Prevalence and potential genetic determinants of young sudden unexplained death victims with suspected arrhythmogenic mitral valve prolapse syndrome

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BACKGROUND Mitral valve prolapse (MVP) is largely considered a benign condition. However, MVP is over-represented consistently in sudden unexplained death in the young (SUDY) cohorts.

OBJECTIVE To determine the prevalence and potential genetic underpinnings of suspected arrhythmogenic MVP in a referral cohort of SUDY cases.

METHODS In this retrospective study, medical records/autopsy reports and whole exome molecular autopsy (WEMA) results for 77 SUDY victims (27 female; average age at death 20.6 ± 8.9 years) were reviewed for evidence of myxomatous MVP and left ventricle (LV) fibrosis. Variants detected in the prespecified 147 WEMA gene panel with a minor allele frequency ≤ 0.001 in public exomes/genomes were classified using the 2015 American College of Medical Genetics (ACMG) guidelines.

RESULTS Overall, 6 of 77 (7.8%; 2 female; average age at death 20.7 ± 6.9 years) SUDY cases had MVP as the lone abnormal postmortem finding. The majority had bileaflet involvement (5/6; 83%) and microscopic LV fibrosis (5/6; 83%). In 2 SUDY cases (33%), subjects were diagnosed with MVP by echocardiography prior to death. Unexpectedly, an ACMG pathogenic/likely pathogenic (P/LP) was more likely to be detected in SUDY cases with MVP than those without (3/6 [50%] vs 9/71 [13%]; P < .05). Interestingly, the 3 variants identified in MVP-positive SUDY cases localized to genes associated previously with a cardiomyopathy/channelopathy predisposition (p.E1518fsX25-DMD, p.S285N-RYR2, and p.R109X-TTN).

CONCLUSION This WEMA series provides additional evidence that the combination of MVP and LV fibrosis underlies an unexpected number of SUDY cases. Whether P/LP variants in cardiomyopathy/channelopathy-susceptibility genes contribute to the pathogenesis of arrhythmogenic MVP requires further investigation.

KEYWORDS Cardiomyopathy; Genetics; Mitral valve prolapse; Sudden cardiac death; Ventricular fibrillation

Introduction
Sudden unexplained death in the young (SUDY) is defined as the natural, unexpected death of an individual between the ages of 1 and 40 years in the absence of a specific root cause/diagnosis following a comprehensive medicolegal investigation with autopsy. Following the introduction of the channelopathic molecular autopsy in 2001, it has become increasingly clear that pathologically silent cardiac channelopathies as well as arrhythmogenic cardiomyopathies in a precardiomyopathic electrical phase are responsible for at least one-third of SUDY cases. Nevertheless, even with the additive power of molecular and expanded family investigations, an underlying root cause is still not identified for the majority of SUDY cases.

Although mitral valve prolapse (MVP) is relatively common (2%–3% of the general population) and often considered benign, the annual rate of sudden cardiac death (SCD) in individuals with MVP (0.2%–0.4%/year) is roughly twice that observed in the general population (0.1%–0.2%/year). Much of this increased SCD risk is attributable to left ventricular dysfunction in the setting of severe mitral regurgitation.

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KEY FINDINGS

- Consistent with prior studies, the prevalence of autopsy-determined, isolated mitral valve prolapse observed in autopsy-inconclusive sudden unexplained death in the young (SUDY) cases (~7.8%) exceeded the widely accepted prevalence of mitral valve prolapse in the general population (~2%-3%).
- Autopsy-inconclusive SUDY cases with autopsy-determined, isolated mitral valve prolapse were more likely to have evidence of left ventricular fibrosis (interstitial, endocardial, etc) on microscopic examination than SUDY cases without mitral valve prolapse.
- Further investigation is needed to determine if an over-representation of pathogenic/likely pathogenic variants in established channelopathy- and cardiomyopathy-susceptibility genes is associated with the increased risk of life-threatening ventricular arrhythmias observed in some individuals with mitral valve prolapse with clinically insignificant mitral regurgitation.

However, life-threatening ventricular arrhythmias are still observed in MVP patients with trivial-to-mild mitral regurgitation. Arrhythmogenic bileaflet MVP syndrome (ABiMVPs), a recently described clinical entity characterized clinically by myxomatous mitral valve disease, annular disjunction, frequent/simple ventricular arrhythmias, repolarization abnormalities, and an increased risk of SCD likely underlies this phenomenon.

