Predicting sudden cardiac death using common genetic risk variants for coronary artery disease

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Aims

Genome-wide association studies (GWAS) have identified many variants associating with an increased risk of coronary artery disease (CAD). We studied the possible association between these variants and the risk of sudden cardiac death (SCD).

Methods and results

A weighted genetic risk score (GRSCAD) was formed from variants most strongly associating with CAD identified by the CARDIoGRAMplusC4D Consortium explaining 10.6% of the heritability of CAD [153 single-nucleotide polymorphisms (SNPs) with \( r^2 > 0.2 \)]. The association between GRSCAD and the occurrence of SCD was studied in three independent autopsy series combining altogether 1035 autopsies with 306 SCDs due to CAD (SCDCAD). The results were replicated in a prospective follow-up study of 2321 patients (mean follow-up time of 6.2 years with 48 incident SCDs of which 39 due to CAD) undergoing clinical exercise test at baseline. In a meta-analysis of the autopsy series, GRSCAD associated significantly with the risk of SCDCAD with age, body mass index, and sex adjusted odds ratio (OR) of 1.042 (1.023–1.061, \( P = 9.1 \times 10^{-6} \)) for one allele increase in GRSCAD. The same association was seen in both sexes. GRSCAD predicted significantly the risk of SCDCAD also in a prospective study setting (Cox regression analysis adjusted with all relevant clinical data): hazard ratio 1.049 (1.010–1.090, \( P = 0.014 \)). In meta-analysis of all cohorts (adjusting further for other genetic markers related to traditional risk factors and QT-interval), the association was highly significant [OR 1.045 (1.028–1.063), \( P = 1.7 \times 10^{-7} \)].

Conclusion

Genetic risk estimate for CAD may also be used to predict SCD.

Keywords

Death · Sudden · Coronary artery disease · Genetics

Introduction

The hereditary component of atherosclerosis is notable, but the genetic background of the disease and especially its most dramatic consequence—sudden cardiac death (SCD)—due to complications of coronary artery disease (CAD) is still poorly understood.

The continuously growing number of genome-wide association studies (GWAS) has discovered many common variants associating...
with myocardial infarction (MI) and CAD with the ultimate GWAS in size (63,746 CAD cases and 130,681 controls) combining the data from two largest consortia (CARDIoGRAMplusC4D Consortium). As a result, 153 loci were identified to associate with CAD at a 5% false discovery rate (46 loci were genome-wide significant), accounting for 10.6% of the heritability of CAD. As CAD is the underlying condition in ~80% of all SCDs, the GWAS results could also be linked to aetiology of SCD.2 Supporting this, individual variants linked with CAD have already been shown to associate with SCD.3,4

Most genetic variants found to associate with the occurrence of SCD are linked with electrophysiological factors leading to fatal arrhythmias (even without the presence of coronary atherosclerosis) and with coagulation factors.5–9 However, the results of individual variants are often not replicable, and their predictive value is weak. For SCD, only one rare genome-wide significant variant (rs4665058-A risk allele frequency of 1.4%) has been discovered with the results properly replicated.7

Genetic risk scores (GRSs) based on genome-wide significant variants have proved useful in predicting the risk for developing CAD and even the risk of acute coronary events beyond traditional risk factors.10,11 In this study, we set out to test whether a GRS formed from the strongest variants associating with CAD as reported by the CARDIoGRAMplusC4D Consortium would predict the occurrence of out-of-hospital SCD caused by CAD. We performed a meta-analysis of three independent prospective autopsy series of Caucasian subjects. For replication we tested whether a similar risk score would predict the risk for SCD during follow-up in a patient population undergoing clinical exercise testing at baseline.

Methods

Autopsy series

The present study comprises three consecutive autopsy series representing a cross-sectional population sample of deaths occurring out of hospital for any reason. The first series (The Helsinki Sudden Death Study, HSDS) was collected between 1991 and 1992 in the region of Helsinki and comprises 300 men aged 35–69 years. The second series (Tampere Coronary Study, TCS) was collected between 2001 and 2004 and comprises 245 men matching the age range of the larger HSDS. In the third series (ongoing Tampere Sudden Death Study, TSDS), a total of 599 cases (men and women) were collected during 2010–13.

