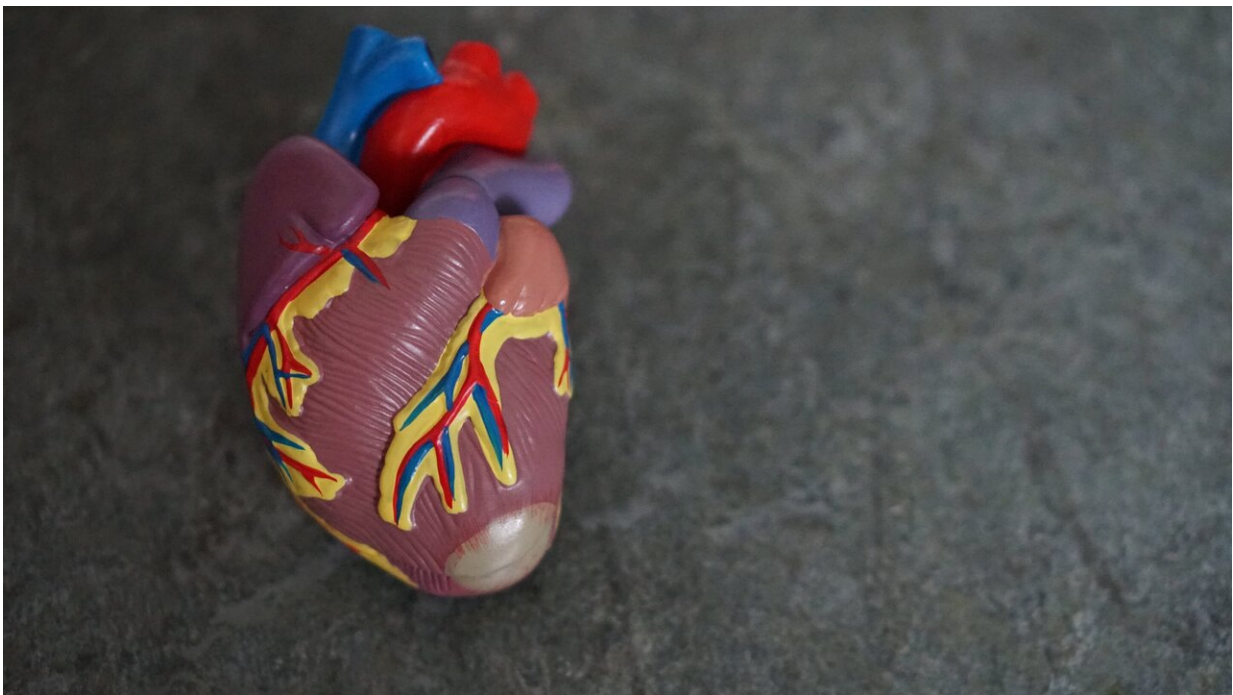


Scientists find additional molecular miscues in a genetic heart disorder that primarily afflicts young people

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New research involving a devastating genetic heart condition suggests that mutations in adhesion proteins—molecules that should support the heart—apparently play a role in disrupting the integrity of the organ's outermost layer, leaving patients vulnerable to sudden cardiac death.

The epicardium, the [heart](#)'s outer cloak, hugs the myocardium—the contractile muscle—the inner and thickest layer of the organ.

Arrhythmogenic cardiomyopathy—ACM—is a heart condition characterized by ventricular arrhythmias typically beginning in adolescence or early adulthood. Arrhythmias refer to irregular heartbeats, which can be too slow or too fast. Miscued beats occur because the heart's electrical impulses don't function properly, and for those with ACM, the condition raises the risk of lethal arrhythmias.

But ACM is stealthy and insidious producing few noticeable symptoms for many patients outside of heart palpitations or fainting spells. For others, the first evidence of ACM is sudden death. When young athletes die suddenly on a basketball court or soccer field, the cause is usually ACM.

While studies long ago revealed the condition to be genetic, with males at somewhat greater risk than females, only now have scientists begun to reveal how specific genetic flaws involving adhesion proteins—the molecular glue designed to hold [heart cells](#) together—undermine the heart instead.

The latest ACM research emerges from a series of elegant studies in the Netherlands that not only offer new insight into the disorder's genetics, but illuminate a possible path toward a customized treatment.

Drs. Arwa Kohela and Eva van Rooij at the Hubrecht Institute of the Royal Netherlands Academy of Arts and Sciences in Utrecht, say the origin of the heart disorder is not where one might expect. They've traced the genetic origins of the disorder to mutations in desmosomal genes that code for adhesion proteins, which serve as support complexes in the heart. Austrian physician-scientist Josef Schaffer coined the term "desmosome" a century ago from the Greek words bond (desmo) and

body (soma).

Desmosomes are specialized adhesive complexes with glue-like properties and the responsibility of maintaining mechanical integrity in tissues. As complexes, desmosomes are composed of multiple proteins, and many of those proteins can contain deleterious mutations in ACM. For people with the disorder, desmosome-expressing cells are a key source of fibroblasts—cells that produce connective tissue—and fatty deposits.

Scientists at the Hubrecht Institute are focusing on the epicardium of the heart because it is a continuous layer and its cells retain the ability to proliferate and differentiate into other cell types throughout life. Epicardial differentiation depends on the integrity of support proteins—especially the desmosomes. Because of the intimate relationship between desmosomes and the epicardium, the new Dutch research suggests the disease has its origins in epicardial tissue.

