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Coronary Artery Calcification and Rheumatoid Arthritis: Lack of Relationship to Risk Alleles for Coronary Artery Disease in the General Population

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Abstract

Objective—Coronary artery disease (CAD) in the general population is characterized by an increased frequency of particular susceptibility single nucleotide polymorphisms (SNPs). Since CAD is increased in rheumatoid arthritis (RA), we sought to determine whether the frequency of these SNPs are increased in RA patients with CAD, hypothesizing that RA could enhance CAD risk by acting through established genetic pathways predisposing to CAD.

Methods—CAD was assessed by coronary artery calcification (CAC) using computed-tomography in 561 patients with RA. 100 SNPs associated with CAD in the general population were genotyped or imputed and their relation to CAC established through multiple regression analysis for individual SNPs and a genetic risk score (GRS) representing their cumulative effect.

Results—91 CAD SNPs were genotyped successfully; 81 exhibited no association with CAC (Agatston units) or different CAC categorizations, either individually or collectively in the GRS. Only rs579459 (*ABO*) and rs17676451 (*HAL*) had a consistent positive association between genotype and CAC score, with a significant increase of the effect allele frequency in both

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homozygous or heterozygous genotype distributions. 5 were variably negatively associated. Furthermore, a positive association was found between DAS28 and CAC and after adjusting for traditional cardiovascular risk factors it was not modified by correcting for the CAD related SNPs GRS.

Conclusion—The increased risk for CAC in RA does not appear to operate primarily through established genetically regulated atherogenic mechanisms that are preponderant in the general population.

Introduction

Individuals with rheumatoid arthritis (RA) have an increased incidence of cardiovascular events, including myocardial infarctions and cardiac deaths (1). This excess in cardiovascular disease cannot be completely explained by traditional atherosclerosis risk factors, and it is thought to be due to an accelerated atherogenic process that appears to be related to one or more elements in the immune response underlying RA (2).

In the general population, 30-60% of the risk of developing coronary artery disease (CAD) is estimated to be genetic (3). Genome-wide association studies (GWAS) have identified and validated over 100 SNPs that are associated with CAD susceptibility. Moreover, the risk of CAD is proportional to the number of these SNPs inherited by an individual (4-21). These SNPs have been associated with increased risk of CAD through diverse mechanisms, including effects on lipid metabolism, plaque stability, and acute myocardial infarction. Still others act through unknown pathways, suggesting varying impacts of different alleles on the biology and pathophysiology of cardiovascular disease. In particular, some SNPs focus attention on novel and intriguing mechanisms contributing to CAD, such as those mapping to the 53 kb region of chromosome 9p21.3, an area without classic genes that encodes an antisense noncoding RNA in the *INK4* locus, designated *ANRIL*, or *CDKN2B-AS1* (22). Homozygosity for 9p21.3 risk alleles confers a population-attributable risk of 21% for CAD (23). Similarly, pathways involving glycotransferase activity encoded at the *ABO* locus are considered to foster development of myocardial infarction in the general population, acting on the stage after development of atherosclerosis (24).

Coronary artery calcification (CAC) detected by computed tomography is a noninvasive validated measure of subclinical CAD in the general population (25). Direct relationships have been established between CAC scores and histologic, intracoronary ultrasonic, and angiographic measures of coronary artery atherosclerosis and plaque burden on a vessel-by-vessel and segment-by-segment basis (26). CAC has been shown to predict incident myocardial infarction even after adjustment for other traditional cardiovascular risk factors (27). Importantly, analogous to CAD, the presence of CAC is also a heritable trait (28) and CAC is significantly higher in individuals with a parental history of CAD (29). In the general population, it is now recognized that many of SNPs predominantly exert their influence at different stages of the biologic events leading to the ultimate development of myocardial infarction, including atherosclerosis, CAC, and CAD (24), and the presence of CAC analogously has been linked to the SNPs associated with CAD across multiple genetic loci (5, 30).

In RA, both the prevalence of positive CAC scores and their magnitude are significantly increased compared with the general population (31). Elevated CAC scores in RA patients have also been shown to independently predict cardiovascular events (32).

Accordingly, we sought to determine whether in the subset of RA patients with CAC, the frequency of the SNPs associated with CAD in the general population would also be significantly increased over their frequency in the subset of RA patients without CAC. If this were found to be the case, it would imply that the effect of RA is to enhance the risk for CAD by acting through established genetic pathways that result in CAD in the general population, resulting in an increase of RA patients having these susceptibility genes in the group with CAC. Alternatively, if the frequencies of these alleles were not found to be significantly increased among RA patients with CAC, it would suggest that increased CAC in RA is a consequence of RA-associated immune mediated mechanisms that act independently of the genetically determined proatherosclerotic pathways operating in the general population.

Material and methods

Study participants and data collection

A total of 561 patients with RA from three different clinic-based cohorts (the ESCAPE-RA cohort from Johns Hopkins University, and two additional cohorts from the University of Pittsburgh and Vanderbilt University) were included in this study. All patients were men or women who were diagnosed by a rheumatologist and who fulfilled the American Rheumatism Association 1987 revised criteria for the classification of RA (33). The *ESCAPE-RA (Evaluation of Subclinical Cardiovascular disease And Predictors of Events in Rheumatoid Arthritis) study* has been described in detail previously (31) and was initiated to study the prevalence, progression, and risk factors for subclinical cardiovascular disease in RA. A total of 197 patients aged 45 to 80 years old with a disease duration >6 months, were recruited from the Johns Hopkins Arthritis Center. The *Pittsburgh cohort* consisted of 195 patients recruited from the University of Pittsburgh Medical Center Arthritis Network outpatient practices. For this cohort patients were only women, 16 years old or older, and disease duration was ≥ 2 years. In the *Vanderbilt cohort*, patients were a minimum age of 18 years old and there were two groups of patients: duration of disease of <5 years (early RA) or >10 years (established RA). In this cohort 169 patients were obtained from a registry of patients with early RA, were referred by local rheumatologists, or were recruited by advertisements. Details of the Pittsburgh and Vanderbilt cohorts have also been previously reported (34, 35). Each study was approved by the Institutional Review Board of the universities and hospitals of the three cohorts with all subjects providing written informed consent prior to enrollment.

Assessments and CAC quantification

Age, gender, race/ethnicity, current and past smoking were assessed from patient-self report. Ninety percent of patients in the three cohorts were of Caucasian ethnicity. Patients filled in a medication usage questionnaire and underwent examination to assess anthropometric measures and blood pressure. Medical records were reviewed to ascertain diagnosis and

medication. Current and past use of glucocorticoids, biologic and non-biologic disease modifying antirheumatic drugs use was queried by detailed examiner-administered questionnaires. Disease activity was measured using the Disease Activity Score in 28 joints (DAS28) through erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), while the degree of disease disability was determined using the Health Assessment Questionnaire (HAQ). Metabolic syndrome was defined using the 2005 National Cholesterol Education Program Adult Treatment Panel III (ATP III) criteria.

Fasting plasma and serum samples were collected and frozen until analysis of circulating lipids, glucose, insulin, high sensitivity C-reactive protein and homocysteine. Rheumatoid factor was assessed by nephelometry with seropositivity defined at or above a level of 40 units. All subjects underwent cardiac computerized tomography using methodology described previously (36). CAC was quantitated using the Agatston method (37). In addition to the Agatston score as a continuous variable, CAC was also categorized as greater than 0 and greater than 10 Agatston units, and 75th and 90th CAC percentiles, adjusted for age, gender and race/ethnicity, were also defined as previously described (38).

Genotyping, imputation, and genetic risk score calculation

We identified SNPs of interest from genome-wide association studies published up to 2014 in which phenotypes studied were myocardial infarction, angiographically defined CAD, and CAC, which we refer to collectively as “CAD”, and where the association between a SNP and CAD exceeded a genome-wide association threshold ($p < 5 \times 10^{-8}$). We identified 100 CAD related disease SNPs in the literature (4-21). Supplementary Table 1 shows the selected SNPs with details of their gene information, effect and non-effect alleles and published odd ratio (OR), or beta coefficient, association effect. RA patients were genotyped using the *ImmunoChip*. This is an *Illumina Infinium* genotyping chip, containing 196,524 polymorphisms (718 small insertion deletions, 195,806 SNPs) designed both to perform deep replication of major autoimmune and inflammatory diseases, and fine-mapping of established GWAS significant loci (39). Because some CAD SNPs in the GWAS studies were identified using alternative chips, such as the *MetaboChip* (40) with a different selection of SNPs not present on the *ImmunoChip*, it was necessary to impute these un-typed SNPs using *Impute2* software (41) after being ‘pre-phased’ using SHAPEIT (42). SNPs with low imputation quality, minor allele frequency <1% or Hardy–Weinberg equilibrium <0.001 were excluded. Of the 100 selected SNPs, 9 were neither able to be genotyped nor successfully imputed (rs17114036, rs6783981, rs1878406, rs273909, rs12205331, rs9268402, rs3184504, rs2895811, rs17228213). A multilocus genetic risk score (GRS) was constructed as previously described using *Plink 1.07* software (43) for each individual by summing the number of CAD alleles (0/1/2) for each of the 86 SNPs weighted by their estimated effect sizes (OR) (rs6783981, rs2026458, rs10811647, rs17676451, rs3809346, rs8001186 were not include in the genetic risk calculation because OR information was not available). Missing genotype values in the GRS calculation were imputed with the cohort-specific averages of risk allele frequencies. Supplementary Table 1 shows SNP specific weights.

Statistical analysis

The hypothesis to be tested in this study design was that in the subset of RA patients with CAC, the frequency of the SNPs known, *a priori* from the literature, to be associated with CAD in the general population would be significantly increased in frequency in the subset of RA patients with CAC, versus their frequency in those RA patients without CAC.

Accordingly the correction for multiple comparisons required in a study with *a posteriori* hypotheses is not appropriate in this study design. In terms of study power, on the basis of previously published findings (44) we assumed that smoking, hypertension and diabetes are associated with approximately 50% of the risk of an acute myocardial infarction. In a European cohort (45), a GRS created from three SNPs that have been credibly associated with CAC explained 2.4 % of the variation in CAC, and a 45-SNP GRS constructed from CAD-associated SNPs explained an additional 4 %. Proceeding with these conservative assumptions, in a multivariable regression model with a α level of 0.05 and a β level of 0.10, and assuming a coefficient of determination of 50% and that this would increase to 52% when adding GRS to the model, we estimated that we would need to enroll 425 subjects.