Coronary artery disease risk factor data were collected by interview of a spouse, a relative, or a close friend of the deceased in HSDS and TSDS. The risk factors covered in the questionnaire were smoking and alcohol consumption habits as well as hypertension, diabetes, or other previous illnesses. The validity of the interview data when obtained is generally considered high.12

The cause of death was determined in a routine manner by the forensic pathologist who performed the autopsy using the same general rules for choosing the underlying cause of death that were used in autopsies not belonging to the study series. The heart was routinely examined, including dissection of all major branches of the coronary arteries and recording the presence or absence of thrombosis as well as acute/old MI. The presence of recent or old MI with or without coronary thrombosis was recorded and histologically confirmed.

In HSDS, the permission to collect the series was obtained from the ethical committee of the Department of Forensic Medicine, University of Helsinki. In TCS and TSDS, the permission was obtained from the ethical committee of Tampere University hospital and from the National Supervisory Authority for Welfare and Health (Valvira).

Clinical study (Finnish Cardiovascular Study)

All consecutive patients who were referred for an exercise test due to any indication at Tampere University Hospital between October 2001 and December 2008 and who were willing to participate in the Finnish Cardiovascular Study (FINCAVAS) were recruited. Genotyping and clinical data were available for 2321 subjects with extensive follow-up data. The study protocol was approved by the Ethics Committee of the Tampere University Hospital District, Finland, and all patients gave informed consent before the interview and measurements as stipulated in the Declaration of Helsinki. See Supplementary material online for a more detailed description of the study.

Classification of coronary artery disease-related sudden cardiac death

The classification of causes of death is based on forensic evidence. Coronary artery disease-related SCD (SCDCAD) was defined as cardiac death caused by coronary atherosclerosis and or with acute or old MI. Non-coronary SCDs (27% of all SCDs) (SCDother) due to cardiomyopathy, myocarditis, valvular disease, and non-classifiable hypertrophy or dilatation of the heart in the absence of significant coronary disease were excluded from the control group. Due to smaller number of observations in the clinical study (FINCAVAS), the analyses were performed by both including all SCDs (n = 48) and focusing only on SCDCAD (n = 39).

Selection candidate single-nucleotide polymorphisms and genotyping

The single-nucleotide polymorphisms (SNPs) selected for the GRS were derived from the GWAS performed by CARDIoGRAMplusC4D Consortium.3 All SNPs associated on a genome-wide significant level were included as well as SNPs strongly associated with CAD [false discovery rate (FDR) <0.05 and linkage disequilibrium of $r^2 < 0.2$] (see Supplementary material online, Table S1 for the present manuscript and also see Supplementary material online for the report by CARDIoGRAMplusC4D Consortium). Together these variants have been estimated to explain ~10.6% of the heritability of CAD.

Genotyping was performed by Affymetrix Genome-Wide Human SNP Array 6.0 chip for HSDS and TCS. Tampere Sudden Death Study was genotyped using Illumina HumanCoreExome chip and FINCAVAS using the HumanCardio-Metabo BeadChip. Precise description of DNA isolation, genotyping, and imputation methods are presented in Supplementary material online.

Statistical analyses

The effects of the CAD/MI SNPs as a whole in the autopsy series were analysed by calculating a GRS of the 153 SNPs fulfilling the selection criteria. All 153 risk variants identified in the GWAS were available in our data, either in true genotyped or well-impputed form (info ≥0.868). The GRSs were constructed by summing up the risk allele dosages of each SNP and applying a specific risk coefficient for CAD previously identified by the CARDIoGRAMplusC4D Consortium for each loci. Weighted allelic risk scores constructed in this manner have been shown to have better power for detecting associations.13

Logistic regression analysis was used to study the association between GRSCAD and SCD both unadjusted and adjusted for age and body mass index (BMI) in all autopsy series separately (also sex adjustment applied in TSDS), and the results were meta-analysed using a fixed effects model (no heterogeneity observed). Unadjusted results are presented in Supplementary material online. The association between GRSCAD...
and SCD in FINCAVAS was analysed by Cox regression analysis adjusted with significant clinical predictors of SCD using a forward selection algorithm. All covariates fulfilled the proportionality assumption based on correlations of survival rankings with Schoenfeld residuals. All results are reported in relative risk changes corresponding to one allele increase in GRSCAD unless stated otherwise. In FINCAVAS, where extensive clinical risk factor data were available, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated. Reclassification statistics were calculated comparing best and integrated clinical risk factor data were available, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated. Reclassification statistics were calculated comparing best possible multivariate model for risk estimation using all but genetic risk factors to the risk estimation model including GRSCAD.

