

# Genetics and Behavioral Medicine: Risk Factors for Cardiovascular Disease

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*This is the second in a series of three articles addressing the intersection of interests in behavioral genetics and behavioral medicine. In this article, we use risk factors for cardiovascular disease as a prototypical trait for which behavioral genetic approaches provide powerful tools for understanding how risk factors, behavior, and health outcomes are related. The approach synthesizes a number of methods and areas of interest in an attempt to arrive at a comprehensive, whole-organism understanding of health-related risk factors and their response to behavioral interventions.*

**Index Terms:** behavioral genetics, cardiovascular disease, environmental influences, genetic epidemiology, obesity, risk factors

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The integration of research designs in behavioral genetics and behavioral medicine presents an exciting challenge to researchers, public health professionals, and policy officials who are interested in a comprehensive perspective on

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public health issues. At its most basic level, behavior genetics encompasses evaluation of genetic and environmental influences on behaviors that contribute to the health of an individual. At another basic level, the relative importance of genetic and environmental influences on health-related traits is one of the fundamental issues addressed in human genetics or genetic epidemiologic investigations. These types of investigations might be used to provide focus to (a) efforts to develop clinical research strategies to identify genes that affect health or (b) efforts to develop intervention strategies that emphasize relevant environmental or genetic factors.

More intriguing, however, are approaches to genetics and health that go beyond simple identification of the relative importance of genetic and environmental influences in a static population. Questions that relate the interplay between an individual's behavior and constellation of health-related characteristics, many of which might at first glance seem to be removed from behavioral issues, present a far greater challenge to genetic investigations because they frequently involve interaction effects. An integrated

understanding of health characteristics and behavioral influences in the context of genetic studies demands sophisticated methodological approaches and a strong interdisciplinary perspective.

A number of public health areas can be effectively studied using such an integrated approach. For example, substance use and abuse, nutrition, stress, and certain cancers can all be viewed from the interface of behavioral genetics and behavioral medicine. Because of the high relevance of cardiovascular disease, we focus in this article on risk factors for cardiovascular disease as a prototypical area of public health that is effectively studied at the interface between genetic epidemiology, behavioral genetics, and behavioral medicine.

### **Risk Factors for Cardiovascular Disease**

#### *Overview of Risk Factors*

Cardiovascular disease has been the focus of a major effort to identify factors that can be targeted to reduce morbidity and mortality associated with cardiovascular problems. A key element of the strategy for undertaking studies of the genetics of cardiovascular disease has been to step back from the most relevant health outcomes themselves, such as myocardial infarction, coronary heart disease, atherosclerosis, stroke, or other important medical outcomes that probably result from a heterogeneous mix of etiologic factors. Instead, the emphasis in genetic studies is on those risk factors that contribute to the likelihood of the occurrence of a cardiovascular event but that are a step upstream of the event itself. Examples of such risk factors include hypertension and fasting serum cholesterol, triglyceride, and lipoprotein levels. This strategy reduces the confounding effect of etiologic heterogeneity, which can be a serious complication in genetic studies.

Although the identification of risk factors for cardiovascular disease is a remarkable public health success story in epidemiology, genetics, and behavioral medicine, cardiovascular disease remains a serious medical problem. The etiology of health problems associated with cardiovascular fitness is complex, with a variety of factors influencing the development and expression of health-related outcomes. These include metabolic factors that are intrinsic to the individual, are related to the most basic lifestyle behavioral characteristics, and are external to the individual. Individual differences in risk factors have been described and detailed in carefully designed and executed epidemiologic studies, and it has been estimated that quantitative risk factors for cardiovascular disease account for at least 50% of the variability in the risk for heart disease.<sup>1</sup>

For some measures, such as total cholesterol, the relationship with cardiovascular disease is clear; whereas for others, such as triglyceride level, the association is less well established. Low levels of high-density lipoprotein cholesterol (HDL) and high levels of low-density lipoprotein (LDL) are associated with increased risk for cardiovascular disease.<sup>2</sup> Apolipoproteins, the protein components of lipoproteins, are also quantifiable risk factors.<sup>3</sup> Elevated levels of lipoprotein A [Lp(a)] and apoB are also associated with the risk for coronary artery disease and stroke.<sup>4</sup>

Blood pressure levels are associated with coronary heart disease and stroke.<sup>5,6</sup> Because it is relatively asymptomatic, high blood pressure often is not treated effectively. There are most likely multiple causes of high blood pressure.