The distributions of all variables were examined. Means and standard deviations were calculated for all normally distributed continuous variables and medians and interquartile ranges were calculated for continuous variables that were not normally distributed. For categorical variables, counts and percentages were calculated. CAC scores were modeled as the natural log of the CAC score plus 1, in order to account for zero scores. In table 2 CAC Agatston units are expressed as median (interquartile range) and U Mann-Whitney test were used to test for the differences in CAC units between allele groups. In this sense, Table 2 describes the comparison of effect allele homozygous vs. heterozygous, and the comparison of the effect allele vs. the non-effect. Similarly, logistic regression analysis adjusted for traditional cardiovascular risk factors (age, sex, diabetes, hypertension, dyslipidemia, and smoking) was used to also study the relation of homozygous against heterozygous, or for the relation of affected allele against the non affected, with CAC expressed as higher than 0 and 10 units or higher than 70th and 90th percentiles. This association analysis in Table 2 was performed using SNPTTEST that can account for some imputation uncertainty (46). Linear trends for the association of GRS and CAC were tested using linear regression with orthogonal polynomial contrasts. To assess the relationship of CAC and GRS with DAS28, three models were constructed, one adjusted for age and sex (model 1), model 2 adjusted for model 1 plus traditional cardiovascular risk factors (diabetes, hypertension, smoking and dyslipidemia) and model 3 that was constructed by adding GRS to both model 1 and 2. All statistical calculations were performed using SPSS software, version 21 (IBM). In all tests, a two-tailed alpha of 0.05 was defined as the level of statistical significance.

Results

Demographic, laboratory, and clinical characteristics

The clinical characteristics of the patients in the three cohorts are presented in Table 1. Average age across the three cohorts was 57.6 ± 10.5 years old, 77% of the patients were women and 89% of the patients were Caucasian. Cardiovascular comorbidity was not different between groups except for a higher prevalence of hypertension, current smoking,

and aspirin intake in the Vanderbilt cohort, where patients with previously known CVD were allowed to enroll. There were no differences between cohorts regarding CAC Agatston score. Median CAC score was 3.12 (interquartile range 0-134.35) in the three cohorts, and 21% and 35% of the patients had a CAC score greater than the 90th and 75th percentile, respectively. RA disease duration was 10 (interquartile range 3-20) years, 44% of the patients were receiving corticosteroid treatment, 32% were receiving anti-TNF therapy, and 65% were seropositive for rheumatoid factor.

Coronary artery disease related SNPs in relation to RA CAC

Table 2 shows the relation of the 91 SNPs related to CAD in the general population to the presence of CAC in the RA cohort. 86 of these SNPs did not exhibit any positive association with CAC in the RA cohort, either considering the affected versus the non-affected allele in homozygous or heterozygous inheritance with the Agatston score as a continuous variable, or in the association analysis using CAC categorizations. Only rs646776 (*CELSR2*), rs602633 (*PSCR1*), rs579459 (*ABO*), rs501120 (*CXCL12*) and rs17676451 (*HAL*) expressed any positive relation with CAC in one or more of the analyses. rs579459 (*ABO*) and rs17676451 (*HAL*) genotype exhibited the most consistent association between genotype and CAC Agatston units, with a significant increase in the frequency of the effect alleles in both homozygous or heterozygous genotype distributions, however, in the case of *ABO*, CAC categorizations, although demonstrating trends to significance, were not significantly associated. The positive associations for the other three SNPs were much less consistent, e.g. for rs501120 (*CXCL12*) there was no association of homozygous or heterozygous genotype distribution with CAC Agatston units, however in heterozygotes there was a positive association with the effect allele A in higher than 10 units CAC categorization (odds ratio 1.96 [1.13-3.41]), although there was no association of any CAC categorizations with the homozygous AA genotype, which would be expected to be more sensitive (Table 2).

Notably, none of the group of the 12 SNPs mapping in the 53 kb region of chromosome 9p21.3, encoding *ANRIL* that are among the strongest predictors of CAD in the general population exhibited any association with CAD. Moreover, in the instance of *PHACTR1*, also strongly positively associated with CAD risk in the general population, three SNPs (rs9369640, rs12526453, and rs1332844) consistently showed a limited and incomplete protective relation with CAC. E.g., in the case of rs1332844, the p value for a homozygous or heterozygous mode of inheritance was respectively 0.01 and 0.08. Additionally *COL4A2* (rs9515203) and *LDLR* (rs2228671) were negatively associated with CAC in the homozygous mode of inheritance.

Number of homozygous SNPs in relation to RA CAC

When the association of the CAD related SNPs with CAC was studied through the non weighted and weighted set of SNPs, no significant association was found. In particular, an increase in the number of both homozygous or heterozygous cardiovascular disease related SNPs was not significantly associated with an increase in *log* CAC Agatston units (Figure 1, panel A). Correspondingly, CAC categorizations in CAC higher than 0 and 10 units, and

higher than 75th and 90 percentiles did not exhibit an increased frequency of homozygous or heterozygous SNPs (Figure 1, panel B).

Additionally, when CAD related SNPs were weighted by their effect sizes, the resulting GRS was not significantly associated with CAC. Furthermore, trend analysis showed no relation between GRS and log CAC Agatston units ($p=0.93$) (Figure 1, panel C).

Genetic risk score, disease activity, and CAC

The relationship between CAC and GRS or disease activity is illustrated in Table 3 through the value of the beta coefficient, which reflects the change in GRS as a function of the change in CAC categorizations. All the categorizations of CAC were associated with higher disease activity scores (DAS 28) after adjusting for age and sex. When this analysis was performed adjusting for traditional cardiovascular risk factors like diabetes, dyslipidemia, hypertension and smoking this relation was maintained in higher than CAC 90th percentile patients (beta coefficient 0.43 [0.04-0.81], $p=0.03$) and was nearly significant in both patients with CAC higher than 10 Agatston units (beta coef. 0.34 [-0.01-0.68], $p=0.06$) or patients within the CAC 75th percentile (beta coef. 0.28 [-0.05-0.60], $p=0.09$).

Conversely, GRS was inversely associated with CAC higher than 0 (- 0.03 [-0.06--0.00], 0.03) and higher than 10 Agatston units (- 0.04 [-0.06--0.01], 0.04) (Table 3). However, in the multivariate analysis, after adjusting for age and sex and for traditional cardiovascular factors, GRS was not related with CAC. In this sense, patients within CAC 90th percentile did not exhibit higher levels of GRS even after multivariate analysis (beta coef. 0.02 [-0.03-0.06], $p=0.50$).

Similarly, the relation between CAC and DAS28 was not modified when the analysis was adjusted for GRS (Model 3). In this regard, when we evaluated the association between CAC 90th percentile patients and DAS28 for the contribution of GRS, the statistically significant association (beta coef. 0.42 [0.04-0.81], $p=0.03$) between CAC and DAS28, was maintained in this set of patients, and was not modified by GRS.

Discussion

The central finding of our study is that RA patients with CAC, compared to those without CAC do not exhibit the elevated frequency of the multiple CAD specific SNPs found at increased frequency among patients in the general population with CAD. This finding suggests that CAC in RA does not develop through the concerted action of the same genes and their related pathways implicated with the development of CAD in the general population. The lack of contribution of these proatherosclerotic genes implies that RA itself should be considered an independent cardiovascular risk factor. Accordingly, we suggest that some factor in the RA immune response primarily contributes to the increased prevalence and incidence of cardiovascular disease in RA through pathways distinct from the proatherosclerotic pathways that operate in the general population to cause CAD.

Cardiovascular disease has an estimated heritability in the general population of 30–60% and genome-wide association studies have identified SNPs at several genomic regions

associated with atherosclerosis, CAD and the progression to myocardial infarction (4-24, 47). However, the role of these CAD SNPs known to be related with cardiovascular disease in general population has not been previously explored in RA patients. In this study we used CAC as a complex cardiovascular trait related with CAD. The use of CAC as a validated CAD equivalent is supported by its ability to predict incident coronary heart disease even after adjustment for traditional cardiovascular risk factors (27).

Because each individual genetic variant specified by a SNP explains a small fraction of the variation in a complex trait and thus has limited predictive capacity for disease risk (48), we also constructed a weighted GRS with all the CAD related SNPs. GRSs are one of the most promising ways to aggregate multiple sets of SNP results into a single genetic predictor, and have been previously applied to different cardiovascular traits in the literature (49). Although still under development (49), they have been successfully used to predict cardiovascular outcomes and intermediate traits or subclinical phenotypes, including coronary heart/artery disease (50), myocardial infarction (51), ischemic stroke (52), or hypertension (53).

We note that we had the power to detect an association with an effect size of 0.1 at an alpha of 0.05. However, the observed effect sizes were much lower if not negligible. For example, if we sought to detect an association of 0.5% (that could be considered clearly insignificant) we would need a sample size of 1731. Moreover, the positive association with the *ABO* SNP supports the notion that this study was sufficiently powered to detect associations of CAD SNPs to confer susceptibility if they were present. Therefore, it is appropriate to infer that the CAD SNPs are unlikely to be a significant source of variability for CAC in RA patients. The *ABO* locus encodes glyco-transferases that when absent in blood group O individuals protect against myocardial infarction (24), although their relation to CAC in RA patients suggests they may foster CAC development in this setting by mechanisms that differ from those in individuals without RA.

The interpretation that factors intrinsic to RA independently contribute to CAC is supported by the finding that CAC is clearly related to disease activity through the DAS28 score. Indeed the increased DAS28 scores in those with higher CAC remained significant even after adjusting for traditional cardiovascular risk factors, as well as by the GRS for alleles influencing CAD in the general population.

Similarly, one immunological mechanism in RA unrelated to CAD SNPs that could potentially contribute to the association is that CAC in RA patients is significantly and independently associated with an elevated percentage of circulating CD28⁺CD57⁺CD56⁺ memory effector CD4 T cells, and with an increased proportion of the CD14^{hi}CD16⁺ monocyte subset bearing an intermediate or 'inflammatory' phenotype (54). These elevated numbers of memory effector T cell and inflammatory monocyte subsets, which are considered an intrinsic element in the immune response mediating RA, may also provision the nascent and clinically unimportant subintimal lipid deposits with effector T cells and inflammatory monocytes that could accelerate the development of advanced atherosclerotic vascular disease.

Additionally, several studies (55) support the association of polymorphic genes involved in influencing RA susceptibility or the severity of effector pathways of RA with cardiovascular disease. These include the association between alleles encoding the HLA-DR shared epitope with both subclinical and clinically evident CV disease (56), and variants belonging to genes implicated in inflammatory and metabolic pathways, such as rs1800629 (*TNFA*), rs909253 (*LTA*), rs1800795 (*IL6*), rs333 (*CCR5*), rs2812378 (*CCL21*), and rs1800470 (*TGFB1*), which have been associated with a higher risk of endothelial dysfunction, different types of cardiovascular events, and cardiovascular mortality in RA (55, 57-60).

