Genetic Contribution to Coronary Atherosclerosis

Victoria L. M. Herrera

Professor of Medicine
Section of Molecular Genetics, Whitaker Cardiovascular Institute
Section of Molecular Medicine, Department of Medicine
Boston University School of Medicine

INTRODUCTION
A perspective for work-in-progress
Understanding the genetic mechanisms underlying coronary artery disease is as complex as it is important. Despite current advances in molecular genetics, genomics and bioinformatics, deciphering the genetic contribution to coronary artery disease remains a challenge. Just as genetic analysis depends on accuracy of phenotypic characterization and stratification, phenotypic characterization of coronary artery disease could benefit from genetic subtyping in order to better determine prognosis and guide management. Nevertheless, despite scientific challenges, clinical mandates reiterate the need to understand genetic mechanisms of coronary artery disease. Understanding genetic paradigms involved in coronary artery disease is imperative towards mechanism-based intervention and prevention.

Without a "Rosetta stone", complexity of a disease can be addressed through paradigmatic analysis - thereafter, assembling paradigms into a framework, and testing said putative framework(s) of pathogenesis. To begin, genetic contribution to coronary artery disease can be subdivided into different pathogenic components or paradigms - with each paradigm representing different genetic concepts, accounting for specific characteristics of coronary artery disease, and which, a priori, would require specific experimental designs for elucidation. Putative paradigms can be hypothesized based on known genetic concepts. Putative genetic paradigms of coronary artery disease need to be concordant with disease characteristics. The accuracy of phenotype characterization - clinical, pathological, biochemical, observations and correlates of disease - plays a major role in genetic analysis.

GENETIC PARADIGMS DEDUCED FROM CLINICAL OBSERVATIONS
Making sense of a growing list of candidate genes
Based on concepts derived from the study of accessible complex traits in different organisms, insight into genetic paradigms can be deduced from the analysis of clinical features of coronary artery disease. A priori, these paradigms need to be identified and genetic factors to each paradigm determined, in order to comprehensively define the genetic mechanisms underlying a complex disease.

COMPLEX GENETIC DISORDER - multiple genes + environmental factors
Epidemiological observations indicate that common coronary artery disease is a complex genetic disorder that is caused by multiple genes (polygenic or multigenic) which interact with specific environmental risk factor(s) - hence a complex genetic disorder. The known features of coronary artery disease - family history as a risk factor or "seems to run in families", differing onset and course of the disease with a spectrum of clinical presentations, underlying pathology and response to intervention are all concordant with a complex genetic disorder.

Multiple genes involved imply that "disease" genes are really "susceptibility" genes - necessary but not sufficient - with each possibly contributing a small but significant effect to the disease phenotype. This makes genetic elucidation more difficult. Interaction with environmental risk factors to elicit disease phenotype is quite characteristic of complex diseases as seen in coronary artery disease wherein diet, stress, smoking are examples of environmental factors that significantly affect disease course. Environmental factor contribution and polygenic susceptibility are also the reasons why it is a challenge to elucidate primary or susceptibility coronary artery disease genes. Gene-environment interactions need to be deciphered as rightly presented from a "clinician's view" [Grant 2003].

PRIMARY GENE-GENE INTERACTION - why it has been so difficult to pinpoint coronary artery disease "susceptibility" genes
Since gene-gene interactions are common in complex polygenic diseases, the likelihood is high that this genetic paradigm exists in coronary artery disease pathogenesis. This notion is supported by the fact that a susceptibility gene has not been identified to date, since interacting gene pairs may not be detected unless specifically tested for. Single gene analysis would not be able to detect either since each gene of an interacting pair would not have any impact without its cognate interacting gene partner.

**GENE-ENVIRONMENT INTERACTION - why some people can "eat butter" and not get coronary artery disease**

Factoring in known environmental risk factors for coronary artery disease to the genetic equation implies a gene-environment interaction paradigm. The impact of a susceptibility gene may depend on the presence of an environmental risk factor - like high fat-high cholesterol diet intake and smoking. Hence, the identification of said susceptibility gene would require an investigative design that includes accounting for said risk factor - a susceptibility gene's impact is detected only in the context of said risk factor.

Additionally, it could be expected that this susceptibility gene-environmental risk factor interaction is specific to each gene and risk factor; that not all susceptibility genes for coronary artery disease are expected to interact with risk factors, and that different subtypes of coronary artery disease implies different risk factor-gene interactions. Gene-environment interactions can contribute to any stage of plaque development - initiation, progression and/or destabilization.