The association between individual SNPs and SCD was studied by a meta-analysis of all studies. All analyses were performed using SPSS Statistics software (version 19.0; SPSS Inc., Chicago, IL, USA) and R language (version 2.13.0). P-values below 0.05 were considered statistically significant.

**Results**

**General characteristics of the autopsy series**

Clinical characteristics of the three autopsy series are presented in Table 1. Altogether 1035 subjects were successfully genotyped with 306 cases of SCD. Controls for the analysis (n = 616) comprised subjects died due to other cardiovascular causes (17%), malignancies (4%), other illnesses (22%), and unnatural causes (57%). Age and BMI associated significantly with SCD [adjusted OR 2.06 (1.24–3.42), P = 0.005]. The genotyped SNPs are listed in Supplementary material online, Table S1.

**Association between coronary artery disease GRSCAD and sudden cardiac death in meta-analysis of autopsy series**

On average, victims died of SCD carried more risk alleles per CAD risk variant compared with controls [unweighted GRS: 154.2 (SD 8.2) vs. 156.8 (SD 8.4), P < 0.001] (Table 1).

In meta-analysis, one allele increase in GRS corresponded to an OR of 1.042 (1.023–1.061, P = 9.1 × 10^{-6}). This means that one standard deviation in GRS corresponded to an OR of 1.44 (1.23–1.69). When we limited the control group to subjects with CAD (n = 147 with previous MI, previous stable disease or revascularization and/or significant >50% coronary stenosis in autopsy), the result remained significant [OR 1.034 (1.009–1.060), P = 0.0081]. Further sensitivity analyses accounting for possible inaccuracies in post-mortem diagnosis of the cause of death did not change the results, and the effect was similar among men and women (see Supplementary material online, Table S7).

In HS and TS, interview data were obtained of previous hypertension (n = 280, 35% of the two cohorts), diabetes (n = 279, 35%), or smoking (n = 353, 45%). Adjusting for these variables did not change the risk attributable to GRSCAD and the association remained significant despite lower sample size (OR estimates between 1.043 and 1.052 with P < 0.001 for all analyses).

In the meta-analysis of all autopsy series, GRS did not associate with the risk of SCD due to other causes [adjusted OR 1.013 (0.987–1.039), P = 0.360].

### Predicting sudden cardiac death using genetic risk score for coronary artery disease in prospective study setting

For replication, we tested whether the GRSCAD would predict the risk for SCD in a population of patients undergoing clinical exercise at baseline (n = 2321, see Table 2 for baseline population characteristics). During the follow-up of ~6.2 years (SD 2.2 years), 48 cases of all-cause SCD and 39 SCD were recorded. According to adjusted Cox regression, GRSCAD associated significantly with the risk of all-cause SCD [hazard ratio (HR) 1.049 (1.010–1.090), P = 0.011] and SCD [HR 1.049 (1.010–1.090), P = 0.014] (see Figure 1 for population stratification by GRSCAD). Significant adjusting variables were age, sex, use of angiotensin-converting enzyme inhibitors, the use of diuretics, prevalent coronary heart disease.

### Table 1 General characteristics of three combined autopsy series (HS, TS, and TS) used in the meta-analysis

<table>
<thead>
<tr>
<th></th>
<th>Combined autopsy series (n = 1035)</th>
<th>Controls, n = 616</th>
<th>Other SCD, n = 113</th>
<th>SCD due to CAD, n = 306</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
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<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m^2</td>
<td></td>
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<td></td>
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<tr>
<td>Men^a</td>
<td></td>
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<td>0.501</td>
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<tr>
<td>Hypertensive, n</td>
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<td>Diabetic, n</td>
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<tr>
<td>Smokers, n</td>
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<td></td>
<td></td>
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<tr>
<td>Heart mass in autopsy, g^c</td>
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<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unweighted genetic risk score</td>
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<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>Weighted genetic risk score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Continuous variables are presented by mean (standard deviation) except for heart mass, which is presented by median (inter-quartile range).

HS, Helsinki Sudden Death Study; TS, Tampere Coronary Study; TS, Tampere, Sudden Death Study; CAD, coronary artery disease; SCD, sudden cardiac death.

^aWomen were only included in the last autopsy series (TS).

^bInterview data only available in a subset of patients in HS and TS.

^cAvailable only in TS and HS.
disease (CHD), achieved metabolic equivalent of task, and serum creatinine.

