

The Clinical Utility of Genetic Data in CVD



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INTRODUCTION

At the American Heart Association 2008 Scientific Session (AHA 2008) entitled "Personalized Genomics: Ready for Primetime?" Dr Eric Topol, Director of the Scripps Translational Science Institute and Editor-in-Chief of theheart.org, shared his own genome-wide scan results; revealing that he has an above average lifetime risk for myocardial infarction (MI) and rheumatoid arthritis. While consumer genome-wide scans have received a lot of press attention, clinicians (and cardiologists in particular) are more concerned with the individual tests that are currently available, such as those identifying people at greater risk for coronary artery disease (CAD)/MI (9p21) and atrial fibrillation (4q25), or those used to predict response to pharmacotherapy such as warfarin (CYP2C9/VKORC1).

Evidence demonstrating its meaningful clinical application will be critical for wider incorporation of genetic information into the management of patients with cardiovascular disease (CVD). At AHA 2008, important data were presented by many researchers that have expanded our understanding of the genetic bases of CVD. This article recaps recent advances in the genetics of CAD, atrial fibrillation (AF), and heart failure (HF), with an emphasis on the clinical impact of these findings.

CORONARY ARTERY DISEASE

Prior studies have implicated a number of alleles linked to CAD, but detailed characterization of these genes has been difficult because the disease is multifactorial and arises from multiple genetic and environmental influences.ⁱ For example, earlier studies in a large family with premature CAD led to the identification of variations in a putative gene on chromosome 15q26 named MEF2A but subsequent studies in other patients have controverted this finding.ⁱⁱ Accordingly, researchers have transitioned away from the "direct candidate gene" approach in favor of genome-wide association scans (GWAS), which use single nucleotide polymorphisms (SNPs) as markers to identify individual or clusters of disease-associated alleles, even if the SNPs themselves have no role in the expression of the disease. Using GWAS, the first commonly found genetic locus to have an

association with CAD has been localized to chromosome 9p21.ⁱⁱⁱ Markers on 9p21 have been validated in multiple white European cohorts with an associated odds ratio for CAD of 1.29 for one copy of the variant (heterozygotes) and 1.70 in homozygotes.^{iv,v}

ARIC: Classification Using Framingham Risk Score and 9p21 Allele

10-Year risk category	FRS alone	0-5%	5-10%	10-20%	>20%	Total reclassified
0-5%	3876	97.8%	2.2%	0	0	87 (2.2%)
5-10%	1869	7.9%	82.9%	9.2%	0	319 (17.1%)
10-20%	2419	0	7.0%	84.2%	8.8%	382 (15.8%)
> 20%	1840	0	0	10%	90%	185 (10%)
	10,004	3936	1805	2394	1869	

At AHA 2008, Brautbar and colleagues. (Baylor College of Medicine, Houston, TX) reported on the clinical utility of screening for genotypes of the chromosome 9p21 allele known as rs1075724 using clinical data from the ARIC study.^{vi} They assessed the prognostic impact of such screening in 10,004 Caucasian patients whose risk had been stratified using the ARIC Cardiovascular Risk Score (ACRS) derived from



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traditional risk factors. Among those with intermediate-low (i.e. estimated 10-year risk for CV events of 5%-10%) and intermediate-high (10%-20%) risk by ACRS, the authors found that determination of patients' 9p21 alleles frequently resulted in reclassification into a different clinical risk stratum with potential changes in clinical management. Similarly, when the 9p21 data were added to the more widely used Framingham Risk Score, 17.1% of intermediate-low and 15.8% of intermediate-high participants were reclassified, respectively (Slide 1). Interestingly, almost 90% of men and women in the two intermediate-risk categories had low-density lipoprotein cholesterol (LDL-C) levels of 100 mg/dL or higher (approximately 55%-66% had levels of 130 mg/dL or higher).

