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Suspected disease-causing gene variants do not cause sudden cardiac death

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In a cautionary tale about our field's ability to determine the functional effects of genomic variants, a group of Danish researchers has refuted a recently proposed association between certain gene variants and sudden cardiac death. A variety of studies had identified several gene variants predicted to increase risk of certain cardiac events, but most are merely associations and not considered predictive. The impetus for using genomics to identify individuals at risk is reasonable, given dramatic disparity between symptoms and potential outcome in cardiac channelopathies. Most people carrying predisposing mutations have no symptoms, yet without warning may go into cardiac arrest. Nonetheless, clinical validation of potential genomic risk assessment tools is urgently needed. As reported in this issue, a research team from the Danish National Research Foundation Centre for Cardiac Arrhythmia at the University of Copenhagen evaluated inherited gene variants associated with Brugada syndrome (BrS) and long QT syndrome, both of which can result in sudden cardiac death. The researchers compared longitudinal registry data with age-matched controls to determine whether gene variants predispose individuals to events such as ventricular fibrillation or other arrhythmias. Whole-exome sequencing of 870 registry patients revealed 23 variants affecting 145 heterozygote carriers. None of these carriers had an abnormal heart rhythm or an increased propensity for syncope or other electrical abnormality of the heart. Nor did they die sooner on average than noncarriers. The results call into question the clinical relevance of the recently identified association of BrS with variants in the *SCN10A* gene. The investigators suggest that improved variant classification methods must be developed before genomic test results can be interpreted for use for patients who may be at risk for cardiac channelopathies. Counseling based on potentially false-positive variants could lead to misdiagnosis, which the authors suggest could have unnecessary and burdensome economic and psychological consequences. —*Karyn Hede, News Editor*

Should athletes be disqualified from sports because of a genetic test?

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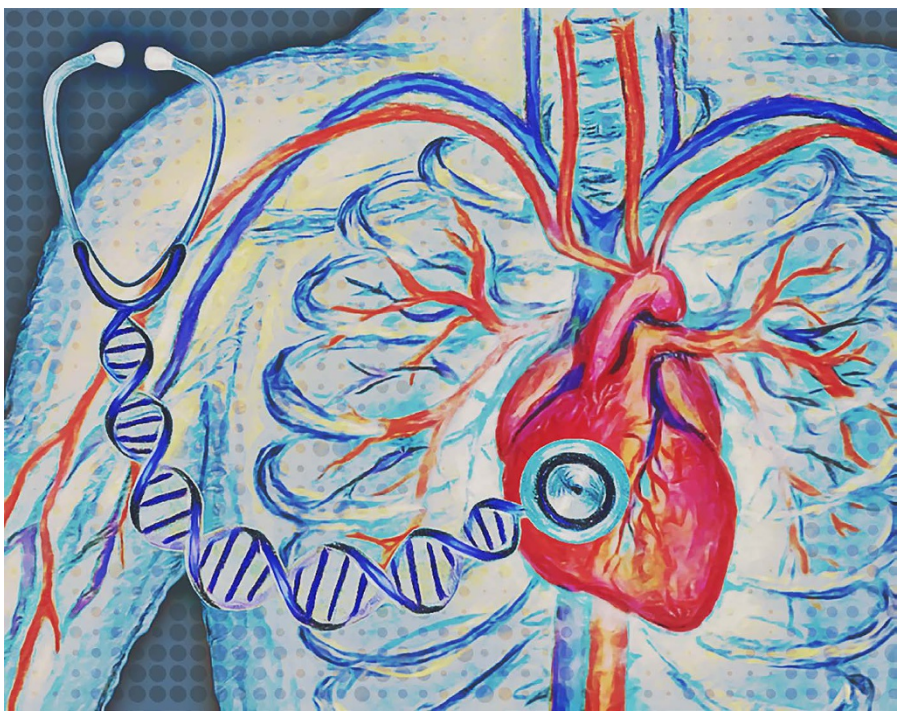
When an elite athlete in the prime of life suddenly collapses and dies while playing their sport, the natural response is to seek ways to stop something so seemingly senseless from happening again. The impetus to screen athletes who may be at risk of sudden cardiac death stems from this reasonable rationale. The problem is that identifying those who are truly at risk is not a simple matter. The risk factors are complex and variable. Some who have a family history of inherited cardiac disease or borderline pathology will never have a cardiac event. For an athlete, cardiac screening can result in disqualification from professional sports, leading to what could be described as employment discrimination, according to Magavern *et al.* In their Commentary, the European physicians argue that not enough consideration has been given to the ethical implications of genetic screening tests administered before athletic participation. They note that when screening becomes mandatory for an eligibility decision, overzealous use of genetic tests could unnecessarily bar athletes, resulting in loss of employment opportunity. Yet, the medical profession has produced no consensus opinion–based disqualification recommendations. Indeed, doctors differ in their recommendations on disqualification of individuals who are genotype-positive and phenotype-negative. The European Society of Cardiology guidelines recommend disqualification based on the finding of a pathogenic mutation alone for conditions such as Marfan syndrome and hypertrophic cardiomyopathy. US guidelines don't go as far, requiring evidence of physical manifestation, such as an abnormal electrocardiogram. Because our knowledge of genetic variant pathogenicity is so limited, the authors call for a public discussion of the ethical place of genetic testing in mandated cardiac screening in which medical eligibility decisions are made. —*Karyn Hede, News Editor*



