Mutations in the ANP Coding Gene Are Involved in Familial Atrial Fibrillation


Study Hypothesis

Community-based cohort studies and familial clustering of the condition suggest a genetic component in the pathophysiology of atrial fibrillation in some patients. It is conceivable that mutations in specific genes cause atrial fibrillation in certain families.

How Was the Hypothesis Tested?

The authors performed a genome-wide linkage analysis and subsequent fine mapping in a family with 11 affected members to identify a chromosomal locus segregating with the condition. Then, candidate genes in the critical region were sequenced and biochemical analyses as well as animal experiments were performed to assess the biological consequences of the detected mutation.

Principal Findings

Linkage analysis and fine mapping revealed a locus on chromosome 1p36-p35 that cosegregates with the condition. Subsequently, the NPPA gene (encoding atrial natriuretic peptide, ANP), located within the critical region, was sequenced and a heterozygous frameshift mutation (c.456 to 457delAA) was identified in all affected family members but was not detectable in nonaffected family members and in 560 controls with normal ECG and echocardiograms. The mutation abolishes the stop codon and extends the reading frame, which results in an extended chimeric protein consisting of the normal 28 amino acids plus an added 12 residues at the carboxy terminus. In carriers of the mutation, plasma concentration of the mutant ANP protein was 5 to 10 times higher than concentration of the wild-type (normal) ANP. Infusion of mutant ANP reduced the monophasic action potential and the effective refractory period in a rat isolated whole heart model.

Implications

The present study identified mutations in the ANP-encoding NPPA gene as a new genetic basis for familial atrial fibrillation and points to perturbations in the ANP-cGMP signaling pathway in cardiac atria in mediating electric instability and arrhythmogenesis, rendering this pathway as a novel potential therapeutic target.

Genetic Loci Encoding Pathways Involved in Metabolic Disorders Are Related to CRP Levels


Study Hypothesis

C-reactive protein (CRP) levels have a heritable component, and large-scale genome-wide association studies may lead to the discovery of common genetic variation influencing circulating CRP levels.

How Was the Hypothesis Tested?

A total of 6345 apparently healthy women (Women’s Genome Health Study cohort), who were free of diabetes and not on lipid-lowering medications, were genotyped for 336 108 single-nucleotide polymorphisms (SNPs) from the Illumina Hap300 panel and an additional set of 45 571 genetic variants in candidate regions thought to be involved in inflammatory, metabolic, or cardiovascular conditions.

Principal Findings

A total of 46 SNPs, clustering in 7 chromosomal regions, displayed evidence for association at a statistical significance level of \( P < 5 \times 10^{-8} \). These loci included chromosome 1q31.3, including the leptin-receptor gene; chromosome 1q23.2, including the CRP gene; chromosome 1q21.3, including the interleukin (IL)-6 receptor gene; chromosome 2p23.3, including a glucokinase regulatory protein gene; chromosome 12q24.31, including the hepatic nuclear factor 1-\( \alpha \) (HNF1A) gene; chromosome 19q13.32, close to the apolipoprotein (APO) E gene; and an intergenic locus on chromosome 12q23.2. The top SNPs for each region had probability values between \( 1.9 \times 10^{-8} \) and \( 6.2 \times 10^{-28} \). Considered together, SNPs in these 7 loci explained 10% of the variation in CRP, after
Mutations in \textit{ABCA1} Gene Are Associated With Low HDL Levels But Not With An Increased Risk for Heart Disease in the General Population


Study Hypothesis

Homozygous mutations in the \textit{ABCA1} gene cause Tangier disease, a rare Mendelian disorder characterized by low circulating high-density lipoproteins (HDL) cholesterol levels. Heterozygous mutations in the \textit{ABCA1} gene may contribute to low HDL levels, modulate cellular cholesterol efflux, and convey an increased risk of ischemic heart disease (IHD) in the general population.

How Was the Hypothesis Tested?

A total of 9022 participants of the prospective Copenhagen City Heart Study (CCHS) and 31241 participants of the cross-sectional Copenhagen General Population Study (GGPS) were genotyped for 7 mutations in the \textit{ABCA1} gene (S364C, T774P, K776N, P1065S, G1216V, N1800H, R2144X). The Copenhagen Ischemic Heart Disease Study (CIHDS; n = 41 961; 6666 cases; 109 heterozygotes), revealed an odds ratio for IHD of 0.93 (95% CI, 0.53 to 1.62) for heterozygotes versus noncarriers.

Implications

Heterozygous loss-of-function mutations in the \textit{ABCA1} gene are associated with low HDL levels and impaired cholesterol efflux but not with an increased odds of IHD in these general population-based samples, suggesting that low HDL in heterozygous \textit{ABCA1} mutation carriers may not be directly related to IHD. The authors postulate that low HDL levels increase IHD risk only when accompanied by an increase in triglycerides and atherogenic remnant lipoproteins, a premise that merits further investigation.

A Common Variant in WW-Domain-Containing Oxidoreductase Gene is Related to HDL Cholesterol


Study Hypothesis

A locus on chromosome 16q23-q24 has been repeatedly linked to low high-density lipoprotein (HDL) cholesterol in families with lipid disorders and in the general population. The authors hypothesized that genes at this locus contribute to the interindividual variation of HDL cholesterol.

How Was the Hypothesis Tested?

