Coronary heart disease (CHD) is the single greatest cause of death worldwide (1, 2). Although CHD is highly heritable, the DNA sequence variations that confer cardiovascular risk remain largely unknown. To identify sequence variants associated with CHD, we undertook a genome-wide association study using 100,000 single-nucleotide polymorphisms (SNPs). To minimize false positive associations without unduly sacrificing statistical power, we designed the study to comprise three sequential case-control comparisons performed at a nominal significance threshold of $P < 0.025$ (Fig. 1). For the initial genome-wide scan, cases and controls were Caucasian men and women from Ottawa, Canada who participated in the Ottawa Heart Study (OHS). Cases had severe, premature CHD with a documented onset before the age of 60 years and culminating in coronary artery revascularization (table S1). To limit confounding by factors that strongly predispose to premature CHD, we excluded individuals with diabetes or plasma cholesterol levels consistent with mono-

**A Common Allele on Chromosome 9 Associated with Coronary Heart Disease**

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Coronary heart disease (CHD) is a major cause of death in Western countries. We used genome-wide association scanning to identify a 58-kilobase interval on chromosome 9p21 that was consistently associated with CHD in six independent samples (more than 23,000 participants) from four Caucasian populations. This interval, which is located near the CDKN2A and CDKN2B genes, contains no annotated genes and is not associated with established CHD risk factors such as plasma lipoproteins, hypertension, or diabetes. Homozygotes for the risk allele make up 20 to 25% of Caucasians and have a ~30 to 40% increased risk of CHD.

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‡These authors contributed equally to this work.

References and Notes

7. Materials and methods are available as supporting material on Science Online.
15. We thank M. Mittmann, D. Le, and E. Schell for design of tiling arrays; K. Kole, D. Barone, and C. Chen for their help with direct RNA labeling; G. Hannen, K. Fejes-Toth, D. Gerhard, and K. Nussbacher for technical discussion and assistance in manuscript preparation; M. Sinai Hospital and A. Nagy, R. Nagy, W. Abramow-Newlyw, J. Rossant, and J. Roder for procurement of the R1mES cell line; and M. Brown and D. Menke at Stanford for help in preparation of mouse embryo fibroblasts. This project has been funded in part with funds from the National Cancer Institute, NIH, under contract no. N01-C0-12400 and from the National Human Genome Research Institute, NIH, under grant no. U1HG003147, and by Affymetrix, Inc. The data discussed in this publication have been deposited in National Center for Biotechnology Information’s Gene Expression Omnibus (GEO, www.ncbi.nlm.nih.gov/geo) and are accessible through GEO Series accession number GSE-7576.

Supporting Online Material

www.sciencemag.org/cgi/content/full/318/5841/DC1

Materials and Methods

Figs. S1 to S14

Tables S1 to S8

References

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Include this information when citing this paper.

**REPORTS**

**Figs. 4.** (A) Distribution of syntenically conserved sRNAs. The fractions of sRNAs in each class (ordinate) found in a syntenic location in both species are shown as percentages of the total number of sRNAs in the class. (B and C) Characterization of syntenically conserved PASRs (B) and TASRs (C). Combined maps of syntenic sRNAs from HeLa and HepG2 human cell lines (black) and R1mES and MEF mouse cell lines (gray) are shown. Syntenic PASR HMSY19 and TASR HMSY5 are shown on either top (+) or bottom (−) strands. Northern blots show HMSY19 and HMSY5 in both species with comparable sizes.
genetic hypercholesterolemia (>280 mg/dL). Controls were healthy Caucasian men (>65 years) and women (>70 years) from Ottawa who had no symptoms or history of CHD (table S1).

Custom oligonucleotide arrays (3) were used to assay 100,000 SNPs arranged at ~30-kb intervals throughout the genome in 322 cases and 312 controls (data set designated as OHS-1). Of these, 9,636 SNPs deviated strongly from Hardy-Weinberg equilibrium ($P < 0.001$) or did not meet quality-control criteria (3), and 17,500 were subpolymorphic (minor allele frequency < 1%) in the sample. The remaining 72,864 SNPs were genotyped in an independent sample of 311 cases and 326 controls from Ottawa (OHS-2) using the same criteria as OHS-1 (table S1). Of these, 50 were associated with CHD at a nominal significance threshold of 0.025, with the same direction of effect (table S2).

