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4. GENETICS OF CARDIOVASCULAR DISEASE

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Several biochemical and environmental risk factors of cardiovascular disease are well established, but genetic risk alleles contributing to the disease in the general population are hotly debated. The reason for such interest in incorporating genetic research into study of atherosclerotic and thrombotic diseases of cardiovascular system, including myocardial infarction, stroke, peripheral vascular disease and venous thromboembolism, is awareness of the fact that these diseases are still the major public health problem and cause of death and morbidity.

Over the past five years public health agencies have begun to examine how advances in genetic research can be used to prevent disease and improve the health of the population. On the other side, dramatic strides in unraveling the environmental influences on classic complex cardiovascular disease have translated into major public health efforts to alter lifestyle and diet. Furthermore, the advances in cardiovascular genetics - basic research in the biology of lipid metabolism, have led to drugs that change the natural history of disease progression. Although the drop in death rates from cardiovascular disease represents one of the major victories for the twentieth-century medicine, the prevalence of disease remains high, especially in CEE and SEE countries.

Classical epidemiological studies have validated a set of criteria that are widely employed in evaluation and management of patients at risk for cardiovascular disorders. The lessons learned from risk assessment of biochemical markers for atherosclerosis are expected to be important in developing strategy to integrate genetics into public health policies and national strategy for prevention of cardiovascular disease. A framework for applying human genome research to disease prevention includes genetic epidemiology, development of screening of target populations, ethical, socioeconomic and legal implications, training and education of professionals and public.

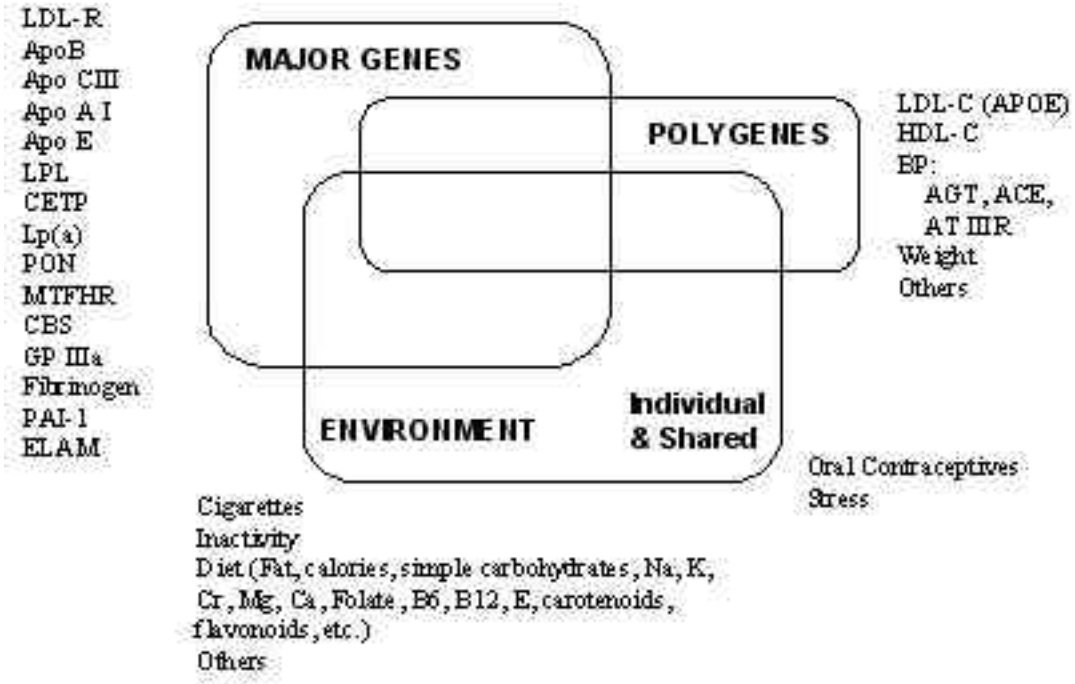

Figure 1. Combined effects of monogenic, polygenic, and environmental factors promoting atherosclerosis

Table 1. Potentially most important genes for the risk of cardiovascular atherosclerosis