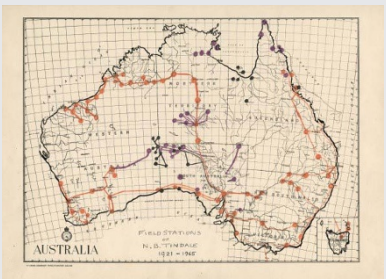
NEWS BRIEFS

The GOAT: greatest genome of all time?

It may be a bit of hyperbole, but researchers at the National Human Genome Research Institute (NHGRI) are touting the recently completed goat genome as a leap in genome assembly that can be extended to any vertebrate genome. "The domestic goat [is] a genome we jokingly call the Greatest of All Time," says Adam M. Phillippy, a researcher in the NHGRI's Computational and Statistical Genomics Branch. The research team actually chose to demonstrate the new assembly techniques using the domesticated goat because it is a critical food source in developing countries. A San Clemente goat named Papadum provided the DNA used in the study, which appeared in *Nature Genetics* on 6 March 2017. Papadum is descended from a herd of inbred animals living on San Clemente Island off the coast of San Diego, California. Starting with the thousands of individual overlapping sequences called contigs, Phillippy and his colleagues developed new optical mapping and the Hi-C chromatin conformation capture techniques to assemble a complete, high-quality genome reconstruction. The new map lacks the gaps that have plagued earlier efforts to sequence not only the goat genome but also the genomes of other animals and even the human genome. "PacBio sequencing, optical mapping, and Hi-C have all been used for genome assembly before, but we showed that by combining all of them together, we could get a very comprehensive and accurate map of the genome at an affordable price," says NHGRI researcher and coauthor Sergey Koren. "Previous methods have left the chromosomes either incomplete or broken into many pieces, making it very expensive to finish." The research team will next apply the techniques to Genome10K, a project to sequence 10,000 genomes, one of each vertebrate genus. To extend the techniques, they are also incorporating emerging nanopore genome sequencing methods that can be applied to real-time diagnosis of human disease.—*Karyn Hede, News Editor*

Brian L. Sayre

Australian Aborigines arrived in a single wave more than 50,000 years ago



South Australian Museum Archives, Norman Tindale Collection (AA 338/22/66)

Two complementary genomic studies encompassing both the Y chromosome and mitochondrial genome have revealed that Australia was first peopled in a single migration event nearly 50,000 years ago. Once established, these early Australians migrated into distinct geographically defined subgroups that have now been traced genetically. The results support folk knowledge asserting a long and independent history on the continent. The Y chromosome study, led by investigators from the Wellcome Trust Sanger Institute, refutes suggestions that migration from Southeast Asia about 5,000 years ago led to admixture with earlier groups of migrants. The new investigation, published 27 February 2017 in *Current Biology*, compared 13 Aboriginal Australian Y chromosomes with 1,269 previously sequenced counterparts from South Asia. The findings revealed no recent gene flow between the groups, supporting genetic divergence in the 50,000-year range. A second study, published 6 March 2017 in *Nature Genetics*, traced mitochondrial genomes of distinct subgroups of Aboriginal communities (two in South Australia, one in Queensland) using DNA extracted from hair samples collected between the 1920s and 1970s. Alan Cooper of the Australian Centre for Ancient DNA at the University of Adelaide, Adelaide, South Australia, and colleagues from several research institutions combined the DNA analysis with ethnographic data collected by the Board for Anthropological Research at the University of Adelaide before aboriginal populations were relocated and removed from ancestral homelands. This analysis was critical to understanding the historical relationships among Aboriginal Australian groups prior to European settlement. The story that emerged was one of a single rapid migration from a first landfall in northern Australia and a rapid peopling of the east and west coasts between 49,000 and 45,000 years ago. Regional patterns of mitochondrial DNA variation reinforce the cultural understanding that people occupied ancestral homelands continuously for 50,000 years, weathering widespread and extreme changes in climate over that time. —*Karyn Hede, News Editor*