Mutations in Sarcomeric Protein Genes Account for a Substantial Proportion of Idiopathic Cardiac Hypertrophy in Children


**Study Hypothesis**

Mutations in sarcomere proteins that are implicated in adult forms of hypertrophic cardiomyopathy may play a role in idiopathic cardiac hypertrophy with onset in childhood, a disorder associated with poor prognosis.

**How Was the Hypothesis Tested?**

Morita and colleagues screened for mutations in 8 genes encoding sarcomeric proteins (MYH7, MYBPC3, TNNT2, TNNI3, TPM1, MYL3, MYL2, and ACTC) using direct sequencing techniques in 84 children with idiopathic cardiac hypertrophy. Mutations in these genes cause adult-onset cardiomyopathy.

**Principal Findings**

The authors identified mutations in almost half of children without a positive family history of cardiomyopathy (25 of 51 affected children) and in two thirds (21 of 33) of affected children with familial cardiomyopathy. Mutations in MYH7 (encoding β-myosin heavy chain) and MYBPC3 (encoding myosin-binding protein C) were the most frequent variants identified in the children. In the subgroup with sporadic (nonfamilial) cardiac hypertrophy, boys were more likely than girls to harbor mutations.

**Implications**

The authors conclude that childhood onset of cardiac hypertrophy should provoke genetic investigation and family assessment because about 50% of cases in this series were attributable to mutations routinely screened for in adults with unexplained cardiac hypertrophy. Identification of such mutations in children with cardiac hypertrophy would raise the possibility that management strategies used for adults with genetic cardiac hypertrophy may improve clinical outcomes in these children.

Variation in the NPPA Gene May Predict Blood Pressure Response to Antihypertensive Drug Class and Modulate Cardiovascular Outcomes in Hypertensive Patients


**Study Hypothesis**

Variation in NPPA gene, which encodes the precursor of atrial natriuretic peptide, may influence the efficacy of different classes of antihypertensive agents both in terms of the extent of blood pressure (BP) lowering and the incidence of clinical cardiovascular disease (CVD) outcomes on follow-up.

**How Was the Hypothesis Tested?**

Using data from the Genetics of Hypertension Associated Treatment (GenHAT; n=38,462) study, a substudy of the randomized, double-blind multicenter Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), Lynch et al performed a post hoc analysis to assess whether the response to and the clinical outcome on antihypertensive treatment is modified by 2 genetic variants (rs5063 and rs5065) within the NPPA gene. Within ALLHAT, patients were randomized to receive either a diuretic (chlorthalidone), an angiotensin-converting enzyme inhibitor (lisinopril), a calcium channel blocker (amlodipine), or an α-adrenergic blocker (doxazosin). The mean follow-up period was 4.9 years.

**Principal Findings**

Overall, in analyses of main effects, neither single-nucleotide polymorphism (SNP) was associated independently with CVD outcomes or with degree of reduction in systolic or diastolic BP (event rates and BP reduction were similar for all genotypes). However, genotype × treatment regimen interactions were observed for rs5065 (for both CVD outcomes and BP reduction), indicating that the association of the minor allele of this SNP with CVD outcomes and BP reduction varied according to treatment drug class. Carriers of the minor allele of the T2238C variant (rs5065; ≈40% of sample) had lower incidence rates of coronary heart disease,
stroke, all-cause death, and combined end points (combined coronary heart disease and combined CVD) when they received treatment with chlorthalidone, as compared with those randomized to amloidipine. Furthermore, C allele carriers displayed greater reductions in systolic and diastolic BP when they were randomized to chlorthalidone treatment (compared with treatment with other drug classes). No pharmacogenetic associations were observed for the G664A variant (rs5063).

Implications
Although the study was retrospective and post hoc in nature and focused on just 2 SNPs in a single gene, these exploratory observations raise the possibility that genetic variations in select candidate genes may influence response to treatment with specific drug classes in patients with hypertension. More definitive prospective pharmacogenetic studies are warranted to evaluate this premise.

Rare Mutations in Renal Salt-Handling Genes Affect Blood Pressure in the General Population

Ji and colleagues postulated that heterozygote individuals harboring rare alleles implicated in these conditions may have lower long-term BP.

How Was the Hypothesis Tested?
Ji and colleagues screened 3125 Framingham offspring study participants for heterozygous mutations in 3 genes implicated in renal sodium handling cause rare mendelian disorders (Gitelman’s and Bartter’s syndromes) characterized by low BP. They performed association analyses relating presence of these rare mutations to long-term BP and the incidence of hypertension.

Principal Findings
The authors identified 30 different mutations in 49 individuals that either were biochemically proven to be functional or for which a functional significance was inferred on the basis of comparative genomic and genetic criteria. Mutation carriers had significantly lower mean long-term values for systolic (−6.3 mm Hg; \( P=0.0009 \)) and diastolic (−3.4 mm Hg; \( P=0.003 \)) BP and a 59% (95% confidence interval: 23% to 71%; \( P<0.003 \)) lower risk of developing hypertension by age 60 years.