1. LIPID METABOLISM		
Gene	**Chromosomal location**	**Function**
Apolipoprotein B (apoB)	2p	component of plasma lipoproteins, particularly LDL; mediates binding to LDL receptor
tHR 71-lle		possibly associated with increased plasma LDL cholesterol and apoB levels; Arg-3531-cys LDL receptor binding defect appears to segregate with Thr allele
Arg-3500-Gln		disorder of hypercholesterolemia known as familial defective apoB-100, due to reduced binding to LDL receptor
Apolipoprotein CIII (apoCIII)	11q	component of plasma proteins
T(625)del, C(482)T, T(455)C, C3175G (Sst)I, C1100T, T3206G		increased plasma triglyceride levels
Apolipoprotein E (apoE)	19q	component of plasma proteins; mediates binding to the LDL and remnant (apoE) receptors
1. LIPID METABOLISM		
Gene	**Chromosomal location**	**Function**
e3/e2, e4		inter-individual variation in plasma total and LDL cholesterol levels, atherosclerotic progression
Cholesteryl ester transfer protein (CETP)	16q	reverse cholesterol transport pathway; possible pro-atherogenic role in presence of dyslipidaemia
lle-405-Val, Asp-442-Gly		increased plasma HDL cholesterol and apoA-I levels
Lipoprotein lipase (LPL)	8p	hydrolysis of plasma triglycerides
T(93)G		increased LPL promoter activity, reduced plasma triglycerides
T(39)C		reduced LPL promoter activity
Asp9-Asn		increased plasma triglycerides, increased atherosclerotic progression
Asn-291-Ser		reduced plasma HDL cholesterol, increased triglyceride levels
Ser-447-Ter		increased plasma HDL cholesterol, reduced plasma triglyceride levels; possible impact on responsiveness to blockers

2. RENIN-ANGIOTENSIN SYSTEM		
Angiotensin-converting enzyme (ACE)	17q	proteolyzes angiotensin I to produce angiotensin II
Alu element insertion/ deletion in intron 16		increased plasma ACE levels; mixed evidence of association with myocardial infarction
Angiotensin II receptor type 1 (ATIIR1)	3q	one of two receptors for angiotensin II, particularly in vascular smooth muscle cells
A1166C		hypertension; possible synergism with ACE conferring risk of myocardial infarction
Angiotensinogen (AGT)	1q	substrate for renin, yielding angiotensin I
Met-235-Thr		increased plasma AGT levels; hypertension
3. HOMOCYSTEINE METABOLISM		
Cystathionine-synthase (CBS)	21q	transulfuration pathway, converting homocysteine to cystathionine, with pyridoxine as cofactor
Ala-114-Va, Ile-278-Thr		pyridoxine-responsive homocystinuria
Arg-125-Gln, glu131asp, Gly-307-Ser		pyridoxine-unresponsive homocystinuria
68-bp insertion		linkage disequilibrium with 278thr
Methylene tetrahydrofolate reductase (MTHFR)	1p	remethylation pathway, generating the 5-methyltetrahydrofolate that serves as the methyl group donor
C677T (Ala/Val)		associated with hyperhomocysteinemia given low dietary folate; increased risk for deep-vein thrombosis in carriers of factor V Leiden
C692T		absence of enzyme activity
4. THROMBOSIS		
Gene	**Chromosomal location**	**Function**
Glycoprotein IIIa (GPIIIa)	17q	component of GPIIb/IIIa platelet adhesion receptor, binding fibrinogen, fibronectin, and von Willebrand factor
Leu-33-Pro		inter-individual variation in platelet adhesion and/or adhesion; mixed evidence of association with risk of coronary thrombosis
Fibrinogen	4q	determinant of plasma viscosity, cofactor for platelet aggregation, precursor of fibrin (component of plaques)
5. LEUKOCYTE ADHESION		
Endothelial leukocyte adhesion molecule-1 (ELAM)	1q	adhesion of leukocytes to activated arterial endothelium; also known as E-selectin
G98T, Ser-128-Arg, Leu-554-Phe		increased risk for severe atherosclerosis

4.1 The goals of genetic epidemiology in cardiovascular disease

- to assess the prevalence of gene variants in different populations
- to assess the magnitude of the risk of disease associated with gene variants
- to assess the contribution of gene variants to the occurrence of CVD
- to evaluate the magnitude of disease-risk associated with gene-gene and gene-environment interaction
- to evaluate the clinical validity of single or cluster gene analysis
- to evaluate the impact of genetic testing on disease prevention or therapy

The task force in genetic testing recognized the need to evaluate several data parameters: analytic validity, clinical validity and clinical utility of a single, or a set of, genetic analyses.

