Genetic Basis of Coronary Atherosclerosis

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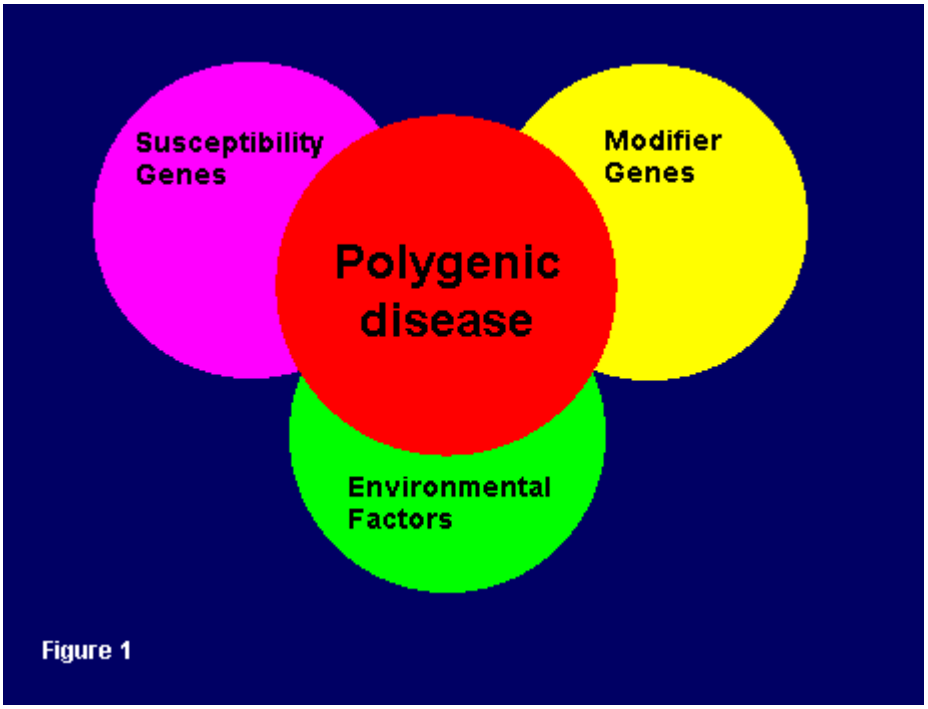
INTRODUCTION

Atherosclerosis is a quintessential complex disease caused by multiple genetic and environmental factors and complex gene-environment interactions (1;2). Atherosclerosis involves multiple vascular territories including coronaries, carotids, and peripheral vessels. Coronary artery disease (CAD) is the most common cause of death in the western hemisphere (3) and by the year 2020 is expected to become the leading cause of morbidity and mortality in the world (4). In the United States alone, CAD is responsible for approximately 1.5 million new cases of myocardial infarction (MI), 350,000 new cases of heart failure, and 500,000 deaths annually (3).

The molecular mechanisms leading to coronary atherosclerosis remain partially understood (1;2). During the past five decades, large-scale epidemiological studies led to identifications of multiple risk factors for CAD (5). While epidemiological studies in families with premature CAD and in monozygotic and dizygotic twins emphasize the significance of genetic factors in susceptibility to coronary atherosclerosis (6), population migration studies underscore the impacts of environmental factors (7). The so-called "traditional" risk factors, such as dyslipidemia, diabetes mellitus, and hypertension, have significant genetic and environmental components (8). Thus, the common forms of CAD result from a combination of environmental and genetic risk factors (Figure 1).