To limit attrition of true positive associations due to inadequate statistical power, we performed the third case-control comparison in a much larger prospective study of CHD risk, the Atherosclerosis Risk in Communities (ARIC) study, which enrolled and followed 11,478 Caucasians (4). Only 2 of the 50 SNPs identified in the Ottawa cohorts were significantly associated with incident CHD in the ARIC population (table S2). These two SNPs, rs10757274 and rs2383206, were located within 20 kb of each other on chromosome 9p21 and were in strong linkage disequilibrium ($r^2 = 0.89$).

To validate the association between rs10757274 and rs2383206 and CHD, we assayed both SNPs in three additional independent cohorts: the Copenhagen City Heart Study (CCHS), a prospective study of ischemic heart disease in 10,578 Danish men and women (5); the Dallas Heart Study (DHS), a population-based probability sample of Dallas County residents (6); and a third sample of 647 cases and 847 controls from the Ottawa Heart Study population (OHS-3). In the CCHS, cases were participants who experienced an ischemic cardiovascular event during the 20-year follow-up period, whereas controls were those who did not develop CHD over the same time interval. In the DHS, cases and controls were defined by using electron-beam computer tomography to measure coronary artery calcium, an index of coronary atherosclerosis (7). In OHS-3, cases were participants that had documented CHD before the age of 55 (men) or 65 (women) years, whereas controls were men aged > 65 years and women aged > 70 years who did not have symptoms of CHD (table S1). In all three validation studies, both SNPs were significantly associated with CHD (Table 1).

The magnitude of CHD risk associated with the risk allele was determined by Cox proportional-hazards modeling in the ARIC and CCHS cohorts. The hazard ratios associated with the risk alleles were comparable in the two populations and indicated a graded increase in risk from noncarriers to heterozygotes to homozygotes (Table 2). The two SNPs (rs10757274 and rs2383206) define an allele that was associated with an ~15 to 20% increase in risk from noncarriers to heterozygotes to homozygotes (Table 2). The two SNPs (rs10757274 and rs2383206) define an allele that was associated with an ~15 to 20% increase in risk from noncarriers to heterozygotes to homozygotes.

Table 1. Association between SNPs rs10757274 and rs2383206 and CHD. Values are numbers of individuals in each genotype group. $P$ values were calculated by $\chi^2$ tests on allele counts. HW, Hardy-Weinberg equilibrium.

| Controls | rs10757274 | Cases | $\chi^2$ | HW $P$ | Controls | rs2383206 | Cases | $\chi^2$ | HW $P$
<table>
<thead>
<tr>
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Table 2. Risk of CHD as a function of rs10757274 and rs2383206 in the ARIC study and the CCHS. ARIC expected event values are based on the log-rank test. ARIC incidence rates are measured in number of events per 10,000 person years of followup. Ranges in parentheses indicate 95% confidence interval.

<table>
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<th>CCHS n (%)</th>
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<th>Hazard ratio</th>
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<th>ARIC study n (%)</th>
<th>CCHS n (%)</th>
<th>CHD incidence</th>
<th>Hazard ratio</th>
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<td></td>
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<td>Number of events</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Observed</td>
<td>Expected</td>
<td></td>
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<tr>
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<td>2293 (26)</td>
<td>255†</td>
<td>295</td>
<td>79 (70–89)</td>
<td>1</td>
<td>3145 (30)</td>
<td>473</td>
<td>61 (55–68)</td>
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<td>553</td>
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<td>1.18 (1.02–1.37)</td>
<td>5335 (50)</td>
<td>792</td>
<td>73 (68–79)</td>
<td>1.26 (1.12–1.42)</td>
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<td>2098 (20)</td>
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<td>rs2383206</td>
<td>2370 (25)</td>
<td>259†</td>
<td>310</td>
<td>78 (69–88)</td>
<td>1</td>
<td>2861 (27)</td>
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<td>64 (58–71)</td>
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<td>2352 (22)</td>
<td>371</td>
<td>78 (71–87)</td>
<td>1.29 (1.12–1.50)</td>
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*P < 0.0111, †P < 0.0041, ‡P < 0.0001, §P < 0.005.

possible confounding covariates (including age, gender, plasma lipid levels, blood pressure, diabetes, and plasma C-reactive protein concentrations; table S3). These analyses suggest that the effect of the chromosome 9 risk allele on CHD was not mediated by any of the established risk factors for cardiovascular disease.