Cholesterol synthesis and absorption can account for some of the variability in total cholesterol levels and consequently can affect the risk for cardiovascular disease.<sup>7,8</sup> Lathosterol is an indicator of cholesterol synthesis. Plasma levels of plant sterols, such as beta-sitosterol and campesterol, can be used as indicators of cholesterol absorption. Although scientists have found evidence of a rare disorder associated with elevated plant sterol levels and premature atherosclerosis,<sup>9</sup> the full epidemiologic association of these measures with cardiovascular disease is not well characterized. Histidine-rich glycoprotein (HRG), which binds plasminogen<sup>10</sup> and heparin,<sup>11</sup> is a glycoprotein for which the physiological function is not well known. The potential antifibrinolytic and procoagulant effects may be the cause of the association of elevated HRG in some patients with venous thrombosis.

The relationship of obesity to the risk for cardiovascular disease is not fully resolved,<sup>12</sup> although consistent evidence of an association between obesity and cardiovascular disease has been reported in epidemiologic studies, such as the Framingham study<sup>13</sup> and a large prospective study by the American Cancer Society.<sup>14</sup> However, it is not clear that obesity is a risk factor independent of any other obesity-related characteristics, such as hyperlipidemia or hypertension. In addition, an inverse relationship may exist between measures of obesity and mortality that is due to the weight-reducing effects of cigarette smoking and cancer.<sup>12</sup>

Many risk factors for cardiovascular disease have a strong behavioral component. In some cases, such as smoking, the behavior itself has a powerful effect on cardiovascular fitness. Other behavioral traits, such as diet or exercise habits, have a less direct but still powerful effect. In still other cases, the nature of the relationship between a behavioral event and cardiovascular fitness is more complex. Cardiovascular reactivity in response to mental or physical stress, for instance, can be used as an indicator of cardio-

vascular fitness and disease. Blood pressure and future hypertension status may be predicted by an individual's cardiovascular reactivity to stressors.<sup>15,16</sup>

#### *Quantitative Genetic Influences on Risk Factors*

The most basic evidence of genetic influences on cardiovascular disease is the observation that a positive family history is an important risk factor for coronary heart disease (CHD), particularly for premature CHD. Large studies of twins provide evidence that this familial risk can be attributed substantially to genetics rather than to environmental influences that are shared by family members.<sup>17-19</sup>

Genetic studies have been conducted on most of the risk factors for cardiovascular disease that have been identified from epidemiologic investigations. Blood pressure has been studied extensively. Evidence from studies of twins (see Snieder et al<sup>20</sup>) suggests that about two thirds of the variance in systolic blood pressure (SBP), and perhaps slightly less of the variance in diastolic blood pressure (DBP), can be attributed to genetic effects, possibly with a drop-off in older individuals. Family studies, by contrast, provide evidence that genetic effects are substantially lower, accounting for approximately one third of the variance in SBP and DBP.<sup>21-24</sup> Genetic dominance or age-related effects that reduce the magnitude of parent-offspring correlations relative to twin correlations are among the possible explanations for the different results.

About 50% of the variation in total cholesterol, HDL, LDL, and triglycerides may be attributable to genetic factors.<sup>25-28</sup> The apolipoproteins ApoA2 and ApoB generally show moderate-to-strong genetic effects. ApoA1 shows greater variability in heritability estimates,<sup>29</sup> and genetic effects on quantitative ApoE, other than the ApoE polymorphism itself, have not been conclusively characterized.