There are some limitations in this study. First, this study should be considered exploratory because the experimental design does not include a validation cohort. Second, although genotyping was facilitated in our study because a considerable proportion of CAD SNPs were fortuitously present on the *ImmunoChip*, the studies exploring susceptibility for CAD in the general population utilized different chips, most notably the *Metabolic* chip, each of which has a different spectrum of SNPs. Therefore we had to use imputation to identify some important polymorphisms, which is still an evolving approach (41). Third, CAC appears at an intermediate stage in the development of atherosclerosis and the assessment of earlier stages of atherosclerosis may prove more sensitive, as would adding the later stage of a myocardial event. Fourth, the association observed between DAS28 and CAC could also be influenced by non-inflammatory comorbidities, such as depression, fibromyalgia, osteoarthritis, etc. that can also lead to higher DAS28 scores.

The role of genetic factors in accelerated cardiovascular disease in RA requires further study to better identify the mechanisms and pathways responsible for this association. To our knowledge, this is the first investigation in which general population CAD related SNPs has been assessed in a large set of RA patients with a reproducible, sensitive, quantitative measure of CAD. Our findings of an absence of association of these CAD related SNPs with CAC in RA is novel and could shed light on the complicated relationship between inflammation and cardiovascular risk in RA patients. In conclusion, we have shown that in RA, even when using all known genetic susceptibility variants associated with CAD in the general population, gene dosage of these susceptible CAD SNPs was not associated with the increased CAC observed in patients. Our findings would support the role of one or more mechanistic features in RA itself as the fundamental responsible factor for the increase of cardiovascular diseases in RA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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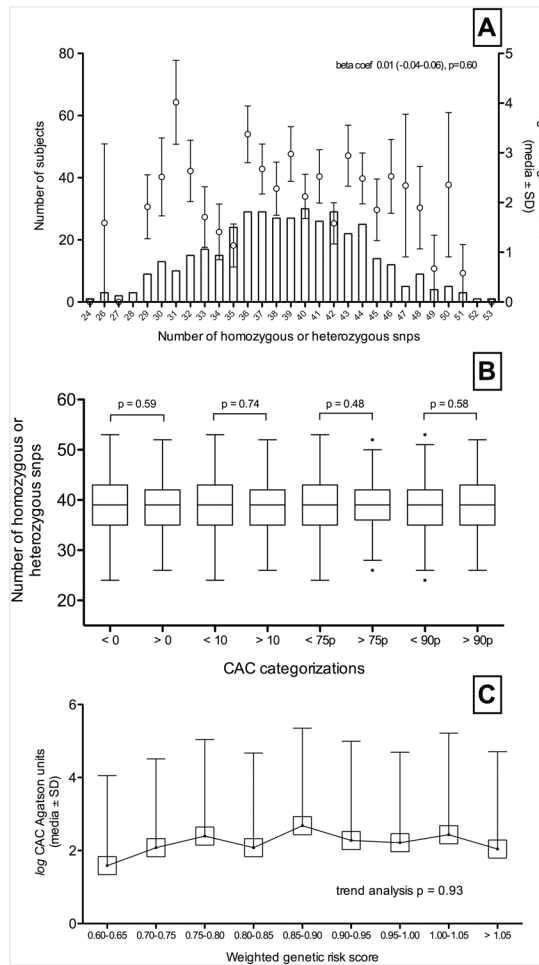


Figure 1. Panel A shows *log* coronary artery calcification (CAC) (mean and standard deviation -SD- Agatston units, right axis) relation with number of coronary artery disease related SNPs (left axis). Panel B shows number of CAD related SNPs (Tukey's boxplots) in every CAC categorization - CAC higher than 0 and 10 Agatston units and higher than percentile 75th and 90th; 'p' values of the difference in every categorization is showed. Panel C depicts a trend analysis of *log* CAC (mean and SD) and its relation with the weighted genetic risk score.

Table 1
Demographic and clinical data of rheumatoid arthritis patients in the three cohorts

	Total (n=561)	Cohorts		
		ESCAPE (n=197)	Pittsburgh (n=195)	Vanderbilt (n=169)
Demographics				
Age, years	57.6 ± 10.5	59.4 ± 8.7	58.8 ± 10.2	54.2 ± 11.8
Sex, female(%)	430 (77)	118 (60)	195 (100)	117 (69)
BMI, kg/m ²	28.5 ± 6.0	28.3 ± 5.3	27.9 ± 6.0	29.2 ± 6.8
Hip circumference, cm				
Female	106.7 ± 14.8	105.5 ± 14.6	105.9 ± 14.3	109.4 ± 15.6
Male	103.0 ± 12.3	100.6 ± 10.7	-	106.7 ± 13.6
Waist circumference, cm				
Female	91.9 ± 16.4	91.7 ± 15.6	91.2 ± 16.7	93.1 ± 16.8
Male	101.4 ± 14.9	101.6 ± 13.3	-	101.1 ± 17.2
Race				
White	502 (89)	169 (86)	184 (94)	149 (88)
Others	57 (10)	28 (14)	10 (5)	19 (11)
Agatston score for CAC				
CAC Agatston units	3.12 (0-134.35)	4.69 (0-175.00)	2.75 (0-93.37)	1.85 (0-150.35)
CAC greater than 0 units, n(%)	307 (55)	107 (55)	117 (60)	83 (51)
CAC greater than 10 units, n(%)	248 (49)	90 (46)	86 (44)	72 (44)
CAC greater than percentile 75, n(%)	195 (35)	63 (32)	75 (39)	57 (35)
CAC greater than percentile 90, n(%)	113 (21)	36 (18)	39 (20)	38 (23)
Previous cardiovascular disease				
Cardiovascular events, n(%)	61 (11)	0 (0)	21 (11)	40 (24)
Comorbidity				
Hypertension, n(%)	235 (42)	76 (38)	71 (36)	88 (52)
Systolic blood pressure, mmHg	129 ± 20	128 ± 19	125 ± 19	133 ± 20
Diastolic blood pressure, mmHg	76 ± 10	76 ± 9	76 ± 10	75 ± 11
Use of antihypertensives, n(%)	210 (37)	79 (40)	67 (34)	64 (38)
Dyslipemia				
On lipid lowering drugs	60 (11)	35 (18)	25 (13)	19 (12)
Diabetes	22 (4)	12 (6)	10 (5)	17 (10)
Previous smoking	291 (52)	115 (58)	96 (49)	80 (47)
Current smoking	81 (14)	23 (12)	17 (9)	41 (24)
Packs/years	0 (0-22)	7 (0-30)	0 (0-14)	0 (0-22)
Postmenopause	249 (44)	92 (47)	157 (81)	74 (47)
Hormone replacement use	85 (15)	16 (8)	69 (35)	-
Metabolic syndrome	90 (16)	44 (22)	46 (24)	55 (36)

	Total (n=561)	Cohorts		
		ESCAPE (n=197)	Pittsburgh (n=195)	Vanderbilt (n=169)
Aspirin	102 (18)	34 (17)	14 (7)	54 (32)
Analytical parameters				
Total cholesterol, mg/dL	197 ± 39	195 ± 38	208 ± 37	186 ± 39
Triglycerides, mg/dL	1116 (86-157)	-	120 (90-156)	111 (80-158)
HDL cholesterol, mg/dL	54 ± 16	49 (41-67)	61 ± 15	43 (37-54)
LDL cholesterol, mg/dL	116 ± 33	116 ± 31	120 ± 35	112 ± 33
Glucose, mg/dL	91 ± 19	89 (83-98)	88 (82-94)	87 (83-94)
Insulin, µU/mL	10 ± 7	6 (4-10)	12 (9-14)	10 (5-19)
Homocysteine, µmol/L	10.7 ± 3.6	9.1 (7.5-10.6)	11.1 (9.6-13.7)	10.5 ± 3.4
Creatinine, mg/dL	0.8 ± 0.3	0.8 ± 0.2	0.9 ± 0.3	0.8 ± 0.2
CRP, mg/L	4.65 (1.75-12.50)	-	5.62 (1.97-13.35)	4.00 (1.22-13.02)
Rheumatoid arthritis				
Disease duration, years	10 (3-20)	9 (4-17)	13 (7-23)	3 (2-18)
Prednisone				
Ever prednisone treatment	458 (82)	147 (75)	172 (88)	139 (82)
Current with prednisone	246 (44)	76 (39)	78 (40)	92 (54)
Current pred. dosage, mg/day	0 (0-5)	0 (0-5)	0 (0-5)	2 (0-5)
Hydroxychloroquine	125 (22)	47 (24)	36 (18)	42 (25)
Methotrexate	360 (64)	125 (63)	115 (59)	120 (71)
TNF inhibitors	179 (32)	85 (43)	59 (30)	35 (21)
Anakinra	2 (0)	1 (1)	1 (1)	0 (0)
NSAIDs	313 (73)	127 (64)	135 (69)	51 (30)
COX2 inhibitors	154 (72)	47 (24)	56 (29)	51 (30)
Minutes of morning stiffness	30 (5-60)	15 (5-30)	30 (0-60)	30 (10-90)
Current biologic DMARD use	149 (27)	89 (45)	60 (31)	32 (19)
Any current use of non-biologic DMARDs	487 (87)	165 (84)	175 (90)	147 (87)
Joint surgery	156 (28)	55 (28)	101 (52)	-
Rheumatoid nodules	197 (35)	89 (45)	108 (55)	-
Global ass. of disease activity	24 (9-47)	21 (5-47)	19 (6-34)	30 (16-55)
MModified HAQ (VU cohort only)	0.500 (0.000-0.875)			0.500 (0.000-0.875)
DAS28 (ESCAPE and VU cohorts)	3.72 ± 1.35	3.66 ± 1.08	-	3.79 ± 1.61
Full HAQ (ESCAPE cohort only)	0.625 (0.125-1.250)	0.625 (0.125-1.250)	-	-
RF (>40 units)	363 (65)	129 (65)	117 (60)	117 (69)

Data expressed as mean (± standard deviation) or median (interquartile range). Dichotomous variables are expressed as number (percentage).

CRP=C reactive protein; HAQ=Health Assessment Questionnaire; DAS28=Disease Activity Score; HDL=High density lipoprotein; LDL=Low density lipoprotein.

DMARD=Disease-modifying Antirheumatic Drug; TNF=tumor necrosis factor; COX-2=cyclooxygenase-2

Modified HAQ is only available for Vanderbilt cohort. DAS28 only for ESCAPE and Vanderbilt cohort. Full HAQ only in ESCAPE series.