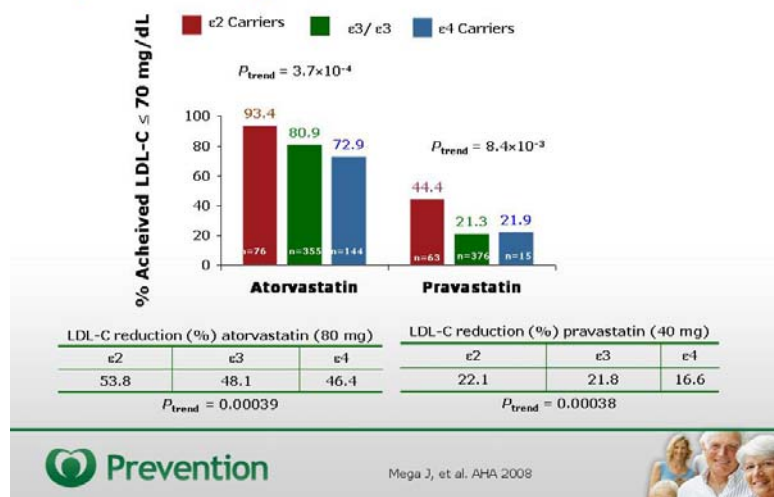
Dr Christie Ballantyne, Chief of the Section of Atherosclerosis and Vascular Medicine at Baylor College of Medicine and Director of the Center for Cardiovascular Disease Prevention at Methodist DeBakey Heart and Vascular Center (Houston, TX), suggested that 9p21 testing could influence how aggressive you are with lipid-lowering targets and that "this is something that ... clinicians can consider in regards to risk assessment. It is an easy test to utilize and can provide helpful information to patients who want to get their optimum information to try to prevent heart attacks." He also noted that "the focus will be on individuals who are a little lower risk (5% to 10%) because of trials like JUPITER and also if you're only treating over 10% [risk category], you're ignoring middle-aged women who we know go on to have heart attacks and strokes later in life." Paynter (Brigham and Women's Hospital, Boston, MA) and colleagues assessed the utility of rs1075724 screening in 22,129 Caucasian women in the Women's Genome Health Study and found that despite a statistically significant association between the higher-risk GG genotype and incident CVD, genotyping did not add prognostic value beyond that provided by the Reynolds Risk Score.^{vii} The Reynolds Risk Score was originally developed to assess risk in women; it includes family history of MI and high sensitivity C-reactive protein (hs-CRP), in addition to traditional risk factors.

PHARMACOGENETICS

Risk stratification using cardiovascular genomics may not only reveal patients who warrant lipid-lowering therapy, but also how those patients will respond to such therapy. Mega (Brigham and Women's Hospital TIMI Study Group, Boston, MA) and colleagues reported on two polymorphisms of apolipoprotein ε (rs7412 and rs429358) that were associated with ε2/ ε3/ ε4 isoforms and correlated with baseline LDL-C levels, as well as the degree of LDL-C reduction following the administration of intensive atorvastatin (80 mg) or pravastatin (40 mg).^{viii} The researchers focused on 1378 statin-naïve patients from the PROVE-IT

TIMI-22 trial. In the original trial of stable ACS patients, achieving target LDL cholesterol (< 70 mg/dL) and/or hs-CRP level (< 2 mg/L) was associated with a significant reduction in rates of recurrent MI and coronary death. While the intensive atorvastatin group was more likely to achieve both target levels, there was a wide variation in patient-to-patient responses.^{ix} It was this

ApoE Genotype and LDL-C Reduction



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observation that prompted the genetic investigation which did indeed show that patients with the $\epsilon 2$ genotype were more responsive to statin therapy (Slide 2).

In contrast, almost 1 in 4 patients with the $\epsilon 4$ genotype did not achieve LDL-C goal even with intensive atorvastatin therapy. Dr Jessica Mega concluded that "these findings add to our understanding of the genetic mechanisms that influence statin efficacy, and suggest that common variants in the future may have the potential to help us tailor our treatments and help us treat our acute coronary syndrome patients."

ATRIAL FIBRILLATION

As has been the case with CAD, GWAS techniques have become more commonplace among studies of the genetic underpinnings of AF.^x There is growing GWAS evidence implicating common genetic variants on chromosome 4q25 for the paired-like homeodomain transcription factor 2 (PITX2) in the genesis of AF.^{xi} Approximately 35% of European and 75% of Asian populations carry at least one of the two most widely replicated variants (rs2200733 and rs10033464). Risk for AF is increased by 1.72 (1.59-1.86) and 1.42 (1.16-1.73) per copy of rs2200733 in people of European or Asian ancestry, respectively.

Several presentations at AHA 2008 supplied important data pertaining to clinically relevant outcomes leading Dr Eric Topol, to proclaim that "the big news this year is the further expansion of knowledge in the topic of atrial fibrillation."

Gulcher and colleagues (decode Genetics, Barrington, IL) confirmed the link between the rs2200733 sequence variant and AF and also demonstrated its association with earlier onset and more recurrent AF.^{xii} Using a GWAS, the investigators found that among 719 AF cases, carriers of rs2200733 developed AF at a significantly younger age (decrease of 1.9 years per risk allele, $P = 0.018$). The variant was associated with all types of AF, but was more strongly associated with lone AF (AF in the absence of traditional AF risk factors such as hypertension or structural heart disease). The risk of recurrence was also more common among carriers (odds ratio = 1.47, $P = 0.045$).