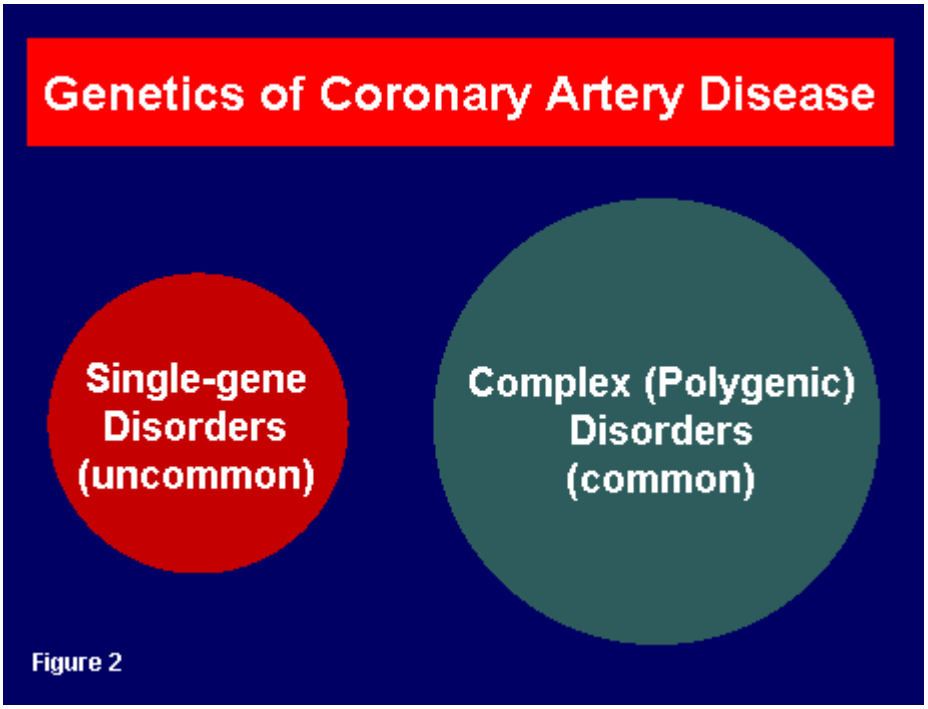
CLINICAL GENETICS

Clinical Genetic studies provide significant insight on the role of genetics in susceptibility to coronary atherosclerosis. Studies in both twins and families have documented the heritability of CAD (the fraction of CAD explained by genetic factors), which exceeds 50% in most studies of twins and families (1). Family studies suggest that the risk of death from CAD increases 5- to 7-fold in first-degree male and female

relatives of patients with CAD (9). Studies in twins show that the concordance rate of MI and angina is 3-fold higher in monozygotic twins than in dizygotic twins (10), and that the concordance rate is even greater in monozygotic twins with premature CAD (age less than 60). Marenberg et al. showed in a study of 3298 monozygotic and 5964 dizygotic twins that the relative hazard of death from CAD when one's twin died of premature CAD (age less than 55 years) is 8.1 (2.7 to 24.5) for monozygotic twins and 3.8 (1.4 to 10.5) for dizygotic twins (7). Collectively, clinical genetic studies have established a major role for genetic factors in susceptibility to coronary atherosclerosis.