In recent years, scientists have made extensive studies of the genetics of obesity,<sup>30-33</sup> which probably arises from complex causes, including genetic, behavioral, and lifestyle characteristics. Obesity presents a particular challenge for genetic analysis because of the heterogeneity of the phenotype itself. It has been suggested<sup>30</sup> that at least four distinct phenotypes are required to understand obesity: excessive total body fat, excessive subcutaneous fat on the trunk and abdominal area, excess abdominal visceral fat, and excessive gluteo-femoral fat. Most genetic studies of obesity have been limited to an investigation of body mass index (BMI: weight in kilograms divided by height in meters, squared), which can be viewed as a crude measurement for total body fat.

A number of studies of the genetics of excess total body fat, as indexed by BMI, have been conducted by investigators, who have used various research designs, including

twin studies, studies of twins reared apart, adoption studies, and nuclear family studies. Although estimates of the importance of genetic and environmental influences vary among those studies, a general consensus is that at least 40% and possibly as much as 60% to 80%<sup>34,35</sup> of the variability in BMI is attributable to genetic effects. Studies in which the researchers have explicitly focused on searching for effects that are environmental in origin have failed to detect any noteworthy effect of shared family experiences in determining individual differences in weight and obesity.<sup>36</sup>

Bouchard and Perusse<sup>30</sup> summarized a number of affectors of the obesity phenotypes, such as energy intake, resting metabolic rate, level of physical activity, and nutrient partitioning. In earlier genetic studies,<sup>37</sup> it appeared that energy intake aggregates in families but may be largely due to shared family environmental or cultural origins. However, food selection of carbohydrate, fat, or protein, expressed as a percentage of total nutrient intake, may be from 11% to 20% of the variation that is genetic in origin.<sup>37</sup>

By contrast, Castro<sup>38</sup> reports stronger genetic influences on energy and macronutrient intake, with no familial environmental influence detected. Resting metabolic rate appears to have 40% to 80% of its variance attributable to genetic effects, although some studies suggest that this genetic effect can be entirely attributed to genetic effects on body weight.<sup>39</sup> Physical activity is a difficult phenotype to operationalize and assess. Perusse et al<sup>40</sup> found a weak genetic contribution to leisure-time energy expenditure observed in the large Canada Fitness Survey. Other measures of physical activity are reviewed elsewhere.<sup>30</sup>

#### *Influences of Specific Genetic Loci on Risk Factors*

Although twin, family, and adoption studies remain important procedures for determining the relative importance of genetic, environmental, and interactive effects on complex traits, an important strategy in contemporary genetic studies is to identify specific genetic loci that contribute a detectable proportion of variation to a quantitative risk factor. This will be useful for either accounting for a substantial total proportion of variation that results from several genes of small-to-moderate effect or for identifying measurable genetic covariates that can be included in comprehensive models of measured genetic and environmental effects and, ultimately, their interaction. A sampling of loci that have been identified as contributing 10% or more to the phenotypic variation in quantitative risk factors is summarized in Table 1.

Bouchard<sup>41</sup> reviewed the current status of molecular markers of obesity in a 1995 article. Twenty genes, loci, or chromosomal regions on a dozen different chromosomes