"Arrhythmogenic cardiomyopathy—ACM—in humans is characterized by fibro-fatty deposits in the ventricles of the heart, but the mechanisms responsible for these deposits are not well understood, and current animal models of ACM do not recapitulate this phenotype well," asserted Kohela, reporting in *Science Translational Medicine*.

During early embryonic heart formation, the epicardium gives rise to coronary smooth muscle cells and myocardial fibroblasts, which provide structural support for both the developing embryo as well as later for the fully formed heart. Integral to a healthy heart is the development of support proteins—the desmosomes—which emerge from epicardial tissue.

Although studies two decades ago involving a Greek population with a unique propensity for ACM pointed to desmosomal mutations in the

disorder, Dutch scientists advanced the research further to clarify why demosomal flaws can so profoundly waylay the epicardium. Indeed, scientists were surprised to pinpoint the possible genetic roots of ACM in genes of the epicardium because the effects of the disease are felt mostly in the myocardium—the beating layer of the heart—where the classic "lub-dub, lub-dub" sounds of the organ are heard through a stethoscope.

The research opens a portal into a keener understanding of ACM, a condition that, in the United States is estimated to affect 1 in every 5,000 individuals. In other parts of the world, such as Northern Italy, prevalence reaches 1 in 1000. ACM has a profound impact on young patients, accounting for 10 percent of sudden cardiac deaths among those under age 18, and 17 percent of sudden cardiac deaths for those under 35.

The disorder is characterized by a constellation of problems, which includes the replacement of healthy heart muscle by scar tissue and fatty deposits. The cardiac-encumbering problems don't end there because the disorder is additionally marked by inflammation, and worst of all, general degeneration of the heart.

It's because of the progressive myocardial degeneration that healthy heart tissue is replaced by scar tissue and fat. In recognition of the disorder's chief hallmark—cardiac arrhythmias—some doctors have called ACM "the most arrhythmogenic form of heart disease known to man."

Going into their research, Kohela and van Rooij faced a particularly daunting problem: There isn't an appropriate animal model to study ACM. Laboratory rodents don't develop the same type of cardiac fat that humans do.

Kohela and colleagues, intent on overcoming the absence of an effective animal model, generated stem cells that have mutations in the plakophilin-2 gene from patients with ACM. The plakophilin-2 gene is expressed in cardiac muscle and is found in the desmosomes. Cells containing mutated plakophilin-2 genes differentiated into epicardial cells.

Stunningly—suddenly—these epicardial cells spontaneously underwent fibro-fatty remodeling, changes that were identical to the fibrotic and fat deposits that replace healthy heart tissue in the disease.

"We used human-induced pluripotent stem cell-derived cardiac cultures, single-cell RNA sequencing, and explanted human ACM hearts to study the epicardial contribution to fibro-fatty remodeling in ACM," Kohela wrote. "Human-induced pluripotent stem cells generated from patients with ACM showed spontaneous fibro-fatty cellular differentiation that was absent in isogenic controls."

Single-cell RNA sequencing and analysis, along with the examination of heart tissue from ACM patients, further revealed that a transcription factor known as TFAP2A mediates this devastating epicardial transition. Having uncovered the factor's deleterious role in ACM, the Dutch team is now suggesting that blocking TFAP2A may be a way to effectively treat ACM.

The transcription factor is controlled by the TFAP2A gene, which provides instructions for making the factor, a protein. As its name suggests, the factor plays a role in mediating DNA transcription. The transcription factor binds to specific regions of DNA and helps control cell division and cell death—apoptosis.

The take-home message from the Dutch research: Epicardial differentiation drives fibro-fatty remodeling in arrhythmogenic

cardiomyopathy.

The new research is part of a growing body of studies investigating a genetic form of heart disease that impacts people who are young. Even though the disorder had been investigated in the 20th century, it wasn't until 2000 when results from a study of patients on the Greek island of Naxos helped lead scientists to the identification of the first disease-causing ACM mutation. Residents of Naxos possessed a rare, recessive form of ACM, researchers found.

Dr. Angeliki Asimaki of Harvard University recounted much of ACM's history of gene research in a 2014 report in the journal *Progress in Pediatric Cardiology* in which contributions from the Naxos analyses were outlined. ACM, according to Asimaki and colleagues "is a disease of the desmosome and paved the way for identification of mutations in desmosomal genes including those encoding desmoplakin, plakophilin-2, desmocollin-2 and desmoglein-2."

Asimaki and colleagues underscored: "ACM-related mutations are present from conception, but the clinical phenotype is not manifested until at least adolescence or more typically early adulthood. It is therefore of pivotal importance to recognize ACM in young individuals early, before the risk of fatal arrhythmias."

Kohela and collaborators in the Netherlands say their research has identified a factor that can be blocked, which promises a way of treating the condition. "Although further studies are needed, our findings suggest that inhibition of TFAP2A might be a target for treating ACM," they concluded.

More information: Arwa Kohela et al, Epicardial differentiation drives fibro-fatty remodeling in arrhythmogenic cardiomyopathy, *Science Translational Medicine* (2021). [DOI:](#)

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