To fine-map the locus associated with CHD, we assayed SNPs spaced at ~5-kb intervals across the region extending 175 kb upstream and downstream of rs10757274 and rs2383206 in 500 cases and 500 controls from the OHS population with GeneChip Human Mapping 500K Array Sets (Affymetrix, Santa Clara, CA). Bars represent values (determined with \( \chi^2 \) tests) for differences in allele frequency between cases and controls. Arrowheads indicate rs10757274 and rs2383206. The asterisk represents rs518394. The risk alleles were associated with CHD at the nominal significance threshold, but neither was in strong linkage disequilibrium with rs10757274 and rs2383206. These data indicate that the risk allele comprises a single haplotype that spans ~58 kb.

Inspection of the UCSC Genome Browser (http://genome.ucsc.edu) and BLAST searches against the National Center for Biotechnology Information (NCBI) (www.ncbi.nlm.nih.gov/blast) nr (nonredundant) nucleotide sequence database revealed no annotated genes or microRNAs within the 58-kb interval. A number of spliced expressed sequence tags (ESTs) map within the interval, but none contained an open reading frame that extends more than a few amino acids. Resequencing of the 58-kb interval in two homozygotes for the risk allele and one homozygote for the reference allele revealed 66 polymorphisms (SNPs plus small insertions or deletions), of which 35 were specific to the risk allele (table S5). Only one of these variants, a copy number variation in a run of nine consecutive CAT repeats (extending from nucleotide 22110787 to 22110814, NCBI build 36.1) mapped to a spliced transcript (BTJ655455) that appears to be part of a large noncoding RNA of unknown function (\( \delta \)). Polymerase chain reaction (PCR) amplification of cDNAs confirmed expression of the transcript in placenta and transformed lymphocytes (fig. S1). It is possible that variation in the expression or function of this transcript may be associated with risk of CHD.

Alternatively the risk allele may alter a regulatory element that affects the expression of a gene (or genes) located outside of the 58-kb interval. Cross-species sequence alignments revealed several conserved segments within the 58-kb interval that may contain such regulatory elements (fig. S2). It is also possible that the risk allele extends beyond the 58-kb interval defined in this study and that the functional sequence variants that confer risk of CHD are located outside of the interval. Resequencing the coding regions of the two genes most proximal to the 58-kb risk locus were associated with CHD at the nominal significance threshold, but neither was in strong linkage disequilibrium with rs10757274 and rs2383206. These data indicate that the risk allele comprises a single haplotype that spans ~58 kb.

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A Common Variant on Chromosome 9p21 Affects the Risk of Myocardial Infarction

Anna Helgadottir,1* Gudmar Thorleifsson,1* Andrei Manolescu,2* Solveig Gretarsdottir,1 Thorarinn Blondal,1 Aslaug Jonasdottir,1 Adalbjorg Jonasdottir,1 Asgeir Sigurdsson,1 Adam Baker,1 Arnar Palsson,2 Gisli Masson,1 Daniel F. Gudbjartsson,1 Kristinn P. Magnusson,1 Karl Andersen,2 Allan I. Levy,3 Valgerdur M. Backman,1 Sigurborg Matthiassdottr,1 Thorbjorg Jonsdottir,1 Stefan Palsson,1 Helga Einarsdottir,1 Steinunn Gunnarsdottir,1 Arnaldur Gylfason,1 Viola Vaccarino,3 W. Craig Hooper,4 Muredach P. Reilly,4 Christopher B. Granger,5 Harland Austin,3 Daniel J. Rader,4 Svati H. Shah,5 Arshed A. Quyyumi,3 Thorbjorg Jonsdottir,1 Stefan Palsson,1 Helga Einarsdottir,1 Steinunn Gunnarsdottir,1 Adam Baker,1 Arnar Palsson,2 Gisli Masson,1 Daniel F. Gudbjartsson,1 Kristinn P. Magnusson,1 Karl Andersen,2 Allan I. Levy,3 Valgerdur M. Backman,1 Sigurborg Matthiassdottr,1 Thorbjorg Jonsdottir,1 Stefan Palsson,1 Helga Einarsdottir,1 Steinunn Gunnarsdottir,1 Arnaldur Gylfason,1 Viola Vaccarino,3 W. Craig Hooper,4 Muredach P. Reilly,4 Christopher B. Granger,5 Harland Austin,3 Daniel J. Rader,4 Svati H. Shah,5 Arshed A. Quyyumi,3 Jeffrey R. Gutcher,6 Gudmundur Thorgeirsson,7 Unnur Thorsteinsdottir,8 Augustine Kong,9† Kari Stefansson9†

The global endemic of cardiovascular diseases calls for improved risk assessment and treatment. Here, we describe an association between myocardial infarction (MI) and a common sequence variant on chromosome 9p21. This study included a total of 4587 cases and 12,767 controls. The identified variant, adjacent to the tumor suppressor genes CDKN2A and CDKN2B, was associated with the disease with high significance. Approximately 21% of individuals in the population are homozygous for this variant, and their estimated risk of suffering myocardial infarction is 1.64 times as great as that of noncarriers. The corresponding risk is 2.02 times as great for early-onset cases. The population attributable risk is 21% for MI in general and 31% for early-onset cases.