To this end, ABiMVPs has emerged as an underappreciated cause of both sudden cardiac arrest (~11%) and SCD (~7%-12%) in individuals <40 years of age. In light of these findings and a recent report that identified a pathogenic truncating variant in FLNC-encoded filamin C, an SCD-predisposing arrhythmogenic cardiomyopathy-susceptibility gene that co-segregated with disease in a small ABiMVPs kindred, we sought to determine the prevalence and potential genetic underpinnings of suspected arrhythmogenic MVP in a single-center referral cohort of SUDY decedents.

Methods

This retrospective necropsy study was approved by the Mayo Clinic Institutional Review Board and the research reported adhered to the Helsinki Declaration. Detailed methods are available in the Online Supplement.

Results

Overall, a total of 123 SUDY cases and specimens were referred to the Mayo Clinic Windland Smith Rice Sudden Death Genomics Laboratory for consideration of a molecular autopsy between January 2012 and December 2017. After exclusion of SUDY decedents without complete pathology records (ie, no gross or microscopic pathology) or analyzable exome sequencing results and where gross/microscopic pathology were suggestive of probable/definitive diagnosis, a total of 77 autopsy-inconclusive SUDY decedents were included in the final analyses (Figure 1). Collectively, this autopsy-inconclusive SUDY cohort was 34% female with an average age at death of 20.6 ± 9.0 years (Table 1). Details regarding SCD circumstances and basic findings on gross and microscopic pathology examination are outlined in Table 1.

Considering prior associations between MVP and an increased risk of SCD, we next sought to determine the prevalence of isolated MVP within this autopsy-inconclusive SUDY cohort. Interestingly, 6 of 77 (7.8%) autopsy-inconclusive SUDY decedents had isolated MVP by premortem transthoracic echocardiography (2/6; 33%) and/or evidence of myxomatous mitral valve disease on autopsy as determined by the referring medical examiner/pathologist (6/6; 100%) (Table 1). Of note, the majority (5/6; 83%) of autopsy-inconclusive SUDY decedents with isolated MVP had bileaft involvement (Table 1). The other autopsy-inconclusive SUDY decedent with MVP had isolated posterior MV leaflet involvement (Table 1).

Although no differences in baseline characteristics were observed between autopsy-inconclusive SUDY decedents with and without isolated MVP (Table 2), SUDY decedents without MVP were more likely to have died during rest or sleep than those with isolated MVP (48/71 [68%] vs 1/6 [17%]; P = .02). However, this observation may be driven, in part, by the number of SUDY decedents with MVP where the SCD circumstance was not reported by the referring medical examiner (3/6; 50%; Table 2). Interestingly, review of medical examiner/pathologist-reported pathology data indicated that SUDY decedents with isolated MVP were more likely to have evidence of left ventricular fibrosis (interstitial, endocardial, etc) on microscopic examination than SUDY decedents without MVP (5/6 [83%] vs 9/71 [13%]; P = .0005; Figure 2a and Table 2). Aside from mitral annular dilatation, no other statistically significant findings included routinely in medical examiner reports were observed between SUDY decedents with and without MVP (Table 2).

Finally, we sought to determine if any differences in the number of American College of Medical Genetics (ACMG)-classified pathogenic/likely pathogenic (P/LP) variants in known SCD-predisposing genes were observed collectively or when subdivided by the cardiomyopathy- or channelopathy-susceptibility genes contained within the pre-determined whole exome molecular autopsy (WEMA) panel (Figure 3). Overall, SUDY decedents with isolated MVP were more likely to possess ≥1 ACMG P/LP variant in any SCD-predisposing genetic heart disease–causative gene(s) than SUDY decedents without MVP (3/6 [50%] vs 9/71 [13%]; P = .05; Figure 2b and Table 2). However, no statistically significant difference in the burden of ACMG P/LP localizing to either cardiomyopathy- or channelopathy-susceptibility genes was observed between SUDY decedents with and without MVP, likely owing to small sample size (Table 2). Details regarding the specific ACMG P/LP
identified in SUDY decedents with and without MVP as well as associated medical examiner/pathologist-provided gross and microscopic pathology findings are detailed in Table 3.