CAC -coronary artery calcification- percentiles were adjusted for age and race as previously described

Table 2
Multivariable regression and association analysis of cardiovascular disease related SNPs relation with coronary artery calcification

rs	Chr	Gene/nearest gene	Effect/non effect allele	Risk allele frequency	Published OR (95%CI)	Ref	Effect allele	n	CAC (units)	p	OR (95%CI)			
											CAC > 0	CAC > 10	CAC > p75	CAC > p90
rs6604023	1	CDC7	C/G	0.09	1.19 (1.13-1.26)									
cell division cycle 7														
					7.8	CC	CC	3	6 (0-114)	0.91	0.45 (0.21-0.99)	0.58 (0.26-1.28)	0.66 (0.31-1.43)	0.79 (0.34-1.84)
intragenic														
					CG	24	0 (0-14)							
					GG	131	4 (0-123)							
					C	27	0 (0-14)	0.05	1.08 (0.42-2.79)	1.11 (0.43-2.88)	1.13 (0.44-2.89)	1.21 (0.46-3.13)		
					G	131	4 (0-123)							
rs4845625	1	IL6R	T/C	0.43	1.04 (1.02-1.07)	6								
interleukin 6 receptor														
						TT	74	3 (0-104)	0.96	1.09 (0.66-1.82)	1.11 (0.66-1.86)	1.25 (0.76-2.05)	0.99 (0.57-1.73)	
intron														
						TC	215	1 (0-152)						
						CC	134	2 (0-107)						
rs17465637	1	MIA3	C/A	0.69	1.20 (1.12-1.30)	8,9,10								
melanoma inhibitory activity family, member 3														
intron														
						CC	196	1 (0-116)	0.68	1.14 (0.70-1.84)	1.33 (0.81-2.17)	1.01 (0.64-1.62)	1.24 (0.73-2.10)	
						AC	193	3 (0-135)						
						AA	36	0 (0-46)						
rs11206510	1	PCSK9	T/C	0.86	1.15 (1.10-1.21)	6,8,10								
proprotein convertase subtilisin/kexin type 9														
intragenic														
						TT	76	1 (0-123)	0.97	-	-	-	-	-
						CT	26	1 (0-40)						
						CC	1	202						

rs	Chr	Gene/nearest gene	Effect/non effect allele	Risk allele frequency	Published OR (95%CI)	Ref	Effect allele	n	CAC (units)	P	OR (95%CI)			
											CAC > 0	CAC > 10	CAC > p75	CAC > p90
rs602633	1	PSRC1	G/T	0.72	1.13	6	T	102	1 (0-102)	0.37	-	-	-	-
proline/serine-rich coiled-coil 1 intragenic														
							GG	113	8 (0-116)	0.03	1.14 (0.52-2.50)	1.17 (0.53-2.61)	0.97 (0.44-2.11)	1.04 (0.45-2.39)
							TG	77	0 (0-26)					
							TT	21	1 (0-335)					
rs599839														
	1	PSRC1	A/G	0.69	1.29 (1.18-1.40)	6,9,10	G	190	1 (0-114)	0.85	1.69 (0.9-3.2)	1.75 (0.9-3.38)	1.60 (0.85-3.02)	1.46 (0.72-2.93)
							T	21	1 (0-335)					
proline/serine-rich coiled-coil 1 5' exon 1														
							AA	96	11 (0-128)	0.06	1.16 (0.53-2.53)	1.23 (0.55-2.77)	1.02 (0.47-2.22)	1.08 (0.47-2.48)
							GA	78	0 (0-117)					
							GG	21	1 (1-335)					
rs17464857														
	1	TAF1A	T/C	0.84	1.02	6	A	174	1 (0-128)	0.96	1.64 (0.86-3.13)	1.85 (0.94-3.63)	1.58 (0.84-3.00)	1.30 (0.65-2.61)
							G	21	1 (1-335)					
TATA box binding protein (TBP)-associated factor, RNA polymerase I, A, 48kDa intron 1														
							TT	297	3 (0-135)	0.12	1.01 (0.41-2.48)	1.10 (0.44-2.72)	1.07 (0.44-2.63)	1.22 (0.49-3.04)
							TG	118	0 (0-86)					
							GG	9	5 (0-111)					
rs646776														
	1	CELSR2	T/C	0.84	1.14 (1.09-1.19)	11	T	415	2 (0-120)	0.95	1.13 (0.67-1.89)	1.24 (0.73-2.12)	1.23 (0.74-2.05)	1.28 (0.71-2.29)
							G	9	5 (0-111)					
cadherin, EGF LAG seven-pass G-type receptor 2 intragenic 3'														
							TT	129	8 (0-122)	0.02	1.25 (0.64-2.42)	1.72 (0.85-3.48)	1.65 (0.82-3.29)	1.30 (0.63-2.71)
							CT	53	0 (0-22)					
							CC	4	0 (0-1)					
							T	182	1 (0-116)	0.15	1.07 (0.43-2.63)	1.16 (0.46-2.94)	0.97 (0.39-2.42)	1.14 (0.45-2.89)

rs	Chr	Gene/nearest gene	Effect/non effect allele	Risk allele frequency	Published OR (95%CI)	Ref	Effect allele	n	CAC (units)	P	OR (95%CI)			
											CAC > 0	CAC > 10	CAC > p75	CAC > p90
rs6544713	2	ABCG8	T/C	0.31	1.06 (1.04-1.09)	6	C	4	0 (0-1)					
ATP-binding cassette, sub-family G (WHITE), member 8														
intron														
			TT				TT	37	0 (0-54)	0.45	1.32 (0.81-2.14)	1.46 (0.89-2.40)	1.35 (0.84-2.16)	1.14 (0.67-1.95)
			TC				TC	185	3 (0-119)					
			CC				CC	202	2 (0-128)					
			T				T	222	1 (10-116)	0.70	0.98 (0.49-1.97)	1.05 (0.51-2.15)	0.88 (0.44-1.75)	1.08 (0.52-2.23)
rs6725887	2	WDR12	C/T	0.12	1.17 (1.11-1.23)	6,8	C	202	2 (0-128)					
WD repeat domain 12														
intron														
			CC				CC	6	141 (40-269)	0.15	1.17 (0.46-3.01)	1.23 (0.48-3.17)	1.03 (0.41-2.60)	1.14 (0.45-2.92)
			CT				CT	86	0 (0-77)					
			TT				TT	333	2 (0-123)					
			C				C	92	0 (0-105)	0.43	1.12 (0.64-1.96)	1.20 (0.68-2.14)	1.16 (0.67-2.00)	1.17 (0.64-2.14)
			T				T	333	2 (0-123)					
rs515135	2	APOB	C/T	0.78	1.08 (1.05-1.11)	6	C	271	3 (0-155)	0.22	0.96 (0.58-1.58)	1.17 (0.70-1.95)	1.07 (0.66-1.74)	1.63 (0.92-2.89)
apolipoprotein B														
intragenic														
			CT				CT	122	0 (0-77)					
			TT				TT	32	2 (0-97)					
			C				C	393	1 (0-123)	0.95	0.94 (0.44-1.98)	1.09 (0.52-2.31)	0.87 (0.42-1.81)	1.04 (0.47-2.28)
			T				T	32	2 (0-97)					
rs2252641	2	TEX41	C/T	0.13	1.06	6	C	3	3 (0-55)	0.95	-	-	-	-
testis expressed 41														
intron														
			TC				TC	19	1 (0-9)					
			TT				TT	73	4 (0-93)					
			C				C	22	1 (0-15)	0.25	-	-	-	-
			T				T	73	4 (0-93)					

rs	Chr	Gene/nearest gene	Effect/non effect allele	Risk allele frequency	Published OR (95%CI)	Ref	Effect allele	n	CAC (units)	P	OR (95%CI)				
											CAC > 0	CAC > 10	CAC > p75	CAC > p90	
rs1561198	2	VAMP5	A/G	0.54	1.05 (1.03-1.07)	6									
vesicle-associated membrane protein intragenic															
			AA				AA	30	0 (0-77)	0.31	-	-	-	-	-
			AG				AG	37	8 (0-138)						
			GG				GG	22	28 (0-91)						
rs2943634	2	IRS1	C/A	0.65	1.08 (0.90-1.31)	8,9				0.47	-	-	-	-	-
insulin receptor substrate 1 intragenic															
			CC				CC	180	4 (0-105)	0.75	1.09 (0.67-1.79)	1.13 (0.68-1.88)	0.97 (0.60-1.56)	1.36 (0.79-2.33)	
			AC				AC	192	1 (0-117)						
			AA				AA	50	0 (0-269)						
rs2123536	2	WDR35	T/C	0.03	1.12 (1.08-1.16)	12				0.66	1.13 (0.59-2.16)	0.93 (0.48-1.80)	0.88 (0.47-1.65)	0.74 (0.38-1.47)	
WD repeat domain 35 intragenic															
			TT				TT	1	0	0.48	-	-	-	-	-
			TC				TC	8	37 (0-81)						
			CC				CC	144	3 (0-129)						
rs9818870	3	MRAS	T/C	0.15	1.07	6				0.86	-	-	-	-	-
muscle RAS oncogene homolog 3'UTR															
			TT				TT	13	1 (0-510)	0.73	1.07 (0.62-1.84)	1.20 (0.69-2.08)	1.17 (0.70-1.98)	1.19 (0.67-2.13)	
			TC				TC	101	2 (0-123)						
			CC				CC	311	1 (0-116)						
rs2306374	3	MRAS	C/T	0.15	1.15 (1.11-1.19)	6,1				0.85	0.95 (0.40-2.24)	0.89 (0.37-2.10)	1.09 (0.47-2.51)	1.41 (0.60-3.34)	
			T				T	114	2 (0-123)						
			C				C	311	1 (0-116)						

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rs	Chr	Gene/nearest gene	Effect/non effect allele	Risk allele frequency	Published OR (95%CI)	Ref	Effect allele	n	CAC (units)	P	OR (95%CI)			
											CAC > 0	CAC > 10	CAC > p75	CAC > p90
muscle RAS oncogene homolog														
intron														
rs1199338	3	MRAS	C/A	0.19	1.08 (1.02-1.13)	11	C	115	2 (0-129)	0.85	1.03 (0.60-1.76)	1.24 (0.72-2.16)	1.22 (0.73-2.05)	1.17 (0.66-2.09)
muscle RAS oncogene homolog														
intron														
rs7692387	4	GUCY1A3	G/A	0.89	1.06 (1.03-1.09)	6	C	45	0 (0-68)	0.64	-	-	-	-
guanylatecyclase 1, soluble, alpha 3														
intron														
rs1842896	4	GUCY1A3	T/G	0.94	1.14 (1.10-1.19)	12	G	326	1 (0-123)	0.35	0.68 (0.28-1.67)	0.75 (0.30-1.87)	0.81 (0.33-2.00)	0.75 (0.30-1.86)
guanylatecyclase 1, soluble, alpha 3														
intragenic														
rs11748327	5	IRX1	C/T	0.79	1.25	13	T	24	0 (0-90)	-	-	-	-	-
iroquoishomeobox 1														
intragenic														
rs11748327	5	IRX1	C/T	0.79	1.25	13	G	0	-	-	-	-	-	-
rs11748327	5	IRX1	C/T	0.79	1.25	13	CC	198	1 (0-144)	0.58	-	-	-	-
rs11748327	5	IRX1	C/T	0.79	1.25	13	TC	100	1 (0-68)	-	-	-	-	-

