Will unanticipated genetic mutations lead to subsequent disease?

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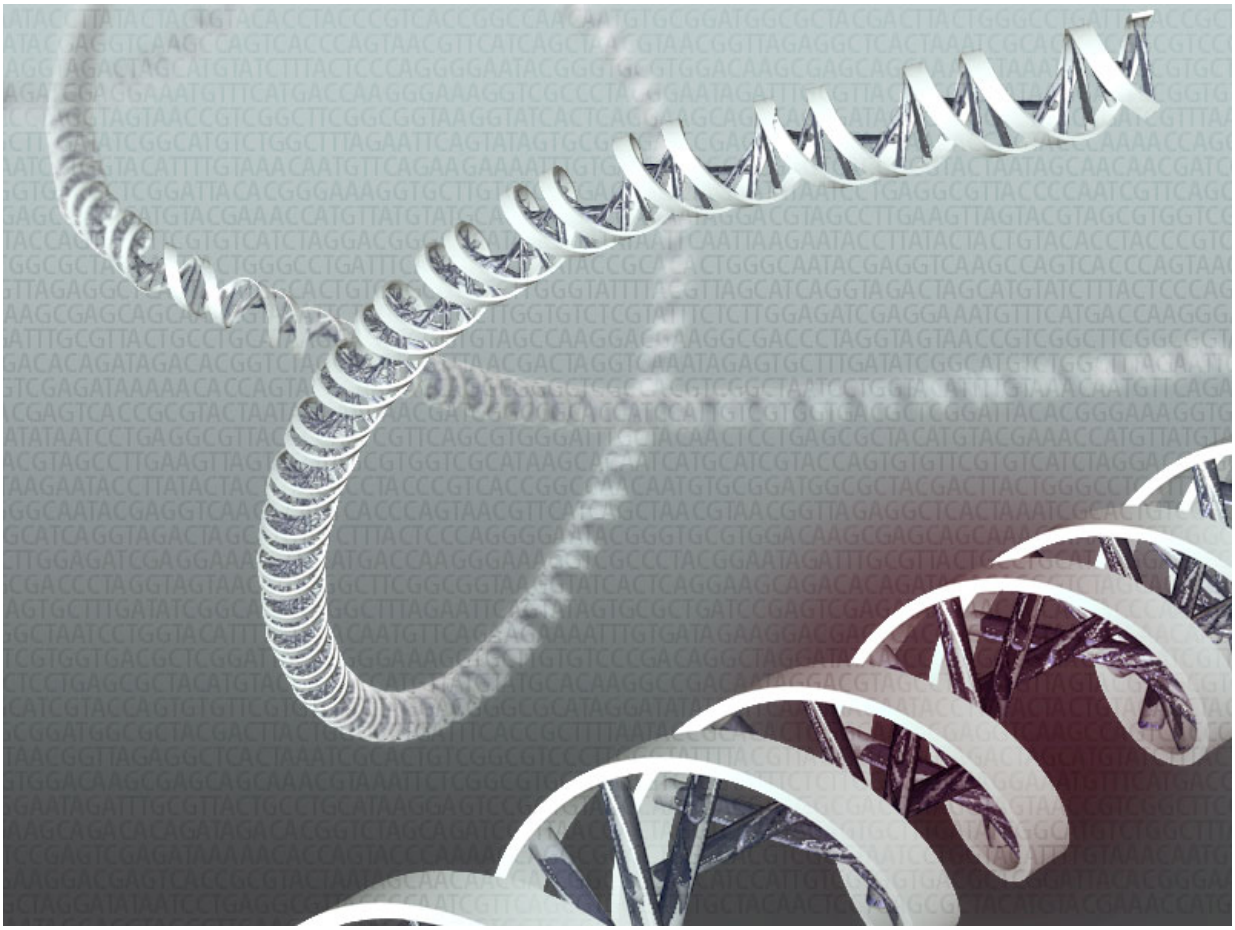

Credit: Credit: Val Altounian / *Science Translational Medicine*

A study published Nov. 9 in the journal *Science Translational Medicine* is

the first to show that mutations in certain cancer and cardiovascular genes put individuals at an increased risk for dominantly inherited, actionable conditions, regardless of family medical history. The study, carried out in two separate populations of African-Americans and European-Americans, finds that individuals carrying these mutations are at about four and six times the risk of developing one of these cancer or cardiac syndromes, respectively. The new work, led by Robert C. Green, MD, MPH, of Brigham and Women's Hospital, Broad Institute and Harvard Medical School, has important implications for the use of genomic sequencing as a future clinical screening tool.