**Table 1** Demographics of the Mayo Clinic Exome Sequenced SUDY Cohort (n = 77)

| SUDY victims (n = 77) | Basic demographics |
|-----------------------|--------------------|
|                       | Female, n (%)      |
|                       | Average age at death, years |
|                       | SCD circumstance  |
|                       | Exertion/emotion, n (%) |
|                       | Rest, n (%)        |
|                       | Sleep, n (%)       |
|                       | Not known/reported, n (%) |
| General autopsy findings | Average heart weight, g |
|                       | Average LV thickness, cm |
|                       | Average RV thickness, cm |
| Mitral valve pathology | Myxomatous mitral valve prolapse, n (%) |
|                       | Anterior leaflet, n (%) |
|                       | Posterior leaflet, n (%) |
|                       | Bileaflet, n (%)    |
|                       | Mitral annular dilation |
| Genetics              | Exome sequencing, n (%) |
|                       | ACMG P/LP variant, n (%) |
|                       | Channelopathy-susceptibility gene, n (%) |
|                       | Cardiomyopathy-susceptibility gene, n (%) |

| ACMG = American College of Medical Genetics and Genomics; LV = left ventricle; P/LP = pathogenic/likely pathogenic; RV = right ventricle; SCD = sudden cardiac death; SUDY = sudden unexplained death in the young. |

SCD decedents with isolated MVP (range 79%–100%) than those without (range 0%–38%).

As such, there is a solid and consistent body of evidence from centers across the globe to suggest a link between isolated MVP, inferobasal left ventricular/papillary muscle fibrosis, ectopy/ventricular arrhythmias arising from ectopic foci within Purkinje fibers, and an increased risk of SCD. From a mechanistic perspective, it is hypothesized that progressive myxomatous degeneration of the mitral valve leaflets observed in MVP is precipitated by the peculiar systolic curling/downward displacement of the posterior mitral valve annulus on the adjacent myocardium that arises in the setting of mitral annular disjunction, defined as the spatial detachment of the mitral annulus from the basal myocardium. The ensuing dilation of the mitral annulus and mechanical traction/stretch placed on the tensor apparatus and adjacent inferobasal myocardium, as well as direct contact from prolapsing leaflets themselves, appears to be responsible for the left ventricular midmyocardial/papillary muscle interstitial fibrosis and focal endocardial fibrous plaques observed at autopsy in SUDY decedents with isolated MVP. In individuals diagnosed with ABiMVPs, these findings are likely reflected by late gadolinium enhancement on cardiac magnetic resonance imaging. In turn, ventricular
ectopy and, in rare cases, premature ventricular contraction–triggered pleomorphic/polymorphic ventricular tachycardia appear to arise secondary to both the direct effect of these mechanical forces and triggered activity as a result of perturbed calcium handling within fibrosed/damaged myocardium.19,20

However, only a small proportion of the >170 million individuals with MVP worldwide21 will experience SCD. Therefore, one has to wonder if the small subset of MVP patients that experience sustained ventricular arrhythmias/SCD are simply the product of bad luck or attributable to an underlying genetic predisposition that results in (1) a high-risk but as of yet not fully delineated MVP subtype/endophenotype, and/or (2) impacts the mechanism(s) that govern the response of the ventricular myocardium and/or His-Purkinje system to the repetitive mechanical trauma of the prolapsing myxomatous mitral valve leaflet(s).

To this end, familial clustering of nonarrhythmogenic MVP has been observed22 and an underlying genetic basis elucidated in individuals with syndromic (eg, FBN1/Marfan, TGFBR2/Loeys-Dietz, ELN/Williams-Beuren, COL genes/Ehlers-Danlos, DMD/Duchenne muscular dystrophy, etc)23 and familial nonsyndromic (ie, FLNA, DCHS1, and DZIP1)24–26 forms of the disease. However, our knowledge of the genetic underpinnings of ABiMVPs is limited currently to the aforementioned co-segregation of a truncating variant (p.Trp43*-FLNC) in FLNC-encoded filamin C, a muscle-specific actin-binding protein that causes an arrhythmogenic dilated cardiomyopathy, with disease in small ABiMVPs kindred.10