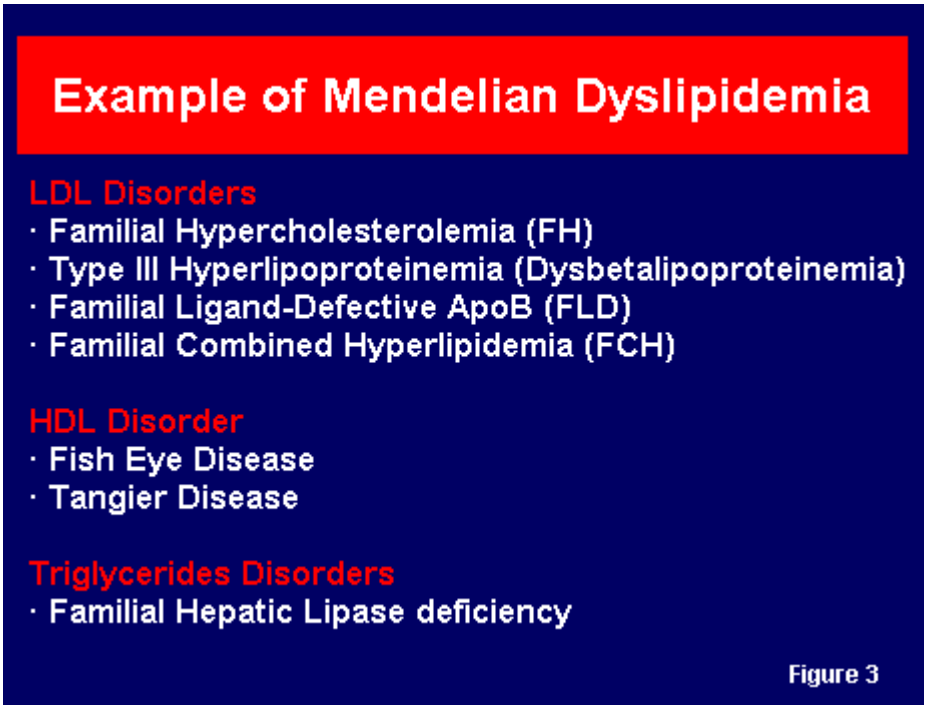
MOLECULAR GENETICS

Completion of the Human Genome Project led to development of genetic, physical and SNP maps of the human genome and provided the opportunity to map and identify the susceptibility genes for not only single-gene (Mendelian) disorders, such as the long QT syndromes and familial hypertrophic cardiomyopathy, but also complex ploygenic (non-Mendelian) traits. In general, coronary atherosclerosis is a complex (polygenic disorder). However, rare single-gene forms of atherosclerosis also exist (Figure 2). The process of mapping the causal genes for Mendelian disorder, known as genetic linkage, is based on demonstration of co-segregation of a known DNA marker with inheritance of a phenotype in a given family. Complex traits, such as coronary atherosclerosis, are caused by genetic and non-genetic factors and complex gene-environment interactions. Therefore, the pattern of inheritance is not Mendelian. Mapping of the susceptibility genes for complex traits are compounded by the lack of perfect co-segregation of a genetic marker with inheritance of the trait, genetic heterogeneity, incomplete penetrance of the risk-allele, phenocopy, high frequency of risk-alleles in the population, influence of environmental factors, and the prevalence competing risk factors (11;12). Thus, it is not surprising that despite the well-established role of genetics in susceptibility to coronary atherosclerosis and in contrast to Mendelian disorders, attempts to identify the susceptibility genes through genome-wide linkage studies have largely failed. As a result, the emphasis has now shifted towards large-scale sequencing to identify simple (single) nucleotide polymorphisms (SNPs) for many candidate genes and large-scale association studies (13). Unfortunately, genetic association studies, in particular case-control studies, have serious limitations and are subjects to spurious results. Consequently, the results of genetic association studies are considered provisional and require proof through experimentation.

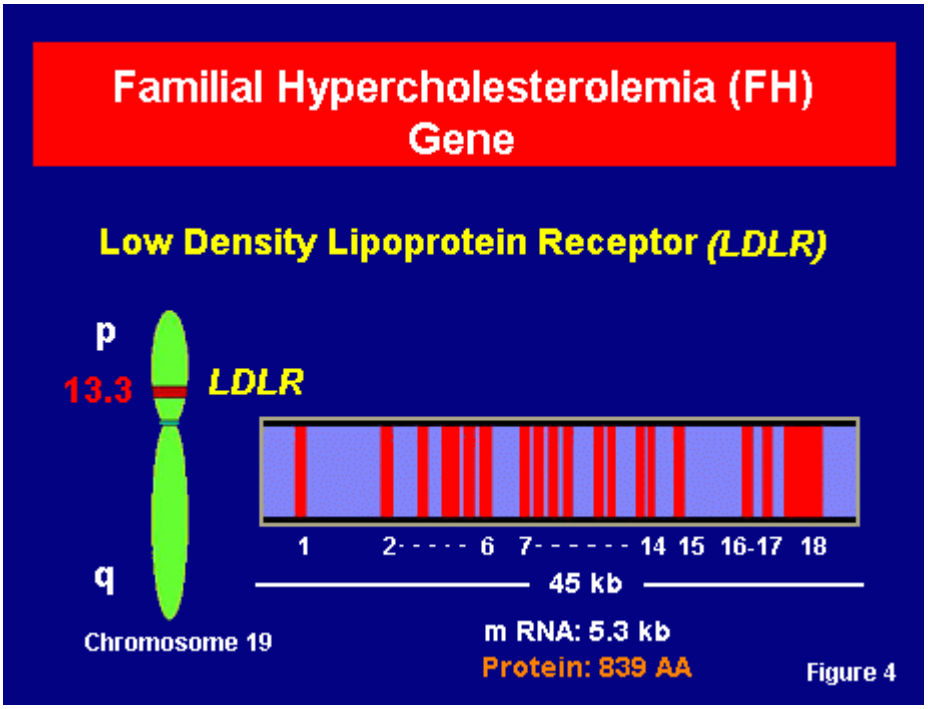


Genetics of Mendelian forms of atherosclerosis: Mendelian forms of atherosclerosis comprise single gene traits inherited as autosomal dominant or recessive or X-linked disorders. These disorders are relatively uncommon and primarily related to dyslipidemia. A partial list of monogenic forms of dyslipidemia leading

to coronary atherosclerosis is shown in Figure 3. Understanding the molecular basis of Mendelian forms of atherosclerosis not only could provide insights into the pathogenesis of specific monogenic disorder, but also sheds significant lights onto the pathogenesis of common non-Mendelian forms of atherosclerosis. We will briefly discuss several examples of Mendelian forms of dyslipidemia causing atherosclerosis.