Analytic validity should answer questions on sensitivity, specificity and predictive values with respect to genotype.

Clinical validity is defined by sensitivity, specificity and predictive values of genotype analysis with respect to phenotype or disease.

Clinical utility should give an answer to the question of what are the benefits and risks that accrue from genetic testing.

Genetic influence on phenotypes can be classified as monogenic or polygenic. Both mechanisms can contribute to risk for cardiovascular disease as illustrated in Figure 1

4.2 Cholesterol, plasma lipids and lipoproteins

It is now well known that the phenotypic variation in cholesterol concentrations in a population is determined by both genetic and environmental factors and that the mean and the 'normal' range of total plasma cholesterol levels vary in different populations. As the total concentrations increase throughout the range observed in the population at large, there is a marked increase in the risk of developing CHD, i.e. the majority of CHD occurs in individuals with cholesterol levels that are distributed near the mean of the population, the CHD risk being graded and continuous without a threshold; only a small fraction of the disease burden is associated with elevated cholesterol levels that are discretely separate from the so-called 'normal range' of variability.

The major classes of apolipoproteins of particular interest for the etiology of CHD are chylomicrons, VLDL (very low density lipoproteins), IDL (intermediate density lipoproteins), LDL and HDL.

Subsequent work, using quantitative immunochemical methods, showed that the level of Lipoprotein A, Lp(a), is a quantitative genetic marker the concentration of which can vary greatly between individuals.

Monogenic traits, such as heterozygous familial hypercholesterolaemia (FH), are of Mendelian inheritance, but polygenically determined cholesterol level is in the offspring approximately halfway between the levels of two parents when the values are measured at about the same age for both generations.

4.3 Family studies support genetic testing

Familial aggregation of CHD has long been known and the data have been reviewed. Studies in the 1960s already showed that the first-degree relatives of affected patients have approximately 2-6–fold higher risk of the disease than those of matched controls. The familial aggregation increases with decreasing age of affected patients. While women have a lower frequency of CHD than men, the first-degree relatives of index women run a higher risk than those of affected index males.

Investigations on premature CHD (defined as CHD occurring before the age of 56 years) in Finland showed a 2.5-fold higher risk (relative to general population) for brothers of male CHD cases and a two-fold higher risk for their sisters. The risk for probands' brothers increased with decreasing age of onset among index cases. Familial aggregation of CHD was also observed in studies in which the index cases had CHD proved by angiography. The various prospective and retrospective studies reviewed by Freidlander clearly show familial aggregation of CHD and support an overall significant independent association of family history of CHD, mainly developed at an early stage of life, with the risk for CHD.

Environmental risk factors can have an exaggerated adverse effect in patients with genetic susceptibility: cigarette smoking, excess body weight, diet, vitamin deficiency, and hypertension. There is mutual overlapping influence of all those and a genetic trait.

4.4 Gene polymorphism and cardiovascular risk

The potentially most important genes for cardiovascular atherosclerosis risk are listed in the above Table. This is not a final list but rather a list of the hitherto most documented genetic risk factors. The growing numbers of genetic variants have significant implication on our recognition of the complexity of the disease. Altogether, today, more than 840 variants of different genes are tested and fast growing data from literature need to be reevaluated on the basis of EBM principles. As CHD candidate genes are identified, there is increasing need for assays capable of the simultaneous genotyping of multiple loci. Studies focused on single markers can be used to assign relative risk values, but this approach provides only a limited context for evaluating genetic risk factors. So far it is evident that some genes are more important in some, but not in other populations.

There is much controversy on results of published epidemiological studies until now. The differences might be due to methodological factors or studied risk groups. In contrast to single gene analysis, multiple markers provide insight into mechanisms of disease susceptibility and identify the key cluster of predictable markers that are clinically informative. New technologies including DNA chip and microarray or reverse-line genotyping might be more important in the future for genetic epidemiology of CHD as well as clinical medicine. But before a final decision is made and genetic markers are used to supplement routine biochemical assays for patient care, there is a need for careful analysis of all studies performed to date.

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