an implantable cardioverter

defibrillator after the identification of an incidental variant in one of these bona fide, irrefutable disease genes. At minimum, the ACMG should convene urgently a panel to provide further clarification and guidance as to which genes really belong on this hit list and what should be the expected clinical response when a patient hosts 1 or more variants within these genes.

The interpretation of findings has always been and will always be a cornerstone of genetic interrogation and precision medicine. To this end, multidisciplinary care is crucial for managing families after an SUD. The integration of cardiologists, geneticists, pathologists, genetic counselors, nurses, and patient support groups is essential for covering the broad range of management issues that arise after a tragic sudden death. It is critical that this diverse group of health care providers include one whom is well versed in the art and science of genetic variant interpretation. Although effectively conveying information to surviving family members and providing psychological and emotional support is crucial, it is just as important that pathologists, physicians, and geneticists communicate clearly and intentionally to achieve a unified diagnosis. Ideally, any potentially relevant findings from autopsy, even if inconclusive, should be shared with the cardiologist who cares for the surviving family members. This information, along with findings from clinical tests of the family, should be used to guide genetic testing. Results of genetic testing should be viewed through the phenotypic lens previously derived from necropsy findings in the deceased and clinical test results from the living. Genetic variants that correlate with a phenotype must further be evaluated by someone qualified to assess the pathogenicity of said variant, and functional characterization may be required. Only once the pathogenicity of a mutation has been demonstrated should this information be shared with a family.

CONCLUSION

Genetic testing is a powerful tool, but it can also be a dangerous weapon. Herein, a WEMA provided closure and clarity for a family that had suddenly lost a son. However, this enlightened conclusion followed on the heels of a misdiagnosis that affected several family

members, stemming from an inappropriate use of genetic testing and an incorrect interpretation of the genetic test results. Although the technological advances in genetic sequencing have been exponential, our ability to interpret the results has not kept pace. Now more than ever, we as care providers need to work together and become more knowledgeable about the tools we use to reliably provide answers and recommendations for the families that have been entrusted to us. In essence, we must become wiser users of genetic testing and even wiser interpreters of the genetic test results so that the promise of precision medicine can be realized. More than ever, we must also strive to be wise clinicians who recognize that phenotyping still matters most.

Abbreviations and Acronyms: ACMG = American College of Medical Genetics and Genomics; CPVT = catecholaminergic polymorphic ventricular tachycardia; ECG = electrocardiogram; ExAC = Exome Aggregation Consortium; HCM = hypertrophic cardiomyopathy; INDEL = insertion/deletion; LOF = loss of function; LQT1 = long QT syndrome subtype 1; LQTS = long QT syndrome; MAF = minor allele frequency; pA/pF = picoamperes per picofarad; SDY = sudden death in the young; SUD = sudden unexplained death; WEMA = whole-exome molecular autopsy; WES = whole-exome sequencing; WT = wild type

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