As abnormalities of the mitral valvuloventricular complex do not appear to be a consistent feature observed in FLNC truncating variant–positive patients,27 it is difficult to argue that FLNC haploinsufficiency results in a developmental and degenerative disorder of the mitral valve apparatus akin to the X-linked mitral valve dysplasia observed in patients with pathogenic variants in the closely related FLNA-encoded filamin A.28 As such, in the setting of repetitive mechanical stress/trauma caused by genetically unrelated myxomatous mitral valve prolapse, it appears more likely that the ABiMVPs-associated p.Trp43*-FLNC variant drives a mal-adaptive and likely profibrotic response within the ventricular myocardium and papillary muscles.10

If indeed this “2-hit” model is responsible for some cases of ABiMVPs, it stands to reason that other genes responsible for SCD-predisposing genetic heart disorders, particularly those associated with arrhythmogenic and/or dilated cardiomyopathies, may be capable of conferring a similar

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**Table 2** Comparison of SUDY victims with and without evidence of mitral valve prolapse at autopsy

|                      | SUDY w/o MVP (n = 71) | SUDY w/ MVP (n = 6) | P value |
|----------------------|-----------------------|---------------------|---------|
| Basic demographics   |                       |                     |         |
| Female, n (%)        | 24 (34%)              | 2 (33%)             | .7      |
| Average age at death, years | 20.6 ± 9.1          | 20.7 ± 6.9          | .9      |
| SCD circumstance     |                       |                     |         |
| Exertion/emotion, n (%) | 14 (20%)            | 2 (33%)             | 1       |
| Rest/sleep, n (%)    | 48 (68%)              | 1 (17%)             | .02     |
| Not known/reported, n (%) | 9 (13%)           | 3 (50%)             | .05     |
| Autopsy findings     |                       |                     |         |
| Mitral annular dilation, n (%) | 0 (0%)            | 2 (33%)             | .005    |
| ACMG P/LP variant, n (%) | 9 (13%)            | 3 (50%)             | .05     |
| Cardiomyopathy-susceptibility gene, n (%) | 7 (9.9%)       | 2 (33%)             | .1      |
| Channelopathy-susceptibility gene, n (%) | 2 (2.8%)       | 1 (17%)             | .2      |

ACMG = American College of Medical Genetics and Genomics; P/LP = pathogenic/likely pathogenic; SCD = sudden cardiac death; SUDY = sudden unexplained death in the young; w/ = with; w/o = without.

*Includes all forms of myocardial fibrosis (endocardial, interstitial, subendocardial, etc) as reported by the referring medical examiner.

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**Figure 2** Medical examiner–identified pathologic and genetic findings in sudden unexplained death in the young (SUDY) cases with and without mitral valve prolapse (MVP). **A:** Percentage of SUDY cases with myocardial fibrosis noted on histopathology. **B:** Percentage of SUDY cases undergoing exome sequencing with a pathogenic/likely pathogenic (P/LP) variant in an SCD-predisposing gene(s).
maladaptive myocardial/electrical response to the mechanical stress/trauma generated by genetically unrelated myocardial MVP. Although the recent discovery of rare variants in LMNA-encoded lamin A/C and the SCN5A-encoded Na<sub>1.5</sub> sodium channel, both arrhythmogenic/dilated cardiomyopathy susceptibility genes, in a patient with suspected ABiMVPS by Mahajan and colleagues, provides additional, albeit limited and anecdotal, evidence in support of this model, the genetic basis of ABiMVPS remains largely unexplored.

To this end, in the current study we demonstrate that 3 out of the 6 (50%) SUDY decedents with autopsy-determined mitral valve prolapse possess an ACMG P/LP variant in 1 of the 147 prespecified SCD-predisposing genes included on our comprehensive WEMA panel. Interestingly, these ACMG P/LP variants localize to genes (DMD-encoded dystrophin, RyR2-encoded ryanodine receptor 2 cardiac calcium release channel, and TTN-encoded titin) linked with varying degrees of strength to either arrhythmogenic and/or dilated cardiomyopathy.