"The field of clinical genetics has been uncertain about recommending genome screening in healthy individuals for two reasons. First, we do not know if those individuals will be at increased risk regardless of their family history. Second, we do not know if identifying individuals carrying these mutations will make a positive difference in their eventual clinical outcomes," said Green, senior author on the research. "This analysis addresses only the first of these questions, but demonstrates that in the aggregate, mutations in a subset of genes are associated with a substantial risk of developing the related condition."

The study combined the work of investigators in genomics, informatics, molecular biology, epidemiology and statistics at multiple institutions to seek insights into a question that has been extremely difficult to answer. If people carry a genetic mutation, what are the chances that they will develop the related condition over a number of years? Addressing this question has been difficult because very few population-based cohorts have had both genetic sequencing and systematic medical testing recorded over time, and highly heritable conditions are relatively rare.

To explore this question, the investigators used data previously collected in two longitudinal cohort studies that investigated heart disease but also collected data on cancer. Data were analyzed from 462 European-

Americans from the Massachusetts-based Framingham Heart Study who had been followed for two decades, and 3,223 African-American participants in the Mississippi-based Jackson Heart Study who had been followed for a shorter period. The researchers screened participants for disease-causing mutations using a panel of 56 genes representing 24 hereditary cancer and cardiac syndromes while blinded to the clinical outcomes in these participants. The researchers also collected clinical and diagnostic test information on the participants while blinded to the genome sequencing results.

The research team then analyzed whether those who carried the mutations went on to develop associated conditions (cancer, heart disease and high cholesterol) more frequently than those who did not carry the mutations. The results were highly significant, indicating that carrying a mutation in one of the 56 genes conferred four times the risk of eventually developing an associated disease in African-Americans and six times the risk in European-Americans. The risk differences were not thought to be due to racial differences, but rather to the fact that the European Americans in the Framingham study were followed longer than the African Americans in the Jackson study, and had more time to develop the clinical features associated with their genetic changes. Importantly, the study combined risks from very different mutations and very different genes into an "aggregate" estimation of the genetic penetrance (the likelihood that someone with a mutation will develop the condition). Thus, these estimates are most relevant to populations, and less relevant to individuals within that population. Nevertheless, it is the first such study to attempt to estimate the effects of such aggregate penetrance within a group.

"These populations are uniquely suited for a study like this because everyone in the Framingham and Jackson cohorts received regular EKGs, echocardiograms and lipid measurements, not just those who had medical problems," said Pradeep Natarajan, MD, MMSc, one of the lead

authors based at Massachusetts General Hospital. "Data of this nature is not available from a typical health care system where only those who have come to medical attention get blood testing or certain types of diagnostic testing."

Eventually, using an individual's genomic variants to predict and prevent future illness may become a routine part of health care. However, it remains to be seen whether identifying individuals with genetic mutations will result in sufficient clinical benefit to merit the risks and costs of downstream imaging studies or procedures. The authors caution that this study does not provide evidence that recognizing genetic mutations directly confers medical benefit. In seeking to explore the related question of clinical outcomes, Green and his team have also implemented a separate randomized clinical trial of medical sequencing called the MedSeq Project, and have organized a Consortium to track medical outcomes among any ostensibly healthy individuals who have been sequenced for predictive purposes.

More information: "Aggregate penetrance of genomic variants for actionable disorders in European and African Americans," *Science Translational Medicine*, stm.sciencemag.org/lookup/doi/ … scitranslmed.aag2367

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