**GENE MODIFIERS - why it's so hard to clinically predict disease course and response to intervention**

In single-gene or monogenic coronary artery disease such as familial hypercholesterolemia, clinical heterogeneity is evident in the course of coronary artery disease implying that other genetic factors, contribute to the disease phenotype. This clinical heterogeneity implies a gene modifier paradigm wherein modifier genes alter the disease characteristic significantly, but are not themselves necessary for disease causation. This becomes an even more complicated issue with polygenic coronary artery disease.

As with gene-environment interactions, detection of modifier genes needs to be factored into investigative designs. With current difficulties in elucidating genetic contribution to coronary artery disease, it could be suspected that modifier genes confound analysis when they are not taken into account. *A priori*, modifier genes can contribute to any stage of plaque development - initiation, progression and/or destabilization.

**SECONDARY GENES - gene networks contributing to disease process**

Distinction of secondary genes (non-mutated genes that contribute to the disease process) from primary genes (mutated genes that contribute to disease causation or disease susceptibility genes) is important to understanding a unifying framework of pathogenesis. More specifically, a primary susceptibility/disease gene is defined as a gene with a functionally significant polymorphism (a mutation) that contributes to disease susceptibility in contrast to corresponding "normal-function" allele sequences. A secondary gene is a non-mutated gene whose expression or function is modulated (by disease processes initiated by primary susceptibility genes), thus contributing to disease initiation or progression.

*A priori*, it can be expected that there are many more secondary disease genes than there are primary causative/susceptibility genes, and that there would be different subset of secondary genes involved in coronary plaque initiation, progression and destabilization. Genes detected in human coronary plaques or identified to alter plaque burden in mouse gene knockout studies would be classified as secondary genes unless they are directly shown to be mutated and contributing to genetic predisposition or susceptibility.

Identification of secondary disease-process genes requires that they be distinguished from "bystander genes" or genes that are changed but do not mechanistically contribute to disease progression. Mouse knockout studies are a robust methodology to sort this issue out. Additionally, in relation to primary genes, secondary genes could be expected to be more in number. Logistically, the central issue then becomes the identification of the secondary genes that are at the "top of the pyramid" or the "master switches" to disease progression. As with modifier genes, different subsets of secondary disease-process genes could be involved in different plaque stages - initiation, progression and destabilization.

**SECONDARY GENE-GENE INTERACTION - how certain diseases can increase risk or exacerbate coronary artery disease**

Disease course is also affected by interaction with discrete diseases - such as hypertension, diabetes, obesity - resulting in exacerbation of coronary artery disease phenotype. The current working hypothesis is that commonalities among secondary genes in both hypertension and atherosclerosis synergistically interact to exacerbate coronary artery disease.

**CLINICAL HETEROGENEITY = GENETIC HETEROGENEITY AND SUBTYPES - why deciphering coronary...**
artery disease genetics in humans has been elusive
In polygenic ("common") coronary artery disease, clinical heterogeneity is even more pronounced manifesting in markedly different disease onset, course, extent of disease, response to intervention and prevention. On top of different disease modifiers, characteristic clinical heterogeneity in polygenic coronary artery disease implies the existence of disease subtypes. Disease genetic subtypes are most likely brought on by human genetic heterogeneity. Put into a genetic paradigm, these observations indicate a priori that there are distinct subsets of susceptibility genes and modifier genes per putative subtype.

GENDER-SPECIFIC MODIFIER GENE INTERACTIONS - why pre-menopausal women are "protected"
Given similar family history for coronary artery disease and risk factors, pre-menopausal female athero-protection suggests putative gender-specific modifier genes that attenuate the impact of co-present susceptibility genes. The converse deduction is that coronary artery disease in pre-menopausal women would imply that they do not have the specific subset of athero-protection modifier genes. Although these genetic paradigms need to be investigated, it becomes evident that analysis of coronary artery disease in women would necessitate distinct analyses of coronary artery disease in pre-menopausal women and in post-menopausal women.

SYNOPSIS
A TEMPLATE FOR ANALYSIS AND RE-ANALYSIS
Relating genetic paradigms to known plaque features, implicated cell players, risk factors, molecular players is important in the investigation of framework(s) of pathogenesis. There remain many unknowns (?), however beginning with an organizing template is critical to the process. This template concept is exemplified in the diagram and table presented below depicting deduced putative interrelationships of genes and coronary artery disease pathogenesis.

![Coronary Artery Disease Pathogenesis: components → turnkeys → framework](image)

**Figure 1.** A working template for coronary artery disease pathogenesis - hypothesis testing
### A First List of Candidate Coronary Artery Disease Genes

**Work-in-progress**

The following genes have been listed in LocusLink database as being linked to coronary artery disease in humans. This is a growing list; these candidate genes need to be further studied and corroborated. Not all will be confirmed as primary genes, however this first list and even further additions to it are key to next step analyses.