Of note, the 16-year-old p.Glu1518fs*24-DMD-positive male SUDY decedent lacked an antemortem diagnosis or clinical history consistent with muscular dystrophy. As such, a severe dystrophinopathy (ie, Duchenne muscular dystrophy) seems highly unlikely. However, cardiac involvement, including MVP, dilated cardiomyopathy, and life-threatening ventricular arrhythmias, is observed in milder dystrophinopathies such as Becker muscular dystrophy. As isolated cardiac presentations are not infrequent in Becker muscular dystrophy, it is entirely possible that p.Glu1518fs*24-DMD could have served as both the MVP- and SCD-predisposing genetic substrate in this particular decedent. However, whether the MVP and left ventricular outflow tract endocardial fibrosis served as an SCD-predisposing substrate cannot be established definitively in the absence of antemortem imaging and/or electrocardiographic investigations.

Whereas p.Glu1518fs*24-DMD could have conceivably given rise to this decedent’s entire clinical picture, this was likely not the case for the p.Ser285Asn-RyR2- and p.R109*-TTN-positive decedents. Like the ABiMVPS-associated p.Trp43*-FLNC variant, the association between autopsy-determined MVP and p.Ser285Asn-RyR2 and p.R109*-TTN, if any, appears to be linked to the possibility of the aforementioned “2-hit” model.

That said, the 16-year-old p.Ser285Asn-RyR2-positive male SUDY decedent suffered a swimming-related SCD highly suspicious for type 1 catecholaminergic polymorphic ventricular tachycardia. As a result, the bileaflet MVP and papillary muscle/endocardial fibrosis observed in this decedent may well have been innocent bystanders.

Although p.Glu1518fs*24-DMD, p.Ser285Asn-RyR2, and p.R109*-TTN each received a P/LP designation according to the 2015 ACMG variant classification and reporting standards, it is important to note that these guidelines, as well as the ACMG guideline-based classification schemes used by commercial genetic testing companies, de-emphasize the critical role of clinical phenotype in variant adjudication. In the absence of an antemortem clinical phenotype in the decedent or the identification of a clinical phenotype via the postmortem comprehensive cardiovascular screening of first-degree relatives, it is difficult to say with any degree of certainty that these ACMG-graded P/LP are truly disease-causative (eg, p.Glu1518fs*24-DMD causes Becker muscular dystrophy, p.Ser285Asn-RyR2 causes CPVT or calcium channel release deficiency syndrome, or

**Figure 3** Whole exome molecular autopsy gene panel. Cardiomyopathy genes (n = 82) are listed in the dark blue box, channelopathy genes (n = 36) are listed in the light blue box, and other potential contributory genes are listed in the gray box. SUDEP = sudden unexplained death in epilepsy; WEMA = whole exome molecular autopsy.
p.R109*-TTN causes DCM). As such, great caution much be exercised when assigning causation to any rare variant identified in an individual with an ambiguous clinical phenotype (eg, SUDY) regardless of how the variant in question is classified according to 2015 ACMG variant classification and reporting guidelines.

Nevertheless, a potential intersection between AbiMVPS and the cardiac channelopathies is not without precedence. We recently reported that concomitant AbiMVPS and genetically-proven long QT syndrome is observed in ~0.7% of patients within our single-center long QT syndrome registry.\(^\text{34}\) Notably, these patients typically have malignant phenotypes with documented ventricular arrhythmias arising from both substrates.\(^\text{34}\) As such, it stands to reason, particularly in light of the emerging role of RyR2 loss-of-function in so-called short-coupled torsades de pointes/premature ventricular contraction–triggered ventricular fibrillation,\(^\text{5,36}\) that genetically mediated calcium handling abnormalities could be exacerbated by the mechanical stress/trauma of prolapsing mitral valve leaflets causing highly arrhythmogenic foci to arise within/adjacent to areas of focal fibrosis (eg, papillary muscles).

As unselected AbiMVPS cohorts undergo exome/genome sequencing, it will be interesting to see if an over-representation of P/LP variants in cardiomyopathy- and channelopathy-susceptibility genes emerges or if the preliminary observations in this and other studies\(^\text{10,29,34}\) have simply arisen owing to chance. Furthermore, next-generation sequencing of arrhythmogenic MVP pedigrees and/or parent-child trios has the potential to identify novel arrhythmogenic MVP-susceptibility genes and enhance our understanding of the molecular mechanisms that underlie this enigmatic disease.