Familial hyperlipidemia: Familial hyperlipidemia (FH) is probably the best example of single gene disorders that leads to coronary atherosclerosis. FH is a relatively uncommon disease that affects 1:500 in the population in heterozygous form, and 1:1000,000 in homozygous state. Affected individuals show severe elevation of plasma levels of total and LDL cholesterol that often range between 350 to 500 mg/dl in the heterozygous subjects and even much higher in the homozygotes. The phenotype is characterized by premature coronary artery disease, tendon xanthomas, and arcus cornealis, which is common during childhood in homozygous subjects and after the age of 20 in heterozygous subjects. The genetic defect in FH is the LDL receptor gene (LDLR). LDLR (Figure 4) is located on the short arm of chromosome 19 and transcribes a 5.3 kb mRNA that translates into a 839 amino acid protein. Over 800 different mutations in LDLR gene are identified. Missense mutations comprise about 60% of the mutations while, 20% are minor rearrangements, 13% major rearrangements, and 7% are splice-junction mutations. Mutations perturb the function of LDL receptors by a variety of mechanisms, including affecting synthesis, transportation, affinity to bind LDL-cholesterol, internalization, and recycling of the receptors. Phenotypic expression of FH including development and severity of coronary atherosclerosis varies according to causal mutations, genetic background, diet, mutations in modifier genes, and environmental and epigenetic factors.

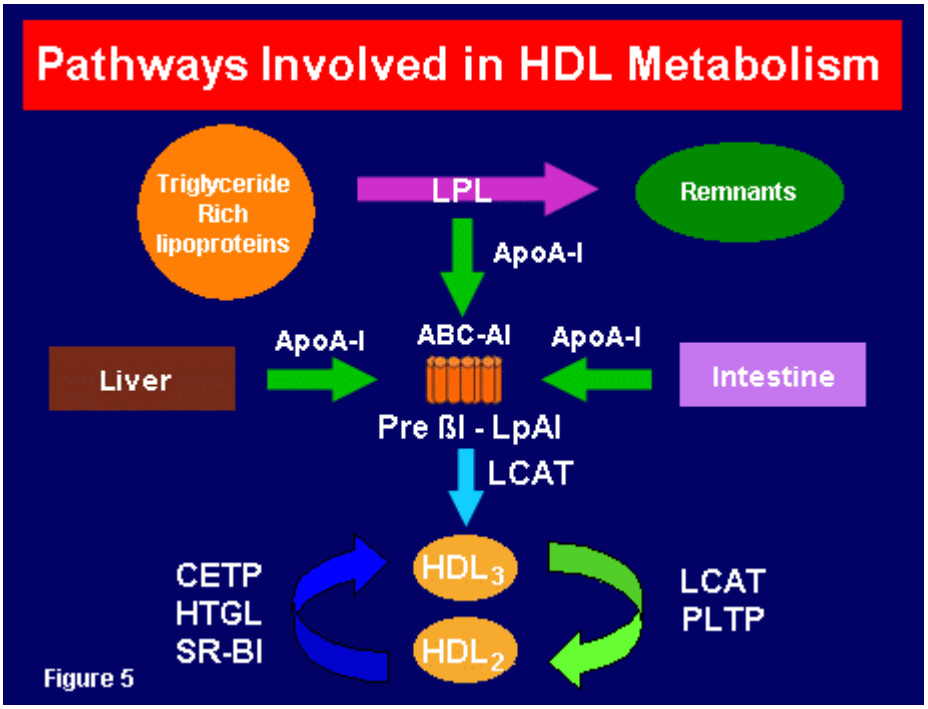


Type III hyperlipoproteinemia (Dysbetalipoproteineamia): The primary defect in type III hyperlipoproteinemis is in APOE gene, which is located on the long arm of chromosome 19. The phenotype is characterized by elevated levels of ß (beta)-very low-density lipoproteins (VLDL), eruptive xanthoma, premature CAD, and peripheral vascular disease. ApoE has three isoforms of ε (epsilon) 2, 3, and 4 which are the consequence of variation in the sequence of codons 112 and 158. ApoE3 isoform is the most common isoform and contains amino acids cysteine and arginine at codons 112 and 158, respectively. The apoE2 and E4 isoforms contain amino acids cysteine and arginine at the polymorphic positions, respectively. The primary defect in type III hyperlipoproteinemia is apoE2 isoform, which contains cysteine at position 158. Substitution of cysteine for arginine at amino acid position 158 changes the tertiary structure of the receptor-binding domain of apoE. As a result, apoE2 isoform binds poorly to LDL receptor leading to accumulation of chylomicron and VLDL in the plasma and vessel walls.

Familial ligand-defective apoB (FLD): FLD apoB is an autosomal dominant defect with a prevalence of approximately 1:500 in the population. The responsible gene is APOB, which is located on chromosome 2. In approximately 95% of the cases, the mutation is R3500Q (arginine is changed to glutamine at amino acid position 3500). The rest include R3500W (W: tryptophan) and R3500C (C:cysteine) mutations. These mutations reduce the affinity of LDL receptor for apoB and thus accumulation of VLDL and LDL cholesterol in the plasma and vessel wall.

