HEART ATTACK

**MEF2A** Myocyte Enhancer Factor 2A Gene

A heart attack, also called a myocardial infarction, occurs when blood flow to the heart is interrupted, starving the heart muscle of oxygen and potentially resulting in tissue damage. This condition most often results from a blood clot blocking one of the coronary arteries that supply the heart. Symptoms of a heart attack include sudden chest pain, shortness of breath, nausea, sweating, and anxiety. Heart attacks are the leading cause of death for both men and women worldwide; an American's lifetime risk of heart attack is one in five, and one million people in the U.S. die of heart attack each year. Among the major risk factors for heart attack are aging, smoking, diabetes, high blood pressure, and high cholesterol. It has long been known that many people inherit a predisposition to heart attack, but the first causative gene, **MEF2A** (Myocyte Enhancer Factor 2Aa), was not identified until 2003. MEF2A, mutated in nearly 2% of all heart attack victims, codes for a protein categorized as a transcription factor, meaning that it plays a role in regulating the activity of other genes. The MEF2A transcription factor specifically affects the expression of several genes in the endothelium that lines the coronary arteries. The deletion of seven amino acids in the MEF2A gene codes for a damaging form of the transcription factor that regulates genes in the endothelium, causing this lining to be more susceptible to formation of artery-clogging plaque. The rupture of such plaque leads to obstructive clots in the artery, resulting in heart attack. Clinical trials begun in 2006 at the Texas Heart Institute are currently evaluating post-heart attack stem cell therapy in which stem cells derived from the patient’s bone marrow are transplanted back into the patient’s heart. Ten days after the heart attack, the patient-derived stem cells in 25, 75, and 150 million increments are implanted through ultrasound-guided injection between the normal and damaged tissue to grow new, functional heart muscle.

**CONGENITAL HEART DISEASE**

**NKX2.5** NK2 Transcription Factor Related Gene, Locus 5

The term “congenital heart disease” describes a variety of different heart defects that interrupt the flow of blood and are present from birth. For instance, a ventricular septal defect (VSD) consists of a hole in the wall that normally separates the two ventricles of the heart, allowing blood to flow from the left ventricle to the right. Depending on the size of the defect, symptoms can range from a mere heart murmur (a swishing sound made by blood passing through the hole), to difficulty breathing, and to heart failure. VSD can result from mutations of the **NKX2.5** (NK2 Transcription Factor Related Gene, Locus 5) gene on chromosome 5, which codes for a transcription factor. The NKX2.5 transcription factor influences the expression of genes that control tissue differentiation during cardiac development. Since a child only needs one mutated copy of the gene to develop a heart defect, adult men and women with known congenital heart defects may want to consult a genetic counselor before having children. Treatments for VSD vary according to the severity of the defect; many small holes close up on their own within eight years, whereas larger defects may require open heart surgery to stitch the hole closed or patch it with a man-made material like Gore-Tex. Patient-derived stem cells may one day be used to repair the hole.

**SUDDEN UNEXPLAINED DEATH SYNDROME**

**RYR2** Rymodine Receptor 2 Gene (Cardiac Sarcomplasmic Reticulum Calcium Release Channel Gene)

Sudden Unexplained Death Syndrome is an extremely challenging medical and social problem involving patients, their relatives, doctors, forensic pathologists, and the medical legal profession at large. Abnormalities of the calcium and potassium ion channels that regulate heartbeat are often responsible for cardiac rhythm irregularities, called arrhythmias, that can be fatal but result in no physical abnormality that can be found during autopsy. This syndrome often occurs in people under the age of 40. One type of Sudden Unexplained Death Syndrome, called familial polymorphic ventricular tachycardia, is an autosomal dominant inherited ion channel disorder with a relatively early onset and a mortality rate of approximately 30% by the age of 30 years. Recently a link has been found between familial polymorphic ventricular tachycardia and mutations in the gene coding for the cardiac sarcomplasmic reticulum calcium release channel protein (Ryanodine Receptor 2 Gene) on chromosome 1. This ion channel protein is present in high amounts in heart muscle. All disease-causing mutations in this gene presumably affect the calcium transport within heart muscle cells causing them to become hyper-responsive to outside nerve stimuli that regulate the heart beat. Mice that have been engineered to carry a human RYR2 mutation exhibit stress-induced irregular heart beat very similar to the human condition, proving that RYR2 mutations cause in fact irregular heart beat. Consequently, the identification of a mutation in the RYR2 gene is tantamount to a diagnosis in patients with Sudden Unexplained Death Syndrome if no anatomical changes can be found.

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