Regardless, the contribution of so-called arrhythmogenic MVP to sudden cardiac arrest and SCD in the young is not trivial. As such, developing a deeper understanding of the potential genetic basis of this enigmatic disorder as well as more advanced means of identifying the small number of individuals with MVP at increased risk for potentially life-threatening ventricular arrhythmias is paramount.

### Limitations
Although this study represents the first WEMA series to investigate both the prevalence and potential genetic underpinnings of isolated MVP in SUDY, it is not without limitations. First, owing to the relatively rare occurrence of unexplained SUDY as well as issues related to the postmortem procurement of genetic material necessary to conduct a WEMA, the current study was limited to 77 SUDY dece- dents. Consistent with prior studies, MVP is clearly over-represented in this SUDY cohort. However, because of small sample size, this study suffers from low statistical power and the likelihood of false discovery is increased. Therefore, the
genetic findings in this work should be viewed as preliminary and require validation in a larger and preferably multicenter cohort of SUDY decedents with isolated MVP and/or patients with a clinical diagnosis of arrhythmogenic MVP.

Similarly, owing to the nature of our nationwide, medical examiner–referred SUDY cohort, the first-degree relatives of most decedents have not sought care at our institution. As a result, our ability to access results of the requisite comprehensive cardiovascular evaluation and cascade genetic testing of first-degree relatives is limited. Therefore, we lack clinical findings such as de novo status and co-segregation data with the potential to further support or refute the pathogenicity of variants such as p.Glu1518fs*24-DMD, p.Ser285Asn-RyR2, and p.R109*-TTN.

In addition, as our WEMA efforts have largely focused on the identification of pathologically “silent” cardiac channelopathies, we did not request or require cardiac or other autopsy specimens be sent to our institution as a condition for enrollment in our research-based SUDY registry. As a result, the gross and microscopic pathology data contained within this study were sourced from those available in the autopsy and pathology reports provided by each referring medical examiner. In many cases, the cardiac autopsy specimens were sent for evaluation by an external, trained cardiac pathologist. However, the lack of independent review by a single, independent cardiac pathologist; expected variability in the content and rigor of each examination; and interindividual variability in reporting standards between cardiac pathologists/pathology groups represents a recognized, inherent limitation of this study. More recently, we now provide a comprehensive cardiac autopsy that includes direct gross and microscopic analysis by our cardiac pathologist (JJM), coupled with postmortem genetic analysis, as a clinical service in an effort to circumvent the potential heterogeneity in the phenotyping of the decedent.

Nevertheless, given that the prevalence of isolated MVP and proportion of isolated MVP decedents with interstitial/endocardial ventricular fibrosis in the current study closely mirror that of several recent prospective and retrospective postmortem SCD studies, we do not suspect this inherent limitation had a substantive impact on our results.

**Conclusion**

Consistent with prior studies, the prevalence of isolated MVP in this WEMA series (6/77; 7.8%) was substantially higher than widely accepted estimates of MVP prevalence within the general population (~2%–3%). As such, this study provides additional evidence to support the substantive contribution of MVP, particularly bileaflet MVP, and associated LV fibrosis to the pathogenesis of SUDY. Whether the over-representation of ACMG P/LP variants in cardiomypathy- and channelopathy-susceptibility genes is associated with the increased risk of potentially life-threatening ventricular arrhythmias observed in some individuals with MVP requires further investigation.

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**Disclosures**

MJA is a consultant for Abbott, Audentes Therapeutics, Boston Scientific, Daiichi Sankyo, Invitae, Medtronic, Myokardia, St. Jude Medical, and UpToDate. MJA and Mayo Clinic are involved in an equity/royalty relationship with AliveCor and Anumana. However, none of these entities were involved in this study in any manner. JRG, JMJ and DJT have no conflicts to declare.

**Authorship**

All authors attest they meet the current ICMJE criteria for authorship.

**Patient Consent**

In this Mayo Clinic Institutional Review Board–approved study (IRB# 1216-97), informed consent was obtained from the next of kin for each of the 77 autopsy-inconclusive sudden unexplained death in the young decedents enrolled.

**Ethics Statement**

The research reported in this work adhered to the Helsinki Declaration.

**Appendix**

**Supplementary data**

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2021.07.006.

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