**TABLE 1**  
**Sample of Genetic Loci That Contribute 10% or More to Variation**  
**in Quantitative Risk Factors**

Locus name	Common gene name	Chromosomal position	Risk factor affected
AGT	Angiotensin	1q42-q43	Blood pressure
APOA-1	Apolipoprotein A1	11q23-q24	ApoA1, HDL cholesterol
APOA-2	Apolipoprotein A2	1q21-q23	HDL cholesterol
APOA-4	Apolipoprotein A4	11q23-qter	HDL cholesterol Triglyceride, Lp(a)
APOB	Apolipoprotein B	2p24-p23	Cholesterol LDL cholesterol, ApoB
APOC-3	Apolipoprotein C3	11q23-qter	Triglyceride
APOE	Apolipoprotein E	19q13.2	Cholesterol Triglyceride LDL cholesterol ApoE, ApoB, Lp(a)
CETP	Cholesterol ester transfer protein	16q13	HDL cholesterol ApoA1
DCP	Dipeptidyl carboxypeptidase (angiotensin I converting enzyme)	17q23	HDL cholesterol Blood pressure, ACE levels
FGA/FGB	Fibrinogen A and B	4q28	Fibrinogen
HRG	Histidine-rich glycoprotein	3q28-q29	Histidine-rich glycoprotein
LDLR	Low-density lipoprotein receptor	19p13.3	LDL cholesterol ApoB
LPA	Lipoprotein (a)	6q26-q27	Lp(a), Triglyceride HDL cholesterol
LPL	Lipoprotein lipase	8p22	Triglyceride
PLAT	Plasminogen activator tissue-type	8p12-p11.2	tPA
PLANH1	Plasminogen activator inhibitor-1	7q21.3-q22	PAI-1

that may be of relevance in the genetics of human obesity have been identified in either human or mouse models. Obesity research provides an important illustration of how information on the effect of genetics obtained in mouse studies can be applied to human research.

**Genotype-Environment Interaction Effects Following Long-Term Behavioral Interventions**

The genetics of risk factors for cardiovascular disease are important, but it is the effects of genotype-environment interaction that indicate whether an individual's sensitivity

to the environment or the individual's lifestyle is genetically determined to any extent.<sup>42,43</sup> Although few studies of humans have been designed and executed to test for genotype-environment interaction effects, Bouchard et al<sup>44</sup> have used monozygotic (MZ) twins exposed to identical controlled environmental exposures pre- and posttreatment as a way of detecting genotype-environment interaction effects. The assumption is that between-pair variability in the response to treatment reflects genotype-dependent response under carefully controlled treatment exposure.

Individual differences exist in the response to long-term



exposure to regular exercise, as assessed by maximal aerobic power ( $\dot{V}_{O_{2max}}$ ) and other measures.<sup>45</sup> The MZ twin approach was employed for the detection of genotype-environment interaction in  $\dot{V}_{O_{2max}}$  response to a 20-week endurance training program. The intraclass MZ twin pair correlation was greater than .70, indicating the existence of a substantial familial, possibly genetic, response to endurance training.<sup>46</sup> Interestingly, a separate investigation of 46 unrelated males who underwent endurance training obtained evidence that variation in mitochondrial DNA sequences, which is extrachromosomal DNA passed only maternally through the mitochondria, contributes to variability in the  $\dot{V}_{O_{2max}}$  response.

A similar research design was used in studies of the response to long-term overfeeding in identical twins. An earlier study,<sup>47</sup> using 6 pairs of MZ twins, was inconclusive because the sample was small and the duration of the overfeeding was brief. In a subsequent investigation, Bouchard and colleagues studied 12 pairs of male MZ twins on long-term overfeeding (100 days of overfeeding by 5.3 mega joules [MJ] or 1,000 kcal for 6 days per week) to assess the genetics of changes in body mass, total body fat, fat distribution, and other variables. The research team noted substantial intrapair similarity with respect to body weight, percentage of fat, fat mass, and estimated subcutaneous fat. After adjustment for gains in fat mass, they found high intrapair similarity with respect to changes in regional fat distribution and amount of abdominal visceral fat.<sup>44</sup> In addition, fasting insulin and glucagon levels increased in response to overfeeding, were correlated with changes in subcutaneous fat, and showed a pattern of change consistent with genetic influences on the response to overfeeding.<sup>48</sup> Those findings could have important implications for understanding the relationship between obesity and non-insulin-dependent diabetes mellitus.