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rs	Chr	Gene/nearest gene	Effect/non effect allele	Risk allele frequency	Published OR (95%CI)	Ref	Effect allele	n	CAC (units)	P	OR (95%CI)				
											CAC > 0	CAC > 10	CAC > p75	CAC > p90	
rs17609940	6	ANKK1A	G/C	0.82	1.07 (1.05-1.10)	6,1	TT	17	1 (0-110)						
ankyrin repeat and sterile alpha motif domain containing 1A															
							GG	285	1 (0-121)	0.50	0.96 (0.58-1.57)	0.76 (0.46-1.27)	0.83 (0.51-1.34)	0.68 (0.39-1.17)	
							CG	123	6 (0-123)						
							CC	17	0 (0-63)						
rs3869109															
	6	HCG27	G/A	0.59	1.14	14	G	408	2 (0-122)	0.50	1.09 (0.47-2.53)	0.94 (0.40-2.20)	1.15 (0.50-2.65)	0.88 (0.37-2.09)	
							C	17	0 (0-63)						
Human leucocyte antigen C															
							GG	145	7 (0-138)	0.12	1.45 (0.88-2.38)	1.59 (0.95-2.64)	1.50 (0.93-2.42)	1.35 (0.79-2.32)	
							AG	213	0 (0-116)						
							AA	66	0 (0-111)						
rs10947789															
	6	KCNK5	T/C	0.95	1.06 (1.03-1.08)	6	G	358	2 (0-123)	0.49	1.40 (0.74-2.66)	1.62 (0.84-3.15)	1.27 (0.67-2.38)	1.81 (0.88-3.76)	
							A	66	0 (0-111)						
potassium channel, subfamily K, member 5															
							TT	96	5 (0-81)	0.91	-	-	-	-	
							CT	11	0 (0-320)						
							CC	0	-						
rs3798220															
	6	LPA	C/T	0.02	1.92 (1.48-2.49)	6,10,15	T	107	5 (0-119)	-	-	-	-	-	
							C	0	-						
lipoprotein A															
							CC	0	-	-	-	-	-	-	
							TC	18	1 (0-105)						
							TT	407	2 (0-121)						

rs	Chr	Gene/nearest gene	Effect/non effect allele	Risk allele frequency	Published OR (95%CI)	Ref	Effect allele	n	CAC (units)	P	OR (95%CI)			
											CAC > 0	CAC > 10	CAC > p75	CAC > p90
rs10455872	6	LPA	G/A	0.05	1.70 (1.49-1.95)	15	C	18	1 (0-105)	0.92	1.26 (0.58-2.70)	0.88 (0.40-1.92)	0.92 (0.43-1.96)	0.94 (0.42-2.14)
							T	407	2 (0-121)					
lipoprotein A														
							GG	0	-	-	-	-	-	-
							GA	45	7 (0-226)					
							AA	378	1 (0-114)					
rs2048327	6	SLC22A3	G/A	0.25	1.06	6	G	45	7 (0-226)	0.18	1.06 (0.56-2.04)	0.83 (0.44-1.60)	0.84 (0.44-1.59)	1.02 (0.51-2.06)
							A	378	1 (0-114)					
solute carrier family 22 (organic cation transporter), member 3														
							GG	13	2 (0-279)	0.47	1.13 (0.64-2.01)	1.13 (0.63-2.03)	0.94 (0.54-1.65)	0.84 (0.44-1.60)
							GA	117	3 (0-150)					
							AA	154	0 (0-107)					
rs6922269	6	MTHFD1L	A/G	0.28	1.23 (1.01-1.50)	8,9	G	130	0 (0-107)	0.49	1.27 (0.55-2.93)	0.89 (0.38-2.09)	0.95 (0.41-2.22)	1.12 (0.47-2.67)
							A	154	0 (0-107)					
methylentetrahydrofolate dehydrogenase (NADP+ dependent) 1-like														
							AA	37	0 (0-123)	0.68	1.17 (0.72-1.90)	1.08 (0.66-1.77)	0.87 (0.54-1.39)	0.89 (0.52-1.52)
							AG	167	3 (0-114)					
							GG	221	1 (0-128)					
rs9369640	6	PHACTR1	A/C	0.27	1.09	6	A	204	2 (0-116)	0.78	0.92 (0.45-1.88)	0.86 (0.42-1.77)	0.64 (0.31-1.31)	0.88 (0.41-1.88)
							G	221	1 (0-128)					
phosphatase and actin regulator 1														
							AA	20	18 (0-281)	0.13	0.61 (0.35-1.06)	0.82 (0.47-1.43)	0.74 (0.43-1.28)	0.76 (0.41-1.41)
							AC	117	0 (0-32)					
							CC	159	5 (0-150)					

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rs	Chr	Gene/nearest gene	Effect/non effect allele	Risk allele frequency	Published OR (95%CI)	Ref	Effect allele	n	CAC (units)	P	OR (95%CI)			
											CAC > 0	CAC > 10	CAC > p75	CAC > p90
rs12526453	6	PHACTR1	C/G	0.30	1.13 (1.09-1.17)	6,8,10	A	137	0 (0-38)	0.01	1.00 (0.42-2.35)	0.81 (0.34-1.93)	0.68 (0.28-1.62)	0.78 (0.32-1.90)
phosphatase and actin regulator 1 intron														
							CC	39	3 (0-218)	0.64	0.71 (0.44-1.15)	0.96 (0.58-1.57)	0.87 (0.54-1.39)	0.79 (0.46-1.35)
							CG	176	0 (0-64)					
							GG	210	4 (0-179)					
rs9349379	6	PHACTR1	A/G	0.91	1.26 (1.14-1.14)	7,16	C	215	0 (0-70)	0.03	0.93 (0.43-1.98)	0.78 (0.36-1.70)	0.73 (0.34-1.55)	0.72 (0.32-1.64)
							G	210	4 (0-179)					
phosphatase and actin regulator 1 intron														
							AA	206	5 (0-191)	0.10	-	-	-	-
							GA	41	0 (0-48)					
							GG	2	109 (0-218)					
rs1332844	6	PHACTR1	C/T	0.74	1.11 (1.07-1.15)	11	A	247	4 (0-147)	0.99	1.27 (0.64-2.51)	0.94 (0.47-1.89)	1.03 (0.52-2.03)	1.01 (0.49-2.11)
							G	2	109 (0-218)					
phosphatase and actin regulator 1 intron														
							CC	155	5 (0-150)	0.01	1.01 (0.43-2.38)	1.24 (0.52-2.94)	1.51 (0.64-3.59)	1.32 (0.54-3.23)
							TC	115	0 (0-31)					
							TT	18	24 (0-343)					
rs2026458	6	PHACTR1	T/C	0.07	0.16 (0.03)*	7	C	270	1 (0-95)	0.08	1.70 (0.99-2.93)	1.29 (0.74-2.25)	1.47 (0.85-2.54)	1.28 (0.69-2.35)
							T	18	24 (0-343)					
phosphatase and actin regulator 1 intron														
							TT	1	218	0.44	-	-	-	-
							TC	17	29 (0-119)					
							CC	113	3 (0-150)					
							T	18	30 (0-121)	0.80	-	-	-	-

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rs	Chr	Gene/nearest gene	Effect/non effect allele	Risk allele frequency	Published OR (95%CI)	Ref	Effect allele	n	CAC (units)	P	OR (95%CI)				
											CAC > 0	CAC > 10	CAC > p75	CAC > p90	
rs4252120	6	<i>PLG</i>	T/C	0.95	1.06 (1.03-1.09)	6	C	113	3 (0-150)						
<i>plasminogen</i>															
							TT	48	4 (0-173)	0.76	-	-	-	-	-
							TC	5	3 (0-13)						
							CC	0	-						
rs12190287	6	<i>TCF21</i>	C/G	0.35	1.08 (1.06-1.10)	6, 10	T	53	4 (0-166)	-	-	-	-	-	-
							C	0	-						
<i>transcription factor 21</i>															
							CC	52	2 (0-116)	0.83	0.75 (0.46-1.22)	0.71 (0.43-1.18)	0.77 (0.47-1.24)	0.93 (0.54-1.61)	
							CG	192	1 (0-129)						
							GG	181	2 (0-118)						
rs6905288	6	<i>VEGFA</i>	T/C	0.58	1.23	14	C	244	1 (0-123)	0.99	0.99 (0.52-1.91)	0.76 (0.39-1.48)	1.11 (0.59-2.11)	0.96 (0.48-1.94)	
							G	52	2 (0-118)						
<i>vascular endothelial growth factor A</i>															
							TT	146	3 (0-158)	0.33	0.83 (0.48-1.44)	0.76 (0.44-1.34)	0.89 (0.52-1.52)	0.89 (0.49-1.62)	
							TC	199	1 (0-125)						
							CC	80	2 (0-61)						
rs12539895	7	<i>COG5</i>	A/C	0.03	1.02	6	T	345	1 (0-129)	0.43	1.17 (0.71-1.94)	1.08 (0.64-1.80)	1.26 (0.78-2.05)	1.08 (0.62-1.86)	
							C	80	2 (0-61)						
<i>component of oligomericgolgi complex 5</i>															
							AA	0	-	-	-	-	-	-	-
							AC	6	46 (1-160)						
							CC	114	2 (0-116)						
rs2023938	7	<i>HDAC9</i>	G/A	0.09	1.07 (1.04-1.11)	6	A	6	46 (1-160)	0.66	-	-	-	-	-
							C	120	2 (0-116)						

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rs	Chr	Gene/nearest gene	Effect/non effect allele	Risk allele frequency	Published OR (95%CI)	Ref	Effect allele	n	CAC (units)	P	OR (95%CI)			
											CAC > 0	CAC > 10	CAC > p75	CAC > p90
histone deacetylase 9														
							GG	7	0 (0-202)	0.72	0.88 (0.49-1.59)	1.11 (0.61-2.04)	0.97 (0.54-1.72)	1.15 (0.61-2.16)
							GA	63	1 (0-128)					
							AA	343	2 (0-121)					
rs11556924	7	ZC3HC1	C/T	0.91	1.09 (1.07-1.12)	6, 10	G	70	0 (0-128)	0.84	0.80 (0.34-1.92)	0.92 (0.38-2.22)	0.97 (0.41-2.29)	0.97 (0.40-2.35)
							A	343	2 (0-121)					
zinc finger, C3HC-type containing 1														
							CC	30	0 (0-66)	0.98	-	-	-	-
							CT	7	0 (0-28)					
							TT	0	-					
rs10953541	7	BCAP29	C/T	0.97	1.08 (1.05-1.11)	11	C	37	0 (0-47)	-	-	-	-	-
							T	0	-					
B-cell receptor-associated protein 29														
							CC	103	2 (0-129)	0.55	-	-	-	-
							CT	6	1 (0-46)					
							TT	0	-					
rs264	8	LPL	G/A	0.95	1.05 (1.02-1.08)	6	C	109	1 (0-121)	-	-	-	-	-
							T	0	-					
lipoprotein lipase														
							GG	241	2 (0-116)	0.83	1.11 (0.51-2.39)	0.94 (0.44-2.02)	1.02 (0.48-2.16)	0.84 (0.38-1.87)
							AG	26	1 (0-179)					
							AA	0	-					
rs2954029	8	(TRIB1)LOC105375745	G/T	0.55	1.04 (1.02-1.06)	6	G	267	2 (0-117)	-	-	-	-	-
							A	0	-					
(tribbles homolog 1) LOC105375745														
							AA	120	5 (0-128)	0.20	0.72 (0.41-1.24)	0.81 (0.47-1.42)	0.76 (0.45-1.29)	0.73 (0.41-1.30)