Coronary artery disease (CAD), including acute myocardial infarction (MI), is the leading cause of death worldwide (1). Identification of the underlying genetic architecture of heart disease may provide improved risk assessment and better measures for prevention and treatment.

The results of this study illustrate both the perils and the promise of whole-genome association. The initial scan and the first replicate screen both generated substantially more SNPs that achieved the prespecified significance threshold than would be predicted by chance alone, as indicated by permutation testing (table S2). Yet only two of these SNPs (comprising one allele) survived further replication, despite the use of a large sample (i.e., ARIC) with high statistical power. This finding highlights the necessity for adequate replication to protect against artifacts that may occur because of population stratification, multiple testing, or other factors to which whole-genome association studies are particularly susceptible. The consistent replication of the chromosome 9 risk allele in six independent study samples indicates that the approach can be productively applied to conditions as complex as CHD, which is known to be influenced by a variety of environmental and genetic factors (2). Furthermore, analysis of 50 randomly selected regions of 500 kb each indicated that the 72,864 informative SNPs used in the initial scan provided 30 to 40% of the power that would be obtained by assaying all phase II Hapmap SNPs. Therefore, scans with denser SNP panels and larger sample sizes may reveal further loci associated with CHD risk.

References and Notes
8. E. Psaman et al., Cancer Res. 67, 1 (2007).
13. We thank T. Hyptt, H. Doelle, T. Naing, L. Nie, K. Moller Rasmussen, M. Refstrup, W. S. Schackwitz, J. Martin, and A. Ustaszewskia for excellent technical assistance and J. Schageman, C. Lee, K. Lawson, and K. Williams for statistical analyses. We are indebted to the staff and participants of the OHS, the DHS, the ARIC study, and the CHFS for their important contributions. Supported by grants from Foundation Le Duc, the Donald W. Reynolds Foundation, NIH (HL-082894), the National Heart, Lung, and Blood Institute Program for Genomic Applications (no. HL-066681), the U.S. Department of Energy (contract no. DE-AC02-05CH11231), the Canadian Institutes of Health Research (no. 44360), the Canadian Foundation for Innovation, the Heart and Stroke Foundation of Ontario (no. NA-5413) the Danish Medical Research Council, the Danish Heart Foundation, and the Research Fund at Rigshospitalet, Copenhagen University Hospital. D.R.C. and D.A.H. have equity interest in Perlegen Sciences.

Supporting Online Material
www.sciencemag.org/cgi/content/full/1124447/DC1
Materials and Methods
Figs. S1 and S2
Tables S1 to S7
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To this end, we conducted a genome-wide association study on Icelandic patients with MI, using the Illumina Hap500 chip. After quality filtering, 305,953 single-nucleotide polymorphisms (SNPs) were tested for association with MI in a sample of 1607 cases, with age at onset before 70 in males and before 75 in females; 6728 patients without a history of CAD were used as controls (2). The results were adjusted for relatedness between individuals and potential population stratification with the use of a method of genomic control (3). Although none of the SNPs were significant after adjusting for the number of tests performed, more signals with P values of less than 10−7 were observed than expected by chance (fig. S1). Hence, we further explored the SNPs with P values that were closest to genome-wide significance.

The strongest association with MI was observed with three correlated SNPs—rs1333040,
rs10757274 and rs2383206 were present at appreciable frequencies among African-Americans in ARIC and DHS, but neither SNP was associated with CHD in either population (table S7). The apparent ethnic differences in association between these SNPs and CHD in ARIC may reflect differences in statistical power in ARIC but cannot explain the ethnic differences observed in DHS, where African-Americans are the largest group. Accordingly, it seems more likely that the functional sequence variants associated with the risk allele in whites are less common in African-Americans. This notion is consistent with our finding that the frequencies of several alleles associated with CHD risk factors differ widely among ethnic groups (9–11). Comprehensive analysis of the locus in African-Americans may allow further refinement of the risk interval.