Familial Combined hyperlipidemia (FCH): FCH is a relatively common disease that affects approximately 1 - 2:100 in the population. It is not yet clear whether FCH is an autosomal recessive or a polygenic disease, and the causal genes and mutations are still unknown. The primary defect is impaired transfer of cholesteryl ester from HDL to LDL and VLDL cholesterol, which results in elevation of LDL and VLDL cholesterol and premature atherosclerosis.

Fish eye disease: Fish eye disease is a rare autosomal dominant disease due to deficiency of lecithin: cholesterol acyltransferase (LCAT). LCAT gene is located on chromosome 16q22.1, and codes for a protein involved in the synthesis from pre -lipoprotein A1 and conversion of HDL_3 to HDL_2 cholesterol (Figure 5). Deficiency of LCAT leads to premature coronary atherosclerosis, proteinuria, anemia, renal failure, and corneal opacification.



Tangier disease: Tangier disease (TD) is an autosomal co-dominant disease characterized by virtual absence of HDL and very low plasma levels of apoA1. Deposition of cholesteryl esters results in characteristics of hypertrophic orange-color tonsils, hepatosplenomegaly and premature coronary artery disease. Recently, mutations in ATP binding cassette transporter (ABCA1) gene in patients with Tangier disease and its allelic variant familial hypoalphalipoproteinemia (HA) were identified (14-18). ABCA1 gene is located on chromosome 9q31 and codes for an mRNA that is 6,783 base pair and a protein that is 2,261 amino acids in size. (15;16)ABCA1 is a transmembrane protein with 12 transmembrane domains (17). It acts as a flippase at the plasma membrane stimulating cholesterol and phospholipid efflux to apoA1 and HDL-C (19). Under normal state, ABCA1 transports free cholesterol to extracellular space where it binds to apoA1, synthesized by the liver, forming nascent HDL particles from VLDL (Figure 5). In the absence of ABCA1, free cholesterol is not transported extracellularly and lipid poor apoA1 rapidly degrades. Recently, common polymorphisms in ABCA1 gene have been associated with coronary atherosclerosis in the general population (20).

Genetics of non-Mendelian forms of atherosclerosis: The Human Genome Project has ushered in new opportunities for studying the genetic non-Mendelian disorders through construction of SNP maps and genome-wide SNPs association studies (13). While there is a considerable debate regarding the best approach for genome-wide SNP association studies, candidate gene approach has emerged as the practical approach that could be pursued at multiple levels. Because SNPs do not exist in isolation, comprehensive analysis of the selected candidate genes is necessary. Moreover, because a positive association does not establish causality and often indicates linkage disequilibrium with the actual mutation, the results are considered provisional pending confirmation through *in vitro* and *in vivo* experimentations (12).

Genome-wide approach: A genome-wide approach to identify susceptibility genes for complex traits is based on analyzing co-segregation of polymorphic DNA markers with inheritance of a phenotype. The principle behind the techniques of genome-wide search is based on the likelihood of sharing a susceptibility-allele between the two relatives who also have inherited the trait. Two sibs with a particular trait are expected to share the susceptibility-allele more often than by chance alone. Analysis is often performed in several hundred sib-pairs. Several variations of allele-sharing methods, including sip-pairs linkage analysis and transmission disequilibrium test (TDT), have been developed and applied to map the susceptibility genes for complex traits (Figures 6A and 6B). They are based on the principle of linkage disequilibrium (LD) to map the location of the susceptibility gene. LD indicates that two DNA markers that are located in close proximity in the genome are more likely to co-segregate than by chance alone.

Techniques based on LD are independent from incomplete penetrance, false positive phenotype, genetic heterogeneity, and the frequency of the risk-related allele. According to the principle of LD, it is expected that the affected sibs share the risk-allele more often than expected by chance alone. Sib-pair linkage analysis is best suited for mapping genes that denote a high genotype-related risk (approximately greater than 4). It is not considered a powerful technique to map the susceptibility genes that confer for a modest risk for a complex trait. TDT is considered a more powerful method to map the susceptibility genes that confer a moderate genotype-related risk. TDT examines transmission of a particular allele from heterozygous parents to their offspring (Figure 6B). An affected offspring is more likely to inherit the disease-related phenotype from a heterozygous parent than by chance alone (50% per random inheritance) or as compared to the unaffected offspring.