Chung (Cleveland Clinic, Cleveland, OH) and colleagues. replicated the association between another 4q25 variant (rs4611994) and AF in secondary phenotype analysis of an MI case/control cohort. Examination of 46 left atrial appendage tissue samples excised at the time of cardiac surgery demonstrated significant association between this genotype and expression of LRIT3 and PITX2, suggesting that these genes should be investigated in mechanistic studies.^{xiii} Importantly, Body (Brigham & Women's Hospital, Boston, MA) and colleagues. conducted a prospective observational study of 1551 consecutive coronary artery bypass graft surgery (CABG) patients and also reported that variations in the PITX2 region were associated with the development of AF in the postoperative period. Dr. Topol explained that "if we could measure this common variant ... we might be able to predict, for example, going into open heart surgery, who should get preventive therapy, such as amiodarone."

In another abstract, Gulcher and colleagues tested more than 1500 ischemic stroke patients and almost 11,000 controls for various genetic variants linked to AF.^{xiv} The most significant two (rs2200733 and rs10033464) were replicated in two large European samples (2224 cases/2583 controls). It is perhaps not surprising that two variants previously associated with AF are also strongly associated with ischemic stroke given that AF is a major risk factor for stroke. What is more intriguing is that although both markers were most strongly associated with cardiogenic stroke, rs2200733 was also significantly associated with noncardiogenic stroke. What this tells us,

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Dr Topol noted "is that a lot of our so-called cryptogenic stroke is actually related to undiagnosed atrial fibrillation."

Looking forward, Dr Topol asked, "Now that we know the gene that is the most important common root cause relationship with AF, can we come up with better ways beyond ablation ... to get at AF using the genomics underpinning?"

HEART FAILURE

HF syndromes arise from a wide variety of etiologies. Accordingly, candidate genes have been identified for individual variants, such as sarcomere gene mutations in hypertrophic cardiomyopathies or mutations encoding for desmosomal proteins in arrhythmogenic right ventricular cardiomyopathy.

At AHA 2008, Granger (Duke University Medical Center, Durham, NC) and colleagues reported a genetic substudy of the CHARM trial in which 14 candidate genes were analyzed for association with clinically significant outcomes in 3239 patients with chronic HF and preserved left ventricular ejection fraction.^{xv} The analysis focused on genes that are associated with HF outcomes rather than the development of HF, such as angiotensinogen and adrenergic receptor genes, and included 165 SNPs. However, none of the genes were significantly associated with outcomes after adjustments were made for multiple testing, challenging some speculative findings from prior smaller studies that influenced the selection of the candidate genes. Dr Granger commented that "one of the lessons ... is that the GWAS, at least for these common variants, looks like a much more robust and reliable way to relate genetic variability in disease and outcome than the 'candidate gene' approach which has been generally disappointing." He noted that further validation is ongoing to rule out false negatives.

BEST Genetic Substudy: Bucindolol/Placebo Time to Event by β_1 and α_{2c} Genotype

	β_1 389 Arg/Arg + α_{2c} WT/WT or DEL	β_1 389 Gly + α_{2c} WT/WT	β_1 389 Gly + α_{2c} DEL
Phenotype:	Very favorable	Favorable	Unfavorable
N	493	413	134
Endpoint HR (95% CI)			
All-cause mortality	0.62 (0.39–0.99)*	0.75 (0.48–1.17)	1.04 (0.43–2.54)
CV mortality	0.52 (0.31–0.88)*	0.60 (0.36–0.97)*	1.11 (0.45–2.78)
HF hospitalization	0.56 (0.39–0.82)**	0.77 (0.53–1.13)	0.73 (0.35–1.53)

WT = wild type; DEL = deletion
* $p < 0.05$ ** $p < 0.01$



O'Connor CM, et al. HFSA 2008; Toronto, ON



Still, pharmacogenetic data hold great promise for guiding future management of HF. Much like the the study by Mega and colleagues supporting a genetic basis for interpatient variability in statin response, a genetic substudy of the BEST trial has suggested that a beneficial response to the investigational beta blocker, bucindolol, in patients with HF depended upon the presence of specific polymorphisms of genes that coded for various adrenergic receptors.^{xvi} The findings were presented by Dr Christopher O' Connor (Duke University, Durham, NC) at the Heart Failure Society of American (HFSA) Scientific Meeting in September, 2008 showing that

almost half of the 1040 patients with systolic HF who were included in the DNA substudy carried particular variants that were associated with an increased response to bucindolol. In the original trial comparing bucindolol with a combination of ACE inhibitors, diuretics and placebo there was no significant difference in all-cause mortality between treatment groups, but the beta blocker was associated with a reduction in the secondary endpoint of CV mortality, HF hospitalization and