* Locus Link address: [http://www.ncbi.nlm.nih.gov/LocusLink/list.cgi](http://www.ncbi.nlm.nih.gov/LocusLink/list.cgi)

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**Table 1.** A working template for understanding putative relationship(s) of genetic contribution, disease predisposition, disease events in coronary artery disease pathogenesis - hypothesis testing

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<thead>
<tr>
<th>Locus ID</th>
<th>Organ Symbol</th>
<th>Description</th>
<th>Position</th>
<th>Links</th>
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<td>19</td>
<td><em>Hs</em> ABCA1</td>
<td>ATP-binding cassette, sub-family A (ABC1), member 1</td>
<td>9q31.1</td>
<td>P, O, H, U, V</td>
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<tr>
<td>369</td>
<td><em>Hs</em> ABCG8</td>
<td>ATP-binding cassette, sub-family C (CFTR/MRP), member 8</td>
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<td>1636</td>
<td><em>Hs</em> ACE</td>
<td>angiotensin I converting enzyme (peptidyl-dipeptidase A) 1</td>
<td>17q23</td>
<td>P, O, H, V</td>
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<tr>
<td>9370</td>
<td><em>Hs</em> APM1</td>
<td>adipose most abundant gene transcript 1</td>
<td>3q27</td>
<td>P, O, H, V</td>
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<td>110519</td>
<td><em>Hs</em> APOA5</td>
<td>apolipoprotein A-V</td>
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<tr>
<td>348</td>
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<td>apolipoprotein E</td>
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<td>174512</td>
<td><em>Hs</em> CAQ14</td>
<td>Circulating adiponectin QTL on chromosome 14</td>
<td>14</td>
<td>P, O</td>
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<tr>
<td>1231</td>
<td><em>Hs</em> CCR2</td>
<td>chemokine (C-C motif) receptor 2</td>
<td>3q21</td>
<td>P, O, H, U, V</td>
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<td>1071</td>
<td><em>Hs</em> CET1</td>
<td>cholesteryl ester transfer protein, plasma</td>
<td>18q21</td>
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<td>1413</td>
<td><em>Hs</em> CHGA</td>
<td>chromogranin A (parathyroid secretory protein)</td>
<td>14q32</td>
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FACTORING IN PLAQUE PATHOGENIC COMPONENTS

Relating pathogenic components to genetic paradigms

Lessons from concordance between studies of human coronary lesions and animal models suggest multiple events which contribute to plaque initiation, progression and destabilization such as:

- **Hyperlipidemia**
• Inflammation (mediators, cells)
• Oxidative stress
• Endothelial dysfunction and activation
• Matrix imbalance
• Coagulation/fibrinolysis imbalance
• Pathological neovascularization
• Altered vascular smooth muscle cell phenotype
• Altered adventitial phenotype
• Vessel-specific vascular susceptibility.

If coronary artery disease - as represented by plaque initiation, progression and destabilization - is the collective manifestation of all these pathogenic components, it becomes almost expected that susceptibility, secondary or modifier genes of coronary artery disease would belong to gene networks implicated in said pathogenic events directly or indirectly. In fact, the current list of candidate coronary artery disease genes already fall into some of the above pathogenic components.

HARNESSING GENETIC PARADIGMS FOR CAD INTERVENTION

If it’s so difficult to decipher the genetics of CAD, why bother?

Interventions directed at primary susceptibility gene-based mechanisms can be expected to be effective a priori, since correction of the mutant gene’s abnormal function can be expected to be beneficial to the organism rather than induce side effects or complications.

Therapeutic targeting of secondary genes which are differentially increased or decreased by the disease process during the course of the disease, can be beneficial but are inherently at risk of affecting normal cellular processes leading to side effects or complications, unless drug delivery is highly specific for diseased processes. Pertinent to harnessing secondary gene mechanisms, it is imperative to find the “master switch” secondary genes - much like the master switches in development.

Although still a work-in-progress with much to be done and a lack of certainty at the moment, encouraging certainty lies in the valid projection that the elucidation of pathways and mechanisms involved through the identification of primary susceptibility genes, secondary disease-process and modifier genes can and will make significant inroads into intervention and prevention of coronary artery disease. Also certain is that said identification requires multidisciplinary collaborations.

References

- Locus Link: http://www.ncbi.nlm.nih.gov/LocusLink/list.cgi
- PubMed Search: key words: genetics coronary atherosclerosis/ genetics coronary artery disease.

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Updating: 11/03/2003