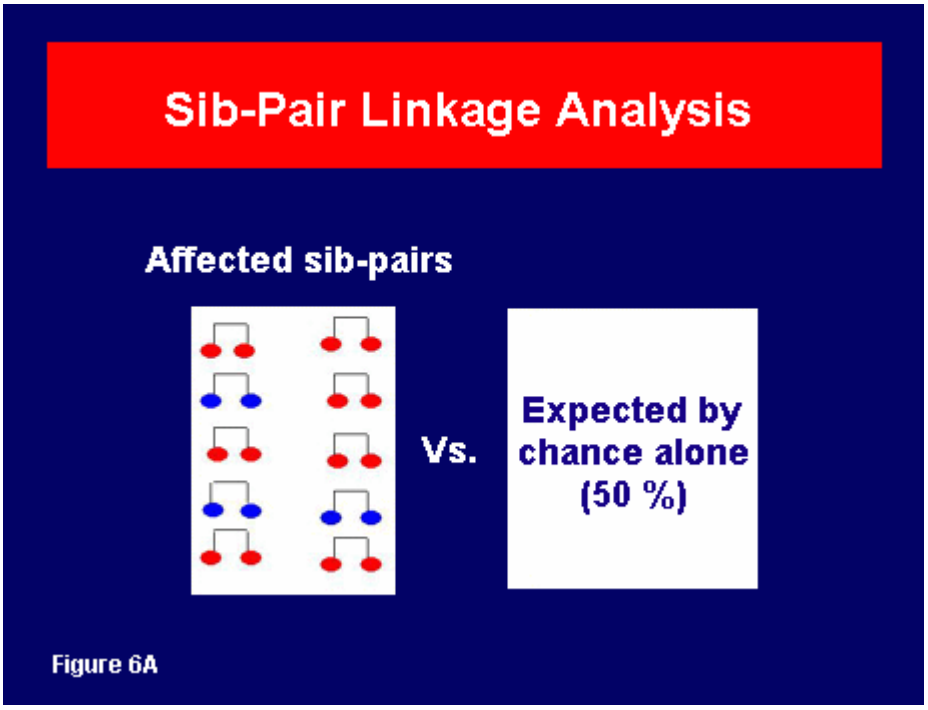


Figure 6A

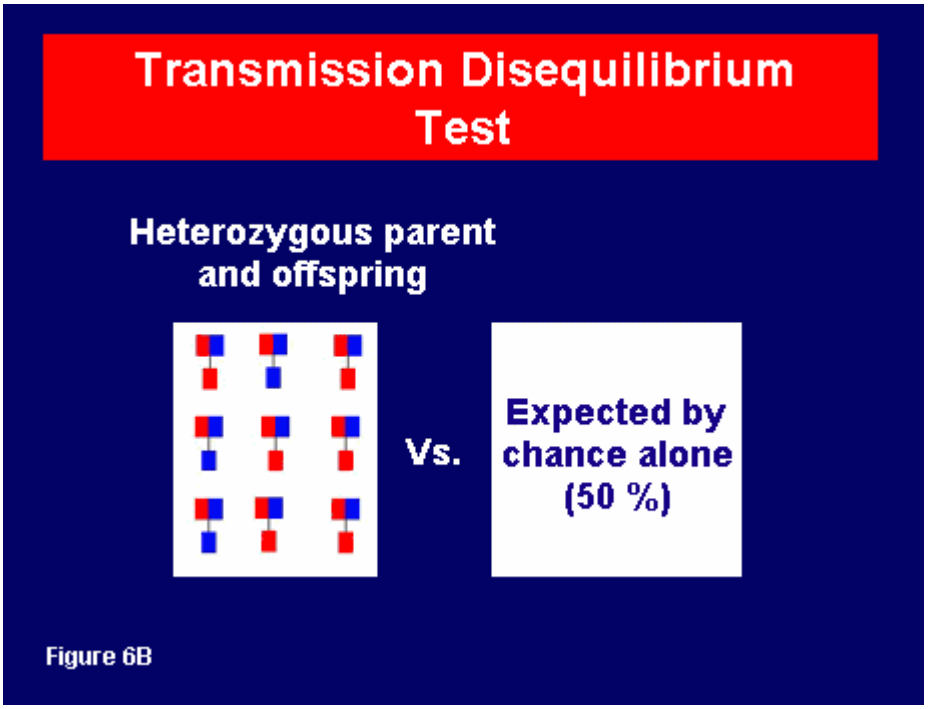
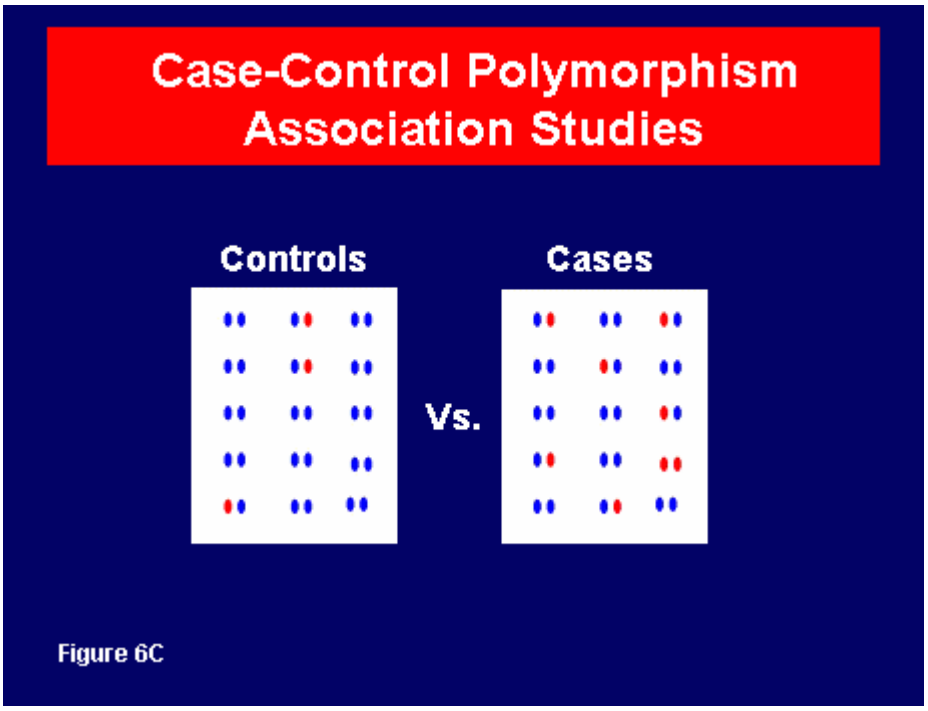