### Genetics of Reactivity of Risk Factors for Cardiovascular Disease in Response to Stress

#### *Blood Pressure Reactivity and Heart Rate*

Repeated increases in heart rate and blood pressure as a consequence of physical or psychological stressors may have a role as a risk factor for cardiovascular disease. A substantial body of research indicates that cardiovascular reactivity includes a genetic component.<sup>49-52</sup> For example, Smith<sup>52</sup> investigated the contribution of genetic factors to cardiovascular reactivity by comparing correlations for blood pressure reactivity for 82 pairs of MZ and 88 pairs of dizygotic (DZ) adult male twins. Blood pressure reactivity was significantly correlated in the MZ pairs and was not

highly correlated in the DZ pairs. Resting blood pressure heritability estimates ranged from 60% to 80%, whereas reactivity heritability estimates were approximately 50%. Although not all studies demonstrate such a large genetic influence on reactivity, a heritable component to reactivity is more consistently found when the task designed to evoke cardiovascular reactivity employs active mental tasks (ie, serial subtraction) rather than passive physical tasks (ie, cold pressor).<sup>49,51,53</sup> Taken as a whole, the conclusion from such studies is that blood pressure changes in response to physical or mental stress conditions are significantly more similar in MZ twins than in DZ twins.<sup>49</sup>

The effect of a psychological challenge on cardiovascular reactivity has been investigated in a number of studies (see Hewitt and Turner<sup>54</sup>). Those studies, which have been limited primarily to males over a wide age range, indicate the existence of moderately heritable responses to laboratory psychological stressors on heart rate and blood pressure. However, they have shown no apparent influences on cardiovascular reactivity measures of shared family environment.

Snieder et al<sup>20</sup> summarized twin studies of blood pressure reactivity with particular attention to differences in the magnitude of genetic effects on reactivity as a function of age. Heritability estimates among the studies ranged from 0.00 to 0.81, with no immediately discernible trend that was a function of age. In their study, Snieder and colleagues modeled age-dependent effects in cross-sectional data by combining a data set of young twins and their middle-aged parents with data from a sample of middle-aged twins. That model provides a simple alternative to a full longitudinal study design. A significant parent-offspring correlation was found for SBP reactivity but not for DPB reactivity. Results in the twin data were somewhat inconclusive, with some models fitting best for young and middle-aged twins and different models fitting best for young twins for two different stress tasks.

#### *Respiratory Sinus Arrhythmia*

The role of changes in blood pressure and heart rate in determining cardiovascular health may be related to regulatory mechanisms, such as the influence on the heart of the autonomic nervous system. This system consists of both sympathetic and parasympathetic efferents that exert opposing effects on the chronotropic state of the heart by their reciprocal influence on the sinoatrial node. Respiratory sinus arrhythmia (RSA) is a noninvasive index of cardiac vagal tone (reviewed by Snieder et al<sup>55</sup>). RSA is the magnitude of change in heart period corresponding to the inspiratory and expiratory phases of the respiratory cycle. Heart

rate typically increases during inspiration and decreases during expiration. Stronger variations in heart rate and correspondingly larger RSA are related to stronger vagal control of the heart. Reduced heart rate variability is associated with cardiovascular disease, hypertension, increasing age, and stress.<sup>56</sup>

Genetic influence on RSA has been examined in two studies.<sup>55,56</sup> In a study of 160 adolescent twin pairs, Boomsma and colleagues<sup>56</sup> found that genetic influences accounted for 25% of the variance under rest and 50% of the variance under stress task conditions, apparently because of a decrease in unique environmental variance during stress. In another study, Snieder et al<sup>55</sup> examined individual differences in RSA of 213 middle-aged twin pairs under rest and under four different stress conditions (reaction time task, mental arithmetic task, tone avoidance task, and cold pressor task). The research team analyzed the data in a genetic model that included age, respiration rate, and RSA in a multivariate analysis. Models specifying only additive genetic and unique environmental factors, with no difference between males and females, provided the best fit to the data under both stress and rest conditions. The total genetic influence on RSA ranged from 28% to 43%, depending on the task. A correction of the RSA for respiration rate did not result in a substantial change in heritability. Under resting conditions, heritability showed only a slight increase—from 31% to 34%—after correction for respiration rate.