Most of the SCD_{CAD} cases occurred among population with CHD at baseline (n = 31). Limiting the analysis to this population revealed more pronounced effect [HR 1.053 (1.008–1.1100), P = 0.022] (see Supplementary material online, methods for the definition of CHD). Among patients without CHD at baseline, the risk estimate was lower [HR 1.026 (0.946–1.112), P = 0.534], but the low number of SCD_{CAD} in this group (n = 8) limits the interpretation of this result. GRS_{CAD} and diagnosis of CHD did not interact significantly predicting the risk of SCD_{CAD} (P = 0.612). Sensitivity analyses performed in the subgroup of patients with measured ejection fraction of left ventricle and after excluding all patients with hypercholesterolaemia did not change the results significantly (see Supplementary material online, Table S1).

At baseline, GRS_{CAD} was seen to associate significantly with the use of lipid-lowering medication, the occurrence of right bundle branch block and prevalent CAD, and suffered acute MI (P ≤ 0.01 for all). Additional adjustments for any of these variables or with baseline lipid values, blood pressure, or measured long QT interval did not change the observed predictive value of GRS_{CAD} on SCD_{CAD} [Significant (P < 0.03) HR estimates ranging between 1.40 and 1.61, with varied sample size due to partially missing data on same factors].

Finally, adding GRS_{CAD} to risk modelling for SCD (preliminary model adjusted with age, sex, use of angiotensin convertase enzyme inhibitors, the use of diuretics, prevalent CHD, achieved metabolic equivalent of task, and serum creatinine) resulted in IDI improvement of 0.010 units [95% confidence interval (CI) 0.002–0.0172, P = 0.010]. NRI was 18.0% (95% CI 2.8–33.2, P = 0.020) and cross-validated (1000 times). NRI was 18.0% (95% CI 2.8–33.2, P = 0.020) and cross-validated (1000 times) net reclassification improvement was 16.0% (95% CI 2.2–31.7, P = 0.022). C-statistic improvement was not significant (from 0.8084 to 0.8132, P = 0.655).
The association between coronary artery disease single-nucleotide polymorphisms and sudden cardiac death in the meta-analysis

Overall 13 SNPs that provided the best model fit were found to associate significantly with $\text{SCD}_{\text{CAD}}$ in the final meta-analysed multivariate model (Table 3). The results for all individually meta-analysed SNPs are presented in Supplementary material online, Table S1.

Discussion

The results of the present study show that genetic propensity modelled by genetic risk scoring using a large set of significant risk loci for CAD associates highly significantly with the occurrence of CAD-related out-of-hospital SCD in a meta-analysis of three independent consecutive autopsy series. Furthermore, genetic risk scoring can be used to predict the risk of SCD over other clinically important risk factors.

Traditionally, SCD is difficult to predict. Although certain patient groups, such as major acute coronary event survivors or heart failure patients, are known to be prone to SCD, they only account for a small number of the cases, because the majority of SCDs occur in the normal adult population. However, ~75% of all SCD victims are men. One of the advantages of the present study is the fact that all included forensic autopsy series (HSDS, TCS, and TSDS) cover almost all SCDs of adult men in the regions of Helsinki and Tampere during the periods when the autopsy series were performed. The largest autopsy series (TSDS) also included women, and the association between $\text{GRS}_{\text{CAD}}$ and SCD was similar in men and women. Forensic autopsy series in Finland comprise practically all SCDs occurring outside hospital. The high autopsy coverage is due to Finnish legislation, which stipulates that medicolegal autopsy is mandatory whenever a sudden death is not due to a known condition and the deceased has not been treated by a physician during his/her latest illness, or when the death has been otherwise unexpected (Act on the Inquest into the Cause of Death, 459/1973, 7th paragraph; http://www.finlex.fi/en/). In Finland, medicolegal autopsy was performed on ~18 and 21% of all persons deceased in 1991–92 and 2001–04, respectively (http://www.stat.fi/ti/l/ksyyt/index_en.html). This number is higher compared with most other high-income countries.

Thus far, family history has been the strongest known predictor of SCD. Sudden cardiac death victims are ~11 times more likely to have two or more first-degree relatives who have also suffered an SCD compared with a control population, but this applies only to a small fraction of the population (~1%). The results of the Paris Prospective Study I are corresponding. Due to its rarity, heavy family history of sudden death is not generally applicable in risk prediction. Unfortunately, we lack the data on parental history of SCD in the present study. Combined, parental history of SCD and genetic profiling could lead to unprecedented results in risk profiling.