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rs	Chr	Gene/nearest gene	Effect/non effect allele	Risk allele frequency	Published OR (95%CI)	Ref	Effect allele	n	CAC (units)	P	OR (95%CI)			
											CAC > 0	CAC > 10	CAC > p75	CAC > p90
intron														
rs579459	9	<i>ABO</i>	C/T	0.23	1.10 (1.07-1.13)	6, 10	TA	223	0 (0-116)	0.33	1.10 (0.65-1.86)	0.88 (0.51-1.51)	0.91 (0.54-1.52)	1.02 (0.57-1.82)
ABO blood group														
							CC	23	122 (4-619)	0.01	1.25 (0.59-2.64)	1.46 (0.70-3.06)	1.34 (0.66-2.71)	1.34 (0.63-2.85)
intra-genic														
							CT	146	4 (0-129)					
							TT	256	0 (0-110)					
rs3217992														
	9	<i>CDKN2B-AS1</i>	A/G	0.25	1.14	6	C	169	6 (0-186)	0.03	1.32 (0.81-2.14)	1.24 (0.75-2.03)	1.00 (0.63-1.60)	1.18 (0.70-2.01)
							T	256	0 (0-110)					
CDKN2B antisense RNA 1														
							AA	12	34 (0-290)	0.38	1.05 (0.47-2.37)	1.42 (0.63-3.19)	1.30 (0.59-2.89)	1.31 (0.56-3.07)
antisense RNA														
							AG	84	2 (0-116)					
							GG	121	0 (0-105)					
rs1333049														
	9	<i>CDKN2B-AS1</i>	C/G	0.55	1.28 (1.07-1.53)	7, 9	A	96	3 (0-147)	0.34	1.07 (0.58-1.95)	1.16 (0.62-2.15)	1.10 (0.6-2.01)	1.06 (0.53-2.11)
							G	121	0 (0-105)					
CDKN2B antisense RNA 1														
							CC	123	1 (0-116)	0.63	0.95 (0.54-1.68)	0.95 (0.53-1.72)	1.14 (0.64-2.01)	0.77 (0.42-1.43)
antisense RNA														
							CG	215	3 (0-149)					
							GG	82	0 (0-81)					
rs10757274														
	9	<i>CDKN2B-AS1</i>	G/A	0.46	1.29 (1.06-1.58)	17	C	338	2 (0-128)	0.25	0.96 (0.57-1.63)	0.89 (0.52-1.54)	0.82 (0.49-1.39)	0.99 (0.56-1.77)
							G	82	0 (0-81)					
CDKN2B antisense RNA 1														
							GG	94	0 (0-95)	0.38	0.96 (0.56-1.65)	1.07 (0.61-1.87)	1.06 (0.62-1.81)	1.24 (0.69-2.23)
antisense RNA														
							GA	203	3 (0-175)					
							AA	128	0 (0-111)					

rs	Chr	Gene/nearest gene	Effect/non effect allele	Risk allele frequency	Published OR (95%CI)	Ref	Effect allele	n	CAC (units)	P	OR (95%CI)			
											CAC > 0	CAC > 10	CAC > p75	CAC > p90
rs1333040	9	CDKN2B-ASI	C/T	0.42	1.13	6	G	297	3 (0-128)	0.39	1.33 (0.79-2.24)	1.38 (0.81-2.37)	1.50 (0.89-2.53)	1.18 (0.66-2.11)
CDKN2B antisense RNA 1 antisense RNA							CC	76	0 (0-118)	0.65	0.62 (0.34-1.13)	0.79 (0.43-1.46)	0.60 (0.33-1.10)	0.95 (0.49-1.81)
							CT	206	3 (0-128)					
							TT	143	1 (0-114)					
rs10811647	9	CDKN2B-ASI	C/G	0.36	-0.212 (0.031)*	7	C	282	2 (0-124)	0.75	0.71 (0.43-1.18)	0.75 (0.45-1.25)	0.75 (0.46-1.22)	0.76 (0.44-1.32)
							T	143	1 (0-114)					
CDKN2B antisense RNA 1 antisense RNA							CC	36	0 (0-95)	0.48	1.17 (0.59-2.33)	0.96 (0.48-1.92)	0.94 (0.48-1.86)	0.97 (0.45-2.11)
							CG	115	3 (0-129)					
							GG	108	0 (0-110)					
rs2891168	9	CDKN2B-ASI	G/A	0.46	1.29 (1.20-1.38)	18	C	151	2 (0-125)	0.57	1.25 (0.54-1.63)	1.23 (0.51-1.67)	1.01 (0.41-1.35)	1.11 (0.43-1.65)
							G	108	0 (0-110)					
CDKN2B antisense RNA 1 antisense RNA							GG	90	0 (0-68)	0.27	0.95 (0.55-1.64)	1.03 (0.58-1.81)	1.02 (0.59-1.76)	1.23 (0.68-2.25)
							GA	199	0 (0-147)					
							AA	125	0 (0-113)					
rs4977574	9	CDKN2B-ASI	G/A	0.45	1.29 (1.23-1.36)	6,8,10	G	289	2 (0-121)	0.52	1.32 (0.77-2.24)	1.30 (0.76-2.24)	1.46 (0.86-2.48)	1.10 (0.61-1.98)
							A	125	0 (0-113)					
CDKN2B antisense RNA 1 antisense RNA							GG	90	0 (0-68)	0.24	0.94 (0.54-1.63)	1.02 (0.58-1.80)	1.01 (0.59-1.74)	1.23 (0.67-2.23)
							GA	201	3 (0-175)					
							AA	128	0 (0-111)					
							G	291	2 (0-128)	0.46	1.31 (0.78-2.21)	1.35 (0.79-2.32)	1.46 (0.86-2.46)	1.16 (0.64-2.07)

rs	Chr	Gene/nearest gene	Effect/non effect allele	Risk allele frequency	Published OR (95%CI)	Ref	Effect allele	n	CAC (units)	P	OR (95%CI)			
											CAC > 0	CAC > 10	CAC > p75	CAC > p90
rs10752778	9	CDKN2B-AS1	G/A	0.46	1.27 (1.19-1.36)	17	A	128	0 (0-111)					
CDKN2B antisense RNA 1 antisense RNA														
			GG				GG	87	0 (0-68)	0.22	1.11 (0.63-1.95)	1.12 (0.62-2.02)	0.96 (0.55-1.68)	1.24 (0.67-2.27)
			GA				GA	213	3 (0-175)					
			AA				AA	125	1 (0-113)					
rs2383207	9	CDKN2B-AS1	G/A	0.56	1.27 (1.18-1.36)	17	G	300	2 (0-128)	0.59	1.05 (0.62-1.77)	1.10 (0.64-1.90)	1.17 (0.69-1.96)	1.02 (0.57-1.83)
CDKN2B antisense RNA 1 antisense RNA														
			GG				GG	140	0 (0-68)	0.13	0.97 (0.58-1.60)	0.81 (0.48-1.37)	0.85 (0.51-1.39)	0.97 (0.55-1.70)
			GA				GA	192	3 (0-177)					
			AA				AA	89	1 (0-116)					
rs2383206	9	CDKN2B-AS1	G/A	0.50	1.30 (1.06-1.58)	17	G	332	2 (0-123)	0.72	1.12 (0.63-1.99)	0.99 (0.55-1.80)	1.11 (0.63-1.98)	1.02 (0.54-1.92)
CDKN2B antisense RNA 1 antisense RNA														
			GG				GG	98	0 (0-68)	0.19	0.99 (0.57-1.70)	0.98 (0.56-1.72)	0.96 (0.56-1.65)	1.14 (0.63-2.06)
			GA				GA	192	3 (0-177)					
			AA				AA	97	1 (0-116)					
rs1537373	9	CDKN2B-AS1	G/T	0.54	1.19 (1.07-1.31)	16	G	290	2 (0-128)	0.66	0.86 (0.68-2.11)	0.81 (0.60-1.92)	1.00 (0.76-2.37)	0.86 (0.61-2.15)
CDKN2B antisense RNA 1 antisense RNA														
			GG				GG	131	0 (0-95)	0.27	1.27 (0.72-2.22)	1.06 (0.60-1.88)	1.23 (0.71-2.14)	0.99 (0.54-1.81)
			GT				GT	194	3 (0-147)					
			TT				TT	99	0 (0-116)					
rs10965219	9	CDKN2B-AS1	G/A	0.49	1.16 (1.05-1.29)	16	G	325	2 (0-123)	0.61	1.33 (0.59-1.63)	1.21 (0.50-1.44)	1.33 (0.57-1.55)	1.26 (0.61-1.86)
			T				T	99	0 (0-116)					

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rs	Chr	Gene/nearest gene	Effect/non effect allele	Risk allele frequency	Published OR (95%CI)	Ref	Effect allele	n	CAC (units)	P	OR (95%CI)			
											CAC > 0	CAC > 10	CAC > p75	CAC > p90
CDKN2B antisense RNA 1 antisense RNA														
			GG				GG	66	4 (0-147)	0.50	1.08 (0.59-1.96)	1.19 (0.65-2.20)	0.98 (0.54-1.77)	0.95 (0.48-1.84)
			GA				GA	123	0 (0-65)					
			AA				AA	70	2 (0-129)					
rs7025486	9	DAB2IP	A/G	0.15	1.10 (1.06-1.14)	19	G	189	0 (0-81)	0.41	0.86 (0.46-1.59)	0.75 (0.4-1.41)	0.89 (0.48-1.64)	0.80 (0.41-1.57)
			A				A	70	2 (0-129)					
DAB2 interacting protein intronic														
			AA				AA	5	0 (0-28)	0.93	-	-	-	-
			AG				AG	16	0 (0-11)					
			GG				GG	65	0 (0-111)					
rs12413409	10	CNNM2	G/A	0.92	1.12 (1.08-1.16)	6,10	A	21	0 (0-17)	0.40	-	-	-	-
			G				G	65	0 (0-111)					
cyclin M2 intronic														
			GG				GG	360	1 (0-128)	0.91	1.02 (0.56-1.86)	0.95 (0.51-1.76)	0.94 (0.52-1.69)	1.03 (0.54-1.96)
			AG				AG	60	3 (0-119)					
			AA				AA	5	24 (0-30)					
rs501120	10	CXCL12	A/G	0.85	1.33 (1.20-1.48)	9	G	420	2 (0-121)	0.97	0.88 (0.34-2.26)	0.84 (0.32-2.18)	0.87 (0.34-2.24)	1.07 (0.41-2.77)
			A				A	5	24 (0-30)					
chemokine (C-X-C motif) ligand 12 intragenic														
			AA				AA	307	3 (0-128)	0.33	0.87 (0.39-1.90)	1.31 (0.59-2.91)	0.83 (0.38-1.82)	1.19 (0.51-2.79)
			GA				GA	96	0 (0-93)					
			GG				GG	17	4 (0-155)					
rs1746048	10	CXCL12	C/T	0.84	1.33 (1.20-1.48)	6,8,10	A	403	1 (0-119)	0.41	1.40 (0.83-2.37)	1.96 (1.13-3.41)	1.25 (0.74-2.11)	1.05 (0.59-1.88)
			G				G	17	4 (0-155)					
chemokine (C-X-C motif) ligand 12														
			CC				CC	306	3 (0-128)	0.34	1.45 (0.86-2.44)	1.97 (1.14-3.40)	1.33 (0.79-2.23)	1.05 (0.59-1.88)