With respect to predictability of RSA for cardiovascular disease, the approximately two thirds of the variance that is not attributed to genetic effects may be related to environmental determinants, such as exercise, diet, and chronic stress. Individual differences in the response to exercise training, particularly with respect to individual differences in aerobic fitness, may be important determinants of RSA. Diet, mediated through body weight, may also be an important determinant of RSA that shows substantial individual differences. The response of the individual to chronic stress, which is likely to be of environmental origin, may be under genetic control, although the results from this study were not conclusive.

## CONCLUSIONS

Genetic epidemiology and behavioral genetic perspectives in behavioral medicine can play an important role in determining the etiology and interrelationships of complex risk factors that have important implications for public health. In this article, we described using risk factors for cardiovascular disease as a model system for the application of the techniques of genetic epidemiology and behavioral genetics to behavioral health problems.

Genetic models can be used to examine risk factors individually in a static population to determine the magnitude of genetic influences on health variables. Such analyses are important for understanding the underlying components of variation in the traits and, ultimately, for identifying specific genes that influence complex traits. The identification of specific genes might make it possible to include them as measured covariates in comprehensive models of risk factors for complex traits. For a full understanding of complex, behavior-related risk factors on health, though, it will be necessary to integrate genetic models, models of the interaction of risk factors and environmental changes, and the effects of lifestyle and behavior.

The examples we have given in this article illustrate the challenges that arise in an attempt to understand individual differences in response to behaviorally mediated change. It is not always a simple matter to define an environmental covariate that is strictly behaviorally mediated—the individual's response may well be genetically mediated. Relatively few studies that attempt to integrate genetic models fully with individual differences in environmental interventions have been reported. Such intervention can take the form of public health programs to alter behavior or lifestyle risk factors or can be more clinical. Only a better understanding of individual differences in risk factors and in the response to interventions will enable healthcare professionals to design health promotion strategies that are most useful and appropriate for individuals rather than for population averages.

Many public health intervention programs aim to pull the overall average population level of cardiovascular risk factors to values in line with greater health promotion and lower risk. At one level, this is a cost-effective strategy that is worth continuing.

The clinician, however, will recognize that mean population levels are not necessarily relevant to an individual's cardiovascular health profile. Our goal in writing this article was to make it clear that an individual's response to any intervention strategy will vary because of many factors, some genetic, some environmental, some interactive, and some apparently random. It is even likely that the profile of some individuals will result in a response to an intervention strategy opposite from that desired. Those individual differences in responses suggest that the most efficacious and cost-effective approach to implementing an intervention requires a level of follow-up of the individual patient to ensure that each person is responding in the desired direction.

Ultimately, research on individual genetic loci, such as those outlined in Table 1, will, in conjunction with information on environmental risk factors, lead to the develop-

ment of individual risk profiles that can be used to tailor intervention strategies that are more likely to be effective at the level of the individual.

To date, only the most gross genetic anomalies are useful in this manner. However, as research in the area of risk prediction and prevention advances, we are likely to see more use of this information and less trial and error in the design of individual risk intervention programs.

A critical aspect to the interpretation of genetic studies of risk factors for cardiovascular disease is that practitioners must be prepared to explain the meaning of genetic risk to individual patients. It is important for the practitioner to recognize that heritability estimates are parameters that do not apply directly to individuals, but rather to defined populations under fixed environmental circumstances.

Even if the genetic composition of a population is unchanged, alterations in nongenetic characteristics of the population can change heritability estimates. Examples of changes that can affect heritability estimates include changes in the age structure of a population, changes in patterns of using tobacco and other substances, and changes in dietary and exercise habits. It is important that the clinician be prepared to counsel patients that the degree to which genes affect risk varies individually but also that adherence to a regimen itself can be an important mechanism for changing the relative balance between genetic and nongenetic influences on risk.

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#### NOTE

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