

Opportunity



Risk stratification biomarkers for sudden death during myocardial infarction

- A unique set of biomarkers to determine the risk for ventricular fibrillation and cardiac arrest

Diagnostics | SNP Markers

2011

Background

Sudden cardiac death (SCD) is one of the most prevalent modes of death in the industrialized world, claiming almost a million deaths annually in Western Europe and the United States. As such, SCD accounts for almost 20 percent of total mortality. Ventricular fibrillation (VF) is the most common underlying arrhythmia.

Most of these deaths occur as a consequence of VF in the setting of a first acute myocardial infarction (MI) referred to as "primary VF". In a third of these cases this occurs as a first clinical event in individuals without known cardiac disease. The present lack of effective methods to identify individuals at risk of SCD in the general population (i.e. prevention of primary VF) represents a fundamental public health problem. Researchers at the Academic Medical Centre in Amsterdam have found a unique set of SNP biomarkers to determine the risk for ventricular fibrillation and cardiac arrest.

The Technology

The present invention is based on a genome-wide association study carried out in the AGNES (Arrhythmia Genetics in the NETHERlandS) case-control population. The AGNES population was ascertained at heart centers in the Netherlands and consists of patients with a first ST-elevation MI (STEMI) complicated by VF (cases) and STEMI patients without VF (controls). The frequency of common genetic variants spread throughout the genome was compared between AGNES cases and controls for discovery of common genetic variants (single nucleotide polymorphisms, SNPs) modulating risk for VF.

This led to the identification of several polymorphisms in various chromosomal segments that were associated with the occurrence of VF, at high statistical significance.

Data

See table below. Leading SNPs at the three loci most strongly associated with ventricular fibrillation in the genome-wide association study in the AGNES case-control set.

a: Only rs2824293 was imputed; the rest of the SNPs were genotyped directly. b: Based on Build 36.2. c: Odds ratios are per copy of minor allele and are adjusted for age and sex. d: The P values are corrected for genomic control factor. eGenes within an area of 1 Mb centered at the SNP are listed.

Applications

This discovery enables the production of a diagnostic method to assess the personal risk profile for VF in subjects. The present lack of effective methods of identifying individuals at risk of SCD in the general population (i.e. prevention of primary VF) represents a fundamental public health problem. The identification of genetic variants modulating susceptibility to VF during acute MI may enable risk stratification in patients with coronary artery disease and ischemic heart disease, providing opportunities for installment of (more-aggressive) preventive strategies (medication and / or ICD) in those at highest risk. We have identified a set of polymorphisms that are associated with risk of arrhythmia during acute myocardial infarction which are interesting for risk stratification for sudden cardiac arrest.

Screening an individual without known cardiac disease is also useful, as many of patients who die because of VF do so in the context of a first myocardial infarction. These patients do not receive any warning beforehand, such that these deaths can only be prevented if such an individual is screened beforehand and is warned about his or her genetic risk of suffering from VF. Such an individual can then adapt his or her lifestyle and/or may be treated with medicaments in order to reduce the risk of VF-associated SCD.

SNP ^a	Chromosome position	Position ^b	Minor allele	Major allele	Frequency of minor allele			Odds ratio (95% CI) ^c	P ^d	Closest genes ^e
					Total	Cases	Controls			
rs2824293	21q21	17,709,385	G	A	0.47	0.53	0.39	1.78 (1.47–2.13)	3.34 × 10 ⁻¹⁰	CXADR, BTG3
rs2824292	21q21	17,709,047	G	A	0.47	0.53	0.39	1.78 (1.47–2.13)	3.36 × 10 ⁻¹⁰	CXADR, BTG3
rs1353342	9q21	78,064,589	A	C	0.23	0.07	0.14	0.46 (0.34–0.63)	3.34 × 10 ⁻⁷	PCSK5, RFK, GCNT1
rs12090554	1q25	183,818,971	A	G	0.23	0.19	0.28	0.58 (0.47–0.72)	7.89 × 10 ⁻⁷	HMCN1, IVNS1ABP

Intellectual Property

A priority filing has been done in November 2009, which has been continued in a PCT filing in November 2010. The patent claims a method to determine whether an individual has a genetic predisposition for VF based on four SNPs.

Inventors

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Key publications

1. Bezzina CR, et al., Genome-wide association study identifies a susceptibility locus at 21q21 for ventricular fibrillation in acute myocardial infarction. *Nat Genet.* 2010 Aug;42(8):688-91.
2. Wilde AA, Bezzina CR. Genetics of cardiac arrhythmias. *Heart.* 2005 Oct;91(10):1352-8.
3. Pazoki R, Wilde AA, Bezzina CR. Genetic Basis of Ventricular Arrhythmias. *Curr Cardiovasc Risk Rep.* 2010 Nov;4(6):454-460.