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rs	Chr	Gene/nearest gene	Effect/non effect allele	Risk allele frequency	Published OR (95%CI)	Ref	Effect allele	n	CAC (units)	P	OR (95%CI)			
											CAC > 0	CAC > 10	CAC > p75	CAC > p90
intragenic														
rs2047009	10	CXCL12	C/A	0.30	1.05	6	CT	100	0 (0-105)	0.53	0.84 (0.39-1.84)	1.23 (0.56-2.71)	0.90 (0.42-1.95)	1.23 (0.53-2.86)
chemokine (C-X-C motif) ligand 12														
intragenic														
							CC	13	44 (0-167)	0.58	-	-	-	-
							AC	61	0 (0-111)					
							AA	73	13 (0-222)					
rs2505083	10	KIAA1462	C/T	0.23	1.07 (1.04-1.09)	20	C	74	0 (0-121)	0.07	-	-	-	-
							A	73	13 (0-222)					
KIAA1462														
intron														
							CC	5	0 (0-104)	0.69	-	-	-	-
							CT	23	1 (0-129)					
							TT	44	9 (0-357)					
rs2246833	10	LIPA	T/C	0.16	1.04	6	C	28	1 (0-116)	0.21	-	-	-	-
							T	44	9 (0-357)					
lipase A, lysosomal acid, cholesterol esterase														
intron														
							TT	1	0 (0-0)	0.27	-	-	-	-
							TC	5	5 (0-110)					
							CC	16	22 (1-338)					
rs1412444	10	LIPA	T/C	0.20	1.09 (1.07-1.12)	11	T	6	2 (0-110)	0.26	-	-	-	-
							C	16	22 (1-338)					
lipase A, lysosomal acid, cholesterol esterase														
intron														
							TT	2	0 (0-0)	0.10	-	-	-	-
							TC	5	5 (0-110)					
							CC	16	22 (1-338)					

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rs	Chr	Gene/nearest gene	Effect/non effect allele	Risk allele frequency	Published OR (95%CI)	Ref	Effect allele	n	CAC (units)	P	OR (95%CI)			
											CAC > 0	CAC > 10	CAC > p75	CAC > p90
rs11203042	10	LIPA	T/C	0.31	1.03	6	T	7	0 (0-110)	0.15	-	-	-	-
lipase A, lysosomal acid, cholesterol esterase intron														
							TT	2	254 (0-508)	0.82	-	-	-	-
							TC	6	7 (0-66)					
							CC	8	63 (2-114)					
rs1075724	10	MIK167	G/A	0.21	1.78 (1.45-2.18)	21	T	8	7 (0-88)	0.44	-	-	-	-
							C	8	63 (2-114)					
antigen identified by monoclonal antibody Ki-67 intergenic														
							GG	0	-	-	-	-	-	-
							AG	25	5 (0-214)					
							AA	34	63 (2-114)					
rs974819	11	PDGFD	A/G	0.31	1.07 (1.04-1.09)	11	G	25	5 (0-214)	0.65	-	-	-	-
							A	34	63 (2-114)					
platelet derived growth factor D intergenic														
							AA	2	0	0.38	-	-	-	-
							AG	1	34 (0-175)					
							GG	5	0					
rs964184	11	ZPFI	G/C	0.15	1.13 (1.10-1.16)	6,10	A	3	0 (0-175)	-	-	-	-	-
							G	5	0					
zinc finger protein 259 intergenic														
							GG	9	4 (0-175)	0.34	1.00 (0.59-1.69)	0.86 (0.50-1.46)	0.86 (0.52-1.42)	0.96 (0.54-1.69)
							CG	110	5 (0-197)					
							CC	306	1 (0-93)					
							G	119	5 (0-197)	0.08	0.89 (0.37-2.12)	1.16 (0.48-2.81)	0.93 (0.39-2.23)	1.00 (0.41-2.47)

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rs	Chr	Gene/nearest gene	Effect/non effect allele	Risk allele frequency	Published OR (95%CI)	Ref	Effect allele	n	CAC (units)	P	OR (95%CI)				
											CAC > 0	CAC > 10	CAC > p75	CAC > p90	
rs9326246	11	ZPFI	C/G	0.06	1.04	6	C	306	1 (0-93)						
zinc finger protein 259															
			CC				CC	1	175	0.43		1.06 (0.56-1.99)	1.36 (0.72-2.59)	1.44 (0.79-2.65)	1.29 (0.67-2.49)
intergenic															
			CG				CG	49	28 (0-227)						
			GG				GG	365	1 (0-114)						
rs17676451	12	HAL	A/G	0.12	-0.17 (0.04)*	7	C	50	31 (0-207)	0.11		-	-	-	-
			G				G	365	1 (0-114)						
histidine ammonia lyase															
			AA				AA	2	157 (34-279)	0.25		2.06 (1.05-4.05)	2.03 (1-03-3.99)	1.98 (1.02-3.85)	1.33 (1.57-2.77)
intronic															
			AG				AG	41	48 (0-175)						
			GG				GG	141	0 (0-54)						
rs7136259	12	ATP2B1	T/C	0.48	1.11 (1-08-1.15)	12	A	43	48 (0-185)	0.00		1.28 (0.51-3.25)	1.36 (0.54-3.47)	1.35 (0.53-3.43)	1.15 (0.45-2.97)
			G				G	141	0 (0-54)						
ATPase, Ca++ transporting, plasma membrane 1															
intronic															
			TT				TT	13	150 (5-393)	0.06		-	-	-	-
			TC				TC	30	0 (0-198)						
			CC				CC	15	18 (0-166)						
rs11066015	12	ACAD10	A/G	0.01	1.41	20,22	T	43	11 (0-257)	0.77		-	-	-	-
			C				C	15	18 (0-166)						
acyl-CoA dehydrogenase family, member 10															
intronic															
			AA				AA	0	-	-		1.05 (0.42-2.63)	0.91 (0.35-2.34)	1.08 (0.43-2.71)	0.91 (0.35-2.34)
			AG				AG	6	1 (0-332)						
			GG				GG	418	2 (0-121)						
			A				A	6	1 (0-332)	0.87		-	-	-	-
			G				G	418	2 (0-121)						

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rs	Chr	Gene/nearest gene	Effect/non effect allele	Risk allele frequency	Published OR (95%CI)	Ref	Effect allele	n	CAC (units)	P	OR (95%CI)			
											CAC > 0	CAC > 10	CAC > p75	CAC > p90
rs4773144	13	COL4A2	G/A	0.43	1.07 (1.05-1.09)	6,10								
collagen, type IV, alpha 2														
intronic														
							GG	80	3 (0-155)	0.47	1.50 (0.85-2.67)	1.68 (0.94-3.01)	1.70 (0.99-2.95)	1.63 (0.90-2.96)
							GA	201	2 (0-108)					
							AA	141	0 (0-123)					
rs9515203	13	COL4A2	T/C	0.96	1.08	6,11								
collagen, type IV, alpha 2														
intronic														
							TT	68	0 (0-91)	0.04	-	-	-	-
							TC	6	38 (31-348)					
							CC	0	-					
rs3809346	13	COL4A2	A/G	0.43	0.15 (0.03)*	7								
collagen, type IV, alpha 2														
intronic														
							AA	80	3 (0-155)	0.48	1.43 (0.86-2.37)	1.27 (0.75-2.15)	1.40 (0.84-2.32)	1.28 (0.72-2.28)
							AG	201	2 (0-108)					
							GG	142	0 (0-122)					
rs9319428	13	FLTI	A/G	0.30	1.05 (1.03-1.08)	6								
fms-related tyrosine kinase 1														
intronic														
							AA	37	0 (0-104)	0.45	1.07 (0.66-1.73)	1.29 (0.78-2.12)	1.15 (0.71-1.84)	1.23 (0.72-2.10)
							AG	173	4 (0-123)					
							GG	208	1 (0-123)					
rs8001186	13	IRS2	A/G	0.36	-0.15 (0.03)*	7								
fms-related tyrosine kinase 1														
intronic														
							A	210	3 (0-119)	0.92	0.72 (0.35-1.45)	0.76 (0.37-1.55)	0.75 (0.37-1.51)	0.94 (0.45-1.97)
							G	208	1 (0-123)					

rs	Chr	Gene/nearest gene	Effect/non effect allele	Risk allele frequency	Published OR (95%CI)	Ref	Effect allele	n	CAC (units)	P	OR (95%CI)			
											CAC > 0	CAC > 10	CAC > p75	CAC > p90
insulin receptor substrate 2														
intronic														
rs173743	15	ADAMTS7 LOC105370915	A/G	0.54	1.06	6	AA	8	65 (1-169)	0.64	-	-	-	-
(ADAM metalloproteinase with thrombospondin type 1 motif, 7) LOC105370915														
intragenic														
							TT	112	1 (0-128)	0.72	1.01 (0.59-1.71)	1.02 (0.60-1.75)	1.25 (0.75-2.07)	1.08 (0.61-1.91)
							CT	235	1 (0-105)					
							CC	78	5 (0-128)					
							T	347	1 (0-117)	0.32	1.73 (0.32-1.03)	0.94 (0.43-1.39)	0.91 (0.45-1.38)	0.82 (0.52-1.83)
rs17514846	15	FURIN	A/C	0.48	1.05 (1.03-1.08)	6	C	78	5 (0-128)					
furin (paired basic amino acid cleaving enzyme)														
intronic														
							AA	96	0 (0-128)	0.16	1.05 (0.61-1.83)	0.94 (0.54-1.64)	0.80 (0.47-1.36)	0.88 (0.48-1.58)
							AC	156	5 (0-105)					
							CC	107	3 (0-129)					
							A	252	1 (0-111)	0.36	1.15 (0.47-1.41)	0.86 (0.39-1.19)	1.30 (0.60-1.75)	1.16 (0.65-2.15)
rs3825807	15	ADAMTS7	A/G	0.60	1.08 (1.06-1.10)	6,10	C	107	3 (0-129)					
ADAM metalloproteinase with thrombospondin type 1 motif, 7														
exon														
							AA	155	1 (0-119)	0.84	0.84 (0.47-1.51)	1.11 (0.61-2.03)	1.16 (0.64-2.08)	0.76 (0.40-1.43)
							GA	202	2 (0-123)					
							GG	68	2 (0-121)					
							A	357	2 (0-121)	0.88	1.33 (0.64-1.75)	1.32 (0.59-1.65)	1.36 (0.63-1.66)	0.97 (0.42-1.28)
rs4380028	15	ADAMTS7	C/T	0.63	1.07 (1.05-1.10)	11,23	G	68	2 (0-121)					