The authors used a stepwise approach. In a first step, 1318 single-nucleotide polymorphisms (SNPs) tagging a 12.4 Mb region around the main linkage signal (previously obtained in Finnish and Dutch families with familial combined hyperlipidemia, FCHL) were successfully genotyped in 322 individuals from families with FCHL (n = 33) or low-HDL (n = 17). In addition, polymorphisms in the \textit{LCAT} and \textit{CETP} genes, interesting candidate genes close to the main linkage signal, were analyzed. In a second step, the 25 most significant SNPs were analyzed in additional FCHL and low-HDL families, and in low-HDL case-control samples. Furthermore, the top SNP was cross-sectionally and longitudinally related to HDL in 2 Finnish community-based cohorts. The functional sig-
The significance of the top SNP was assessed with luciferase and electrophoretic mobility-shift assays (EMSA).

**Results**

A total of 15 SNPs within the *ATBF1*, *CNTNAP4*, *ADAMTS18*, *WWOX*, and *CDH13* genes and in the intergenic region between the *MAF* and *DYNLRB2* genes (*P* < 0.01) and 10 additional SNPs with a *P* < 0.05 from within those genes were selected after the first step analyses and evaluated in additional families and case-control samples in step 2. In a combined analysis of 102 dyslipidemic families with a total of 933 individuals and in 475 low-HDL cases and controls, rs2548861 within the *WWOX* gene displayed the strongest evidence for association in family-based association analyses (*P* = 0.001) and in case-control samples (*P* = 0.0004). One copy of the rs2548861 T allele was associated with a 17% increased risk of low HDL. The combined analyses of all familial (including additional 55 Mexican FCHL families) and case–control samples revealed a *P* = 6.9 × 10⁻⁷ (Bonferroni-adjusted: *P* = 0.0009), rs2548861 was also associated with low HDL cholesterol in 4447 community-dwelling male participants (METSIM cohort), age 50 to 70 (*P* = 0.03), and with the mean of 4 HDL measurements, obtained over a 21-year period in participants aged 3 to 18 years at enrolment (*P* = 0.004; *n* = 1561; the T risk allele explained 1.5% of the variance in HDL levels in the Young Finns cohort). Functional analyses indicated that the variant rs2548861 resides in a functional cis-regulatory element that has an allele-specific effect. The mechanism underlying the association with HDL is unknown, although it is known that *WWOX* modulates transcription and is involved in apoptosis, carcinogenesis, and in steroid metabolism.

**Implications**

Genetic and functional data link a genetic variant in the *WWOX* gene to interindividual variation in HDL levels in families with dyslipidemia and in the general population. Additional studies are warranted to clarify the molecular mechanisms underlying the observed association.

**Common Genetic Variation in SLCO1B1 Is Associated With Statin-Induced Myopathy**


**Study Hypothesis**

Genetic variants may contribute to the susceptibility for statin-induced myopathy, a rare side-effect of high-dose statin therapy, and genome-wide association analyses may help identify the genetic basis for the condition.

**How Was the Hypothesis Tested?**

A genome-wide association study was performed in 85 patients who developed definitive or incipient myopathy during the course of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial, and in 90 controls, matched for sex, age, estimated glomerular filtration rate, and use or nonuse of amiodarone at baseline. The SEARCH trial included 12 064 participants with prior myocardial infarction who were randomized to receive either 20 or 80 mg simvastatin. Cases and controls both were derived from group assigned to receive 80 mg simvastatin. Overall, 316 184 SNPs were successfully genotyped. The top SNPs were replicated in the Heart Protection Study (*n* = 16 664 individuals genotyped, 23 cases with definitive or incipient myopathy), which included participants with preexisting occlusive vascular disease or diabetes who were randomized to 40 mg simvastatin or placebo.

**Principal Findings**

One SNPs (rs4363657) in intron 11 of the *SLCO1B1* gene was strongly associated with statin-induced myopathy (*P* = 4 × 10⁻⁸). The odds ratio per copy of the C allele (prevalence of 13%) was 4.3 (95% CI, 2.5 to 7.2). Analyses of additional SNPs in that gene, discovered by genotyping and imputation, revealed one nonsynonymous SNP (rs4149056, Val174Ala) in exon 6 in high LD (r² > 0.95) with rs4363657, and with a similar odds ratios for myopathy. Consistently, rs4149056 was associated with myopathy in the Heart Protection Study (odds ratio, 2.6; 95% CI, 1.3 to 5.0) per copy of the C allele, and also with smaller reductions in LDL cholesterol levels on statin treatment (*P* < 0.001). *SLCO1B1* codes OATP1B1 an organic anion-transporting polypeptide that modulates the hepatic uptake of statins and other drugs. The C risk allele of the variant has been associated with increased blood levels of statins, which may explain the greater risk of myopathy associated with this variant.

**Implications**

Genotyping of genetic variants in the *SLCO1B1* gene may identify individuals with an increased risk for myopathy when treated with high-dose statins or other drugs transported by OATP1B1. Therefore, the study raises the possibility that typing of specific variants within *SLCO1B1* may improve safety monitoring and tailoring of statin dose in patients treated with theses drugs, a premise that warrants further testing in future studies.
Summary of Recent Articles of Interest
Wolfgang Lieb and Ramachandran S. Vasan

doi: 10.1161/CIRCGENETICS.108.829374

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circgenetics.ahajournals.org/content/1/2/154

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Genetics can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Genetics is online at:
http://circgenetics.ahajournals.org/subscriptions/