Genomic autopsy identifies cardiomyopathy variants

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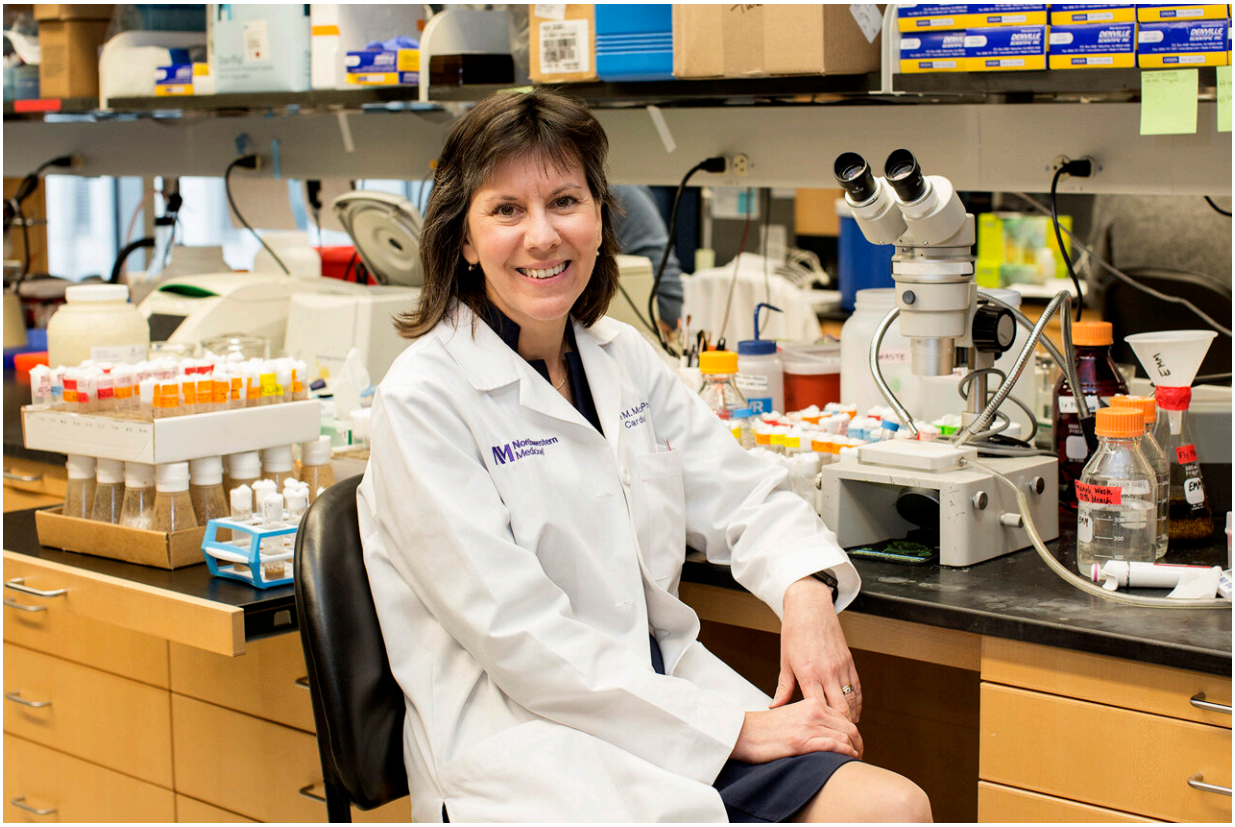

Elizabeth McNally, MD, PhD, the Elizabeth J. Ward Professor of Genetic Medicine, was senior author of the study published in *JAMA Cardiology*. Credit: Northwestern University

Postmortem genetic testing, or genomic autopsy, of young individuals

who experienced sudden death revealed many had known genetic variants that are associated with cardiomyopathy, according to a Northwestern Medicine study published in *JAMA Cardiology*.

These findings indicate that genomic autopsy can improve care for families after a sudden death in a young patient, as it can prompt genetic testing of family members for such variants, according to Elizabeth McNally, MD, Ph.D., the Elizabeth J. Ward Professor of Genetic Medicine and senior author of the study.

"It's very important for state and county medical examiners to save blood samples, because analyzing those samples can give families options about testing themselves after sudden death of a young individual," said McNally, who is also a professor of Medicine in the Division of Cardiology, of Biochemistry and Molecular Genetics and director of the Center for Genetic Medicine.

Sudden death in young people—the study focused on those under the age of 44—is often linked to genetic cardiomyopathies: diseases of the heart muscle that impair blood flow to the rest of the body and can lead to heart failure. Genomic autopsies are also useful for informing family members of possible genetic risk, which can help guide their medical care and reduce their risk.

In the current study, the Northwestern team performed whole-genome sequencing on samples from more than 100 patients who had died, comparing them to sex- and genetic ancestry-matched controls. The investigators found 13 percent of the decedents had genetic variants known to contribute to cardiomyopathy and irregular heart rhythms.

The investigators also examined variants of uncertain significance: genetic variants in genes known to contribute to cardiomyopathy, but whose specific pathogenicity is unknown. A multivariate analysis

revealed that more variants of uncertain significance were correlated with a lower age of sudden death, pointing to their usefulness as a measure of cardiac risk.

"It suggests that individuals who have a pathogenic gene change, plus a bunch of variants of uncertain significance, may have a higher risk of sudden cardiac death," McNally said. "This is what we call oligogenic inheritance: the contribution of a few different genes that when combined, create a person's risk."

While current clinical genetic testing panels look for known pathogenic variants, incorporating some measure of variants of uncertain significance could also improve assessment of cardiac risk, according to McNally. Importantly, discovery of pathogenic variants is not determinative—while they contribute to risk of cardiac death, these risks can be mitigated by lifestyle practices and medical management.

"You might be born with genomic risk, but there are many other environmental and lifestyle influences that influence how that risk is expressed," McNally said. "It means we should monitor these individuals much more closely, and treat them to reduce risk."

Additionally, the process of collecting genetic information from decedents was complex, requiring outreach to 60 county or state medical examiners in 24 different states. This network was coordinated by Robert Gregory Webster, MD, assistant professor of pediatrics in the Division of Cardiology and the lead author of the study.

"Practices on saving blood samples vary from examiner to examiner, so we hope this study encourages the practice and helps families navigate important next steps after losing a loved one," McNally said.

More information: Gregory Webster et al, Genomic Autopsy of

Sudden Deaths in Young Individuals, *JAMA Cardiology* (2021). DOI: 10.1001/jamacardio.2021.2789