rs	Chr	Gene/nearest gene	Effect/non effect allele	Risk allele frequency	Published OR (95%CI)	Ref	Effect allele	n	CAC (units)	P	OR (95%CI)			
											CAC > 0	CAC > 10	CAC > p75	CAC > p90
ADAM metalloproteinase with thrombospondin type 1 motif, 7 exon														
			CC				CC	162	2 (0-129)	0.61	0.79 (0.41-1.51)	0.96 (0.50-1.86)	0.90 (0.48-1.70)	0.82 (0.41-1.62)
			TC				TC	212	1 (0-91)					
			TT				TT	51	5 (0-150)					
rs12936587														
	17	<i>RAI1</i>	G/A	0.69	1.07 (1.05-1.09)	6,10	C	374	1 (0-116)	0.36	1.06 (0.65-1.73)	0.95 (0.58-1.58)	1.09 (0.68-1.75)	0.94 (0.55-1.61)
			T				T	51	5 (0-150)					
retinoic acid induced 1 intragenic														
			GG				GG	97	4 (0-81)	0.32	1.24 (0.66-2.32)	0.88 (0.48-1.63)	0.69 (0.38-1.28)	0.91 (0.47-1.77)
			AG				AG	92	17 (0-250)					
			AA				AA	17	0 (0-64)					
rs2281727														
	17	<i>SMG6</i>	C/T	0.32	1.04	11	G	189	5 (0-129)	0.16	1.08 (0.48-2.44)	1.39 (0.61-3.16)	0.92 (0.41-2.08)	1.51 (0.64-3.6)
			A				A	17	0 (0-64)					
smg-6 homolog, nonsense mediated mRNA decay factor LOC105371487 RNA antisense														
			CC				CC	36	0 (0-28)	0.28	0.83 (0.41-1.66)	0.67 (0.33-1.39)	0.81 (0.40-1.65)	0.86 (0.40-1.85)
			CT				CT	144	0 (0-129)					
			TT				TT	161	3 (0-197)					
rs1231206														
	17	<i>SMG6</i>	A/G	0.30	1.07 (1.05-1.09)	6	C	180	0 (0-105)	0.18	0.76 (0.45-1.27)	0.77 (0.45-1.32)	0.67 (0.4-1.12)	0.72 (0.4-1.27)
			T				T	161	3 (0-197)					
smg-6 homolog, nonsense mediated mRNA decay factor RNA antisense														
			AA				AA	30	0 (0-23)	0.30	0.81 (0.48-1.37)	0.80 (0.46-1.38)	0.75 (0.44-1.26)	0.77 (0.43-1.37)
			AG				AG	134	0 (0-129)					
			GG				GG	161	3 (0-197)					
rs216172														
	17	<i>SMG6</i>	C/G	0.29	1.07 (1.05-1.09)	10	A	164	0 (0-114)	0.22	1.14 (0.49-2.08)	1.01 (0.37-1.63)	1.12 (0.44-1.92)	1.09 (0.43-2.04)
			G				G	161	3 (0-197)					

rs	Chr	Gene/nearest gene	Effect/non effect allele	Risk allele frequency	Published OR (95%CI)	Ref	Effect allele	n	CAC (units)	P	OR (95%CI)					
											CAC > 0	CAC > 10	CAC > p75	CAC > p90		
smg-6 homolog, nonsense mediated mRNA decay factor													0.85 (0.50-1.43)	0.81 (0.47-1.39)	0.76 (0.45-1.28)	0.81 (0.46-1.44)
RNA amitsense													0.24	0.25	0.25	0.24
rs15563	17	UBE2Z	C/T	0.53	1.01 (0.99-1.03)	6	C	162	0 (0-114)	0.25	0.91 (0.45-1.86)	0.71 (0.34-1.48)	0.85 (0.41-1.76)	0.91 (0.42-1.99)		
ubiquitin-conjugating enzyme E2Z													0.68	0.68	0.68	0.68
exon													0.26	0.26	0.26	0.26
rs46522	17	UBE2Z	T/C	0.53	1.06 (1.04-1.08)	6,10	T	29	1 (0-105)	0.26	-	-	-	-		
ubiquitin-conjugating enzyme E2Z													0.64	0.64	0.64	0.64
intron													0.28	0.28	0.28	0.28
rs1122608	19	SMARCA4	G/T	0.78	1.14 (1.09-1.18)	6,8,10	T	82	0 (0-43)	0.28	-	-	-	-		
SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4													0.44	0.44	0.44	0.44
intron													0.65	0.65	0.65	0.65
rs2228671	19	LDLR	C/T	0.94	1.09 (1.02-1.15)	11	G	399	2 (0-129)	0.65	0.71 (0.35-1.46)	0.77 (0.37-1.59)	0.66 (0.33-1.33)	1.05 (0.48-2.28)		

rs	Chr	Gene/nearest gene	Effect/non effect allele	Risk allele frequency	Published OR (95%CI)	Ref	Effect allele	n	CAC (units)	p	OR (95%CI)			
											CAC > 0	CAC > 10	CAC > p75	CAC > p90
low density lipoprotein receptor exon														
			CC				CC	307	0 (0-121)	0.03	-	-	-	-
			TC				TC	42	35 (0-129)					
			TT				TT	1	0					
rs2075650														
	19	TOMM40	G/A	0.14	1.11	6	C	349	2 (0-128)	-	0.55 (0.28-1.07)	0.63 (0.32-1.23)	0.54 (0.29-1.03)	0.48 (0.25-0.94)
			T				T	0	0					
translocase of outer mitochondrial membrane 40 homolog intron														
			GG				GG	8	8 (1-262)	0.43	1.49 (0.63-3.50)	1.18 (0.50-2.80)	1.20 (0.51-2.84)	1.49 (0.62-3.60)
			GA				GA	99	4 (0-148)					
			AA				AA	317	1 (0-116)					
rs9982601														
	21	KCNE2	T/C	0.03	1.19 (1.13-1.27)	6,8,10	G	107	4 (0-153)	0.18	1.66 (0.97-2.83)	1.20 (0.70-2.06)	1.03 (0.62-1.73)	1.07 (0.60-1.89)
			A				A	317	1 (0-116)					
potassium channel, voltage gated subfamily E regulatory beta subunit 2 intergenic														
			TT				TT	0	-	-	-	-	-	-
			TC				TC	14	66 (0-129)					
			CC				CC	206	1 (0-115)					
rs7278204														
	21	KCNE2	G/A	0.02	1.09 (1.03-1.15)	11	T	14	66 (0-129)	0.15	1.43 (0.63-3.26)	1.60 (0.70-3.64)	1.46 (0.65-3.29)	1.19 (0.52-2.74)
			C				C	206	1 (0-115)					
potassium channel, voltage gated subfamily E regulatory beta subunit 2 intergenic														
			GG				GG	0	-	-	-	-	-	-
			GA				GA	9	79 (0-171)					
			AA				AA	215	1 (0-115)					
rs7278204														
			G				G	9	79 (0-171)	0.36	1.35 (0.57-3.21)	1.51 (0.64-3.56)	1.28 (0.54-3.02)	1.39 (0.58-3.32)
			A				A	215	1 (0-115)					

CAC is expressed as median (25p-75p). 'p' values represent U-Mann Whitney test for the comparison of homozygous for the effect allele versus heterozygous (upper row) and the comparison of the effect allele vs. the non-effect.

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Logistic regression analysis (odds ratios, OR - 95% confidence interval-) adjusted for traditional cardiovascular risk factors (age, sex, diabetes, hypertension, dyslipidemia, and smoking) express the relation of homozygous against heterozygous, or for the relation of affected allele against the non affected, with CAC expressed as higher than 0 and 10 units or higher than 70th and 90th percentiles.

Effect allele and homozygous forms, and significant p values, are depicted in bold.

* Refers to beta coefficient (standard error).

Table 3
Coronary artery calcification relation with disease activity score and genetic risk score

	DAS28 (beta coef. 95% CI, p)			
	Unadjusted	Model #1	Model #2	Model #3
	Univariate model	Adjusted for age and sex	Adjusted for Model 1 plus diabetes, hypertension, smoking and dyslipidemia	Adjusted for Model 1 and 2 plus GRS
CAC > 0	0.15 (-0.13-0.43), 0.30	0.37 (0.04-0.70), 0.03	0.09 (-0.27-0.45), 0.62	0.08 (-0.28-0.44), 0.65
CAC > 10	0.24 (-0.04-0.52), 0.09	0.48 (0.16-0.80), 0.00	0.34 (-0.01-0.68), 0.06	0.32 (-0.02-0.68), 0.07
CAC > 75th	0.39 (0.10-0.68), 0.01	0.46 (0.16-0.76), 0.00	0.28 (-0.05-0.60), 0.09	0.27 (-0.06-0.59), 0.10
CAC > 90th	0.52 (0.18-0.86), 0.00	0.55 (0.21-0.89), 0.00	0.43 (0.04-0.81), 0.03	0.42 (0.04-0.81), 0.03

	Genetic risk score (beta coef. 95% CI, p)		
	Unadjusted	Model #1	Model #2
	Univariate model	Adjusted for age and sex	Adjusted for Model 1 plus diabetes, hypertension, smoking and dyslipidemia
CAC > 0	- 0.03 (-0.06--0.00), 0.03	-0.01 (-0.04-0.02), 0.51	-0.01 (-0.05-0.03), 0.66
CAC > 10	- 0.04 (-0.06--0.01), 0.04	-0.01 (-0.04-0.03), 0.68	-0.01 (-0.04-0.04), 0.95
CAC > 75th	- 0.01 (-0.04-0.02), 0.59	0.00 (-0.03-0.03), 0.91	0.01 (-0.03-0.05), 0.72
CAC > 90th	0.01 (-0.03-0.04), 0.69	0.01 (-0.03-0.05), 0.57	0.02 (-0.03-0.06), 0.50

CAC = coronary artery calcification; CI = confidence interval

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