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death, or heart transplantation.^{xvii} In the genetic substudy, specific genotypes were associated with very favorable, favorable, or unfavorable responses to the drug (Slide 3). Homozygous carriers of the Arg 389 variant of the β_1 adrenergic receptor alone had a 3-to-4-fold increase in the activity of the adrenergic receptor and a subsequent increased effect of bucindolol.

In reviewing the findings, Dr Granger commented that "the caveat is that it is a single substudy analysis and there are other effective beta blockers...but it's an interesting example of where pharmacogenetics might be helpful in the future."

CONCLUSION

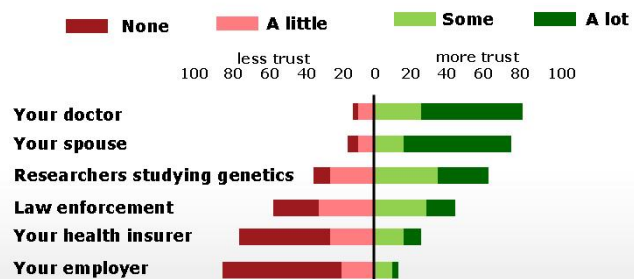
Presenters at AHA 2008 seemed to share a sentiment of excitement about the remarkable progress in the field of cardiovascular genomics and the imminence of its clinical impact, along with a sense of uncertainty regarding its optimal role in patient care.

"We're right on the cusp of taking the field much further forward," reported Dr Topol, but Dr Granger cautioned, "We're at a time where we are coming up with more and more definitive findings but it's still not clear exactly how these will impact onto practice."

He added that "there are some of these tests , and I'll use 9p21 as an example, where the information contained in that test may shift a substantial number of patients... to where they are at a high enough risk that they warrant more aggressive treatment, for example with statins." He concluded, "The message I think is: Stay tuned, we're at this very exciting time, there is some clinical applicability of these tests now but a lot of work to do to figure out how to best implement them to improve patient care."

Dr David Herrington of Wake Forest University agreed, saying "there was a lot of interesting discussion about the broad topic of personalized medicine and ... what the future may hold for us as clinicians who are attempting to incorporate the use of genetic information in our clinical practice." Translation of advances in genetic research to useful clinical applications may require a better appreciation of the nuances of communicating with patients regarding genetic testing and diagnosis. In the multicenter TRIUMPH STUDY, Lanfear and colleagues reported considerable variation in patients' willingness to participate in genetic testing that occurred on the basis of study site, suggesting that the mode of delivery of information may play a crucial role in determining whether patients are open to the development and use of cardiovascular genomics in their care.^{xviii} On a similar note, Dr Topol presented data from a US poll conducted by the Genetics and Public Policy Center at Johns Hopkins University showing that

US Poll*, Answers to: "How Much Do You Trust Each of the Following to Have Access to Your Genetic Test Results?"



Source: Genetics and Public Policy Center <http://www.dnapolicy.org>



*Taken 02/27/07 to 03/04/07
N = 1199 Adults ≥ 18 years



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when it comes to genetic information, consumers are quite trusting of their physicians, but are far less so of their employers and health insurers (Slide 4).^{xix}

In summary, it is clear that the data emerging from AHA 2008 have significantly advanced the field of cardiovascular genomics and demonstrated their great potential clinical value. Genomics and pharmacogenetics may influence future diagnosis and management of common cardiovascular pathologies including CAD, AF, and HF. As Dr Topol concluded, "So ... it's very exciting times indeed in the cardiovascular genomics world."

TRIAL ABBREVIATIONS AND ACRONYMS

ARIC: Atherosclerosis Risk in Communities Study

BEST: Beta Blocker Evaluation of Survival Study

CHARM: Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity

JUPITER: Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin

PROVE-IT TIMI-22: Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction

TRIUMPH: Translational Research Investigating Underlying Disparities in Myocardial Infarction Patients' Health Status

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^{xiii} Chung MK, Wagoner DRV, Smith JD, et al. Abstract 4403: significant single nucleotide polymorphism associated with atrial fibrillation located on chromosome 4q25 in a whole genome association study and association with left atrial gene expression. *Circulation*. 2008;118:S_882.

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