To study whether the GRS actually could predict the risk of SCD, we used a prospective follow-up study (FINCAVAS, $n = 2321$) of patients who underwent clinical exercise testing at baseline. The population does not represent general population as all patients were enrolled to the study on clinical, not investigational, indications. Overall, 20.5% of the population had history of AMI and 39.8% of the population had CAD. In this population, $\text{GRS}_{\text{CAD}}$ predicted significantly all-cause SCDs as well as $\text{SCD}_{\text{CAD}}$ with the observed risk estimate being most evident among subjects with CAD. The association was also significant in the autopsy series when the control group was limited to subjects with CAD. This proves that the association does not only reflect that SCD victims have higher prevalence of CAD. Whether $\text{GRS}_{\text{CAD}}$ can be used to predict SCD among general population warrants further investigation. However, it is safe to assume that among population undergoing exercise testing, the predictive value of the GRS is high and reclassification benefit is significant despite any clinical information obtainable including all traditional risk factors for CAD and SCD. Perhaps angiography or perfusion imaging could reveal more precise estimates of the risk. However, for asymptomatic subjects, these methods are not indicated. Genetic testing, with its rapidly decreasing costs, could provide a cost efficient and safe alternative when combined with other easily obtainable clinical parameters and patient history.

![Figure 2](https://example.com/figure2.png)
According to meta-analysis of all the cohorts, 15 variants associated significantly with SCD in univariate analysis (of which only two seemed to have paradoxically protective impact on the occurrence of SCD). In multivariate analysis, 13 loci persisted as significant including rs1333049, which has been previously linked with SCD. Other discovered variants have not been previously linked with SCD.

Unfortunately, our autopsy series do not include lipid and blood pressure measurements. However, adjustment with BMI, which correlates moderately with both lipid values and blood pressure, did not change the risk attributable to GRS, and the result was successfully replicated in a population with extensive risk factor data. Furthermore, repeating the meta-analysis after excluding all genome-wide significant variants for CAD are not associated with lipid or blood pressure values did not change the results (data not shown). These results are in line with functional evidence showing that most of the currently known genome-wide significant variants for CAD are not associated with lipid values, blood pressure, or diabetes. Finally, we also repeated the analyses after adjusting extensively for other genetic risk factors by forming additional GRSs for lipids, blood pressure, and QT-time in all cohorts. These GRSs are based on genome-wide significant variants from large study consortia with the results of the largest GWAS for lipid values representing ~25–30% of the genetic variance for serum lipid values. Although, the genetic variance is not a surrogate for actual serum lipid measurements or BP measurements, prolonged genetic exposure is shown to have very substantial risk in defining CHD risk. However, we found little evidence that genetic propensity for these factors would be strongly associated with SCD, but due to lack of power in our study, we cannot rule out the possibility of weaker genetic effects affecting the risk of SCD.

In conclusion, a GRS formed of the most significant common genetic risk variants for CAD associates very significantly with the occurrence of SCD due to CAD, and it can be used to predict SCD above clinical risk factors in a population undergoing clinical exercise testing. Quantifiable genetic propensity for CAD may in the future be used as a tool in clinical decision-making regarding individually tailored medical treatment for preventing SCD.

### Supplementary material

Supplementary material is available at European Heart Journal online.

### Funding

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### Conflict of interest

None declared.

### References


### Table 3

<table>
<thead>
<tr>
<th>Nearest loci</th>
<th>Risk allele</th>
<th>Frequency</th>
<th>OR (95% CI)</th>
<th>P-value</th>
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<tr>
<td>rs16986953</td>
<td>AK097927</td>
<td>A</td>
<td>0.066</td>
<td>1.91 (1.30–2.80)</td>
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<td>rs1333049</td>
<td>CDKN2BAS</td>
<td>C</td>
<td>0.438</td>
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<tr>
<td>rs11619057</td>
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<td>0.158</td>
<td>1.53 (1.15–2.02)</td>
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<td>0.840</td>
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</tr>
</tbody>
</table>

Model constructed by using general linear modelling with stepwise procedure employing Akaike Information Criterion for evaluating model fit.

OR, odds ratio; CI, confidence interval; SCD, sudden cardiac death.

*Significant heterogeneity observed between studies ($I^2 = 64.9$%), random effects model $P = 0.2542$ for OR $0.77$ (0.50–1.20).

**Significant heterogeneity observed between studies ($I^2 = 61.5$%), random effects model $P = 0.2085$ for OR $1.34$ (0.85–2.13).