Implications
The results are consistent with the notion that genetic variants that influence renal salt handling contribute to BP variation at the population level.

Editor’s Note
Readers may also want to refer to an interesting review article that compares and contrasts the effects of common versus rare variants and estimates that the average number of rare variants each person may carry may be \( \approx 10 \), and given their high penetrance, these variants may influence disease risk and treatment decisions. See Bodner W, Bonilla C. Common and rare variants in multifactorial susceptibility to common diseases. Nat Genet. 2008;40:695–701. Review. PMID: 18509313.

Lipid Genotype Score Is Related to Incident Cardiovascular Events and Improves Risk Reclassification

Kathiresan and colleagues generated a genotype score based on 9 polymorphisms (representing 9 different loci) that have previously been related to low-density lipoprotein (5 loci; \( APOB, APOE \), \( HMGCR, LDLR, \) and \( PCSK9 \)) or high-density lipoprotein cholesterol levels (4 loci; \( ABCA1, CETP, LIPC, \) and \( LPL \)). The genotype score for each individual could vary from 0 to 18 (0, 1, or 2 copies of the unfavorable allele of each of the 9 SNPs).

Study Hypothesis
Several known and novel genetic loci influence circulating lipid levels. Therefore, common genetic variants that modulate lipid levels may also be associated with risk of CVD events, and these variants may improve risk prediction beyond that offered by traditional risk factors, including plasma lipids.

How Was the Hypothesis Tested?
In 5414 participants of the community-based Malmö Diet and Cancer Study, Kathiresan and colleagues generated a genotype score based on 9 polymorphisms (representing 9 different loci) that have previously been related to low-density lipoprotein (5 loci; \( APOB, APOE \), \( HMGCR, LDLR, \) and \( PCSK9 \)) or high-density lipoprotein cholesterol levels (4 loci; \( ABCA1, CETP, LIPC, \) and \( LPL \)). The genotype score for each individual could vary from 0 to 18 (0, 1, or 2 copies of the unfavorable allele of each of the 9 SNPs).

Principal Findings
Plasma low-density lipoprotein levels increased and high-density lipoprotein levels decreased as the genotype score rose. A total of 238 individuals developed a first cardiovascular event (myocardial infarction, ischemic stroke, death from coronary heart disease) during a median follow-up of 10.6 years. Although the genotype score was independently predictive of incident CVD after adjustment for traditional risk factors and baseline lipid levels (15% increase in risk per copy of an unfavorable allele), the score did not improve risk discrimination (C statistic was 0.80 for models without and with the genotype risk scores). Knowledge of the genotype risk score did, however, modestly improve risk reclassification: 26% of individuals assigned to an intermediate Adult Treatment Panel III risk category were recategorized into a lower or higher level when genotype score was considered.

Implications
Although this investigation focused on a limited set of SNPs that influence lipid levels, it does provide proof of the concept that genotype risk scores may influence CVD risk and may hold the potential for improving risk prediction and stratification. The authors postulate that lipid SNPs may offer...
incremental information over single-occasion lipid levels because they may capture effects on lipids over the life course or because they may influence atherogenesis via mechanisms other than modulation of circulating lipid levels.

**MC4R Is Associated With Obesity Risk in the Community**


**Study Hypothesis**

Genome-wide association studies of large samples will likely uncover common variations that influence interindividual variation in body mass index (BMI).

**How Was the Hypothesis Tested?**

Loos and colleagues performed an initial meta-analysis of genome-wide association data for BMI from 16 876 individuals of European descent, followed by attempts at replication of hits in a larger sample, and a combined meta-analysis on BMI data for more than 77,000 adults.

**Principal Findings**

In the initial meta-analyses that included 4 European community-based cohorts (n=11 012) and 3 disease-case samples (n=5864), polymorphisms in the recently described FTO gene displayed the strongest association signal with BMI. Of the remaining SNPs, rs17782313 near the MC4R displayed strong evidence for association. Rare mutations in the MC4R gene cause mendelian forms of early-onset obesity. The association of rs17782313 with BMI could be replicated in additional community-based cohorts and disease-case samples (total n=60 352). In a combined analyses of all genotyped adults (n=77 228), each copy of the rs17782313 risk allele was associated with an increase in BMI of 0.22 kg/m². Furthermore, each copy of the risk allele was associated with an 8% and a 12% risk increase for overweight (BMI ≥25 kg/m²) and obesity (BMI ≥30 kg/m²), respectively. Overall, the MC4R variant explained only 0.14% of the variance of adult BMI.

**Implications**

The study replicated the findings for FTO, identified the potential contribution of variation in MC4R, and noted some additional signals that were nominally significant and would require additional replication.

**Editor’s Note**


**Disclosures**

None.
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