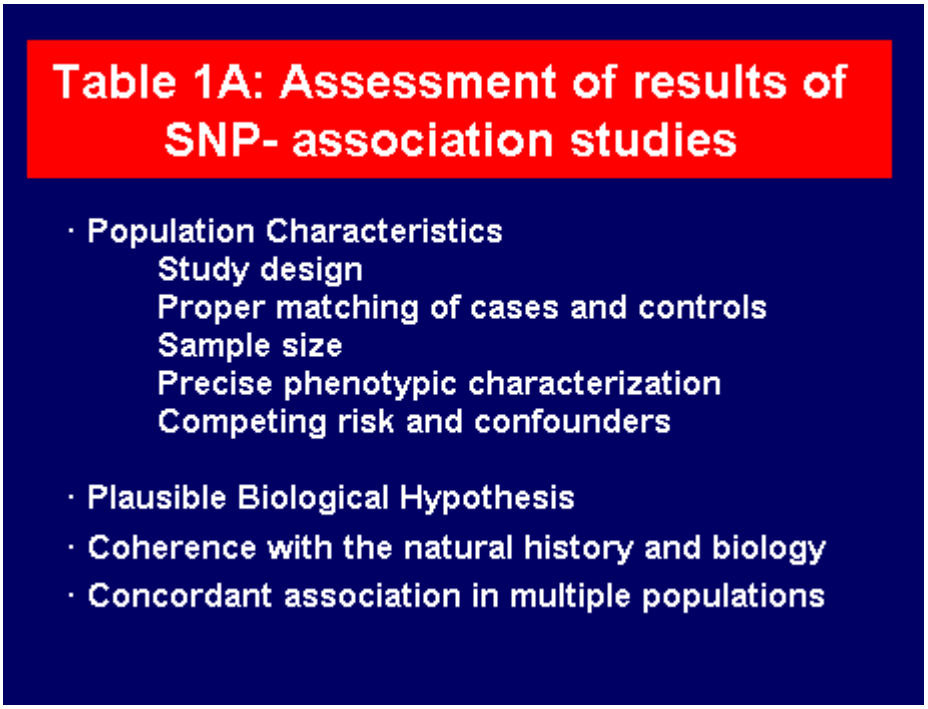
Figure 6B

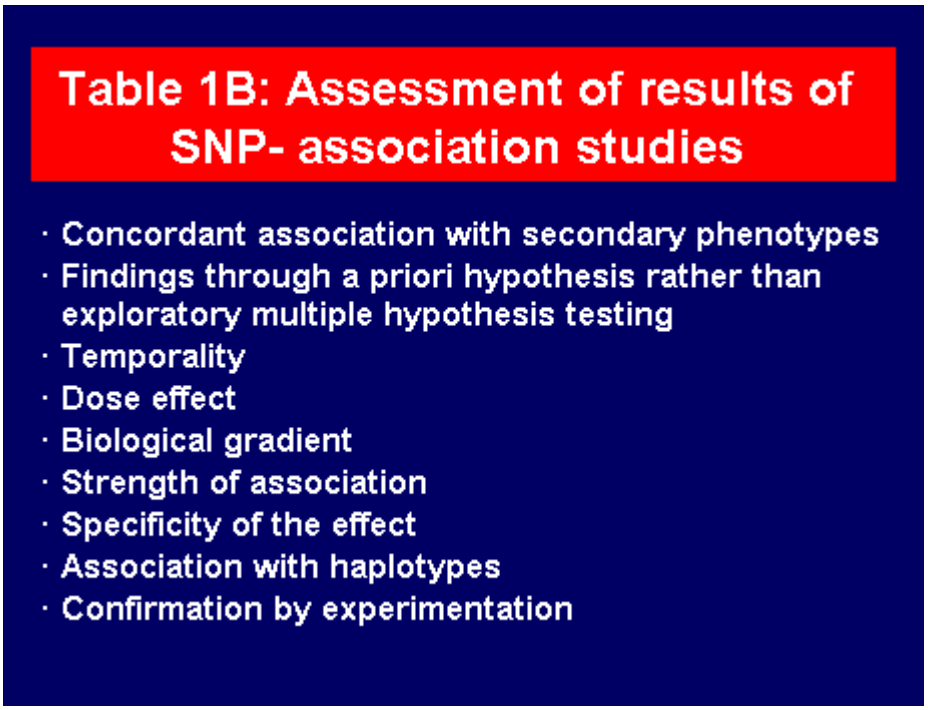
The conventional linkage techniques have limited power to map susceptibility genes with small or moderate effects. Therefore, the emphasis shifts towards using SNPs to perform large-scale genome-wide

association studies (Figure 6C). Unfortunately, LD studies using SNPs to detect an association with a phenotype have a high rate of spurious results. Therefore, it is not surprising that the results of the vast majority of the association studies using SNPs have not been concordant. Recently, SNP maps of human genome have been generated with the hope of performing whole-genome LD studies. It is estimated that 500,000 to 1,000,000 SNPs will be needed to perform genome-wide LD studies. It is anticipated that the development of comprehensive SNP maps of the human genome and highly efficient high-throughput genotyping techniques along with the advances in bioinformatics will make it possible to map the susceptibility genes for complex traits such as coronary atherosclerosis. Genome-wide association studies in thousands of phenotypically well-characterized subjects in conjunction with functional genomics, and proteomics could lead to identification of the individual susceptibility genes for complex traits, genetic determinants of the clinical outcome, pharmacogenetics, and response to medical and surgical interventions.



Candidate gene approach: Unlike genome-wide studies, the candidate gene approach requires a priori understanding of the potential involvement of the specific gene under investigation in susceptibility to the trait of interest. Candidate genes are often selected based on the evidence driven from molecular biology studies implicating a specific molecule in the pathogenesis of the traits. Commonly, the association of biologically functional SNPs in the candidate gene with the phenotype is analyzed in a case-control study and less often in a prospective study, which is more robust. The aim of an association study is to show that a variant of the candidate gene is associated with the presence or severity of the phenotype, clinical outcome or response to treatment (pharmacogenetics). A positive association does not establish the causality and often the marker is in LD with the risk-allele. Linkage disequilibrium simply illustrates a non-random segregation of two DNA markers and frequently occurs when two markers (the associated allele and the true mutation) are in close genetic proximity on a chromosome. Thus, they co-segregate more often than expected by chance alone. Unfortunately, association studies have a high rate of spurious results, as described earlier and are considered provisional. This is particularly problematic in retrospective case-control allelic association studies performed in a small sample size. The design of an association study, characteristics of the study population, sample size, biological plausibility, functional significance of the SNPs, strength of the association, presence of genetic and biological gradients and other issues listed in Table 1 (A and B) are helpful in assessing the results.





Candidate genes for coronary atherosclerosis: This approach assesses the role of the known genes and their functional variants in susceptibility to MI. Therefore; it is based on a priori knowledge of the candidate genes. It is commonly performed through a case-control allelic association study. The aim of an association study is to show that a variant of the candidate gene (risk-allele) is more common in cases than in matching controls or is associated with a severity of a phenotype, clinical outcome, or response to therapy in a prospective study (Figure 6C). A positive association does not establish the causality of an allele or a gene. Often, it is a marker that is in LD with the actual mutation.

Biological complexity of atherosclerosis denotes involvement of a large number of genes and their functional variants in its pathogenesis. Initial insights into identification of individual responsible genes for CAD were provided through progress in the molecular biology of atherosclerosis that led to identification of a number of important factors involved in vascular homeostasis and thrombosis, providing the needed knowledge to perform case-control association studies of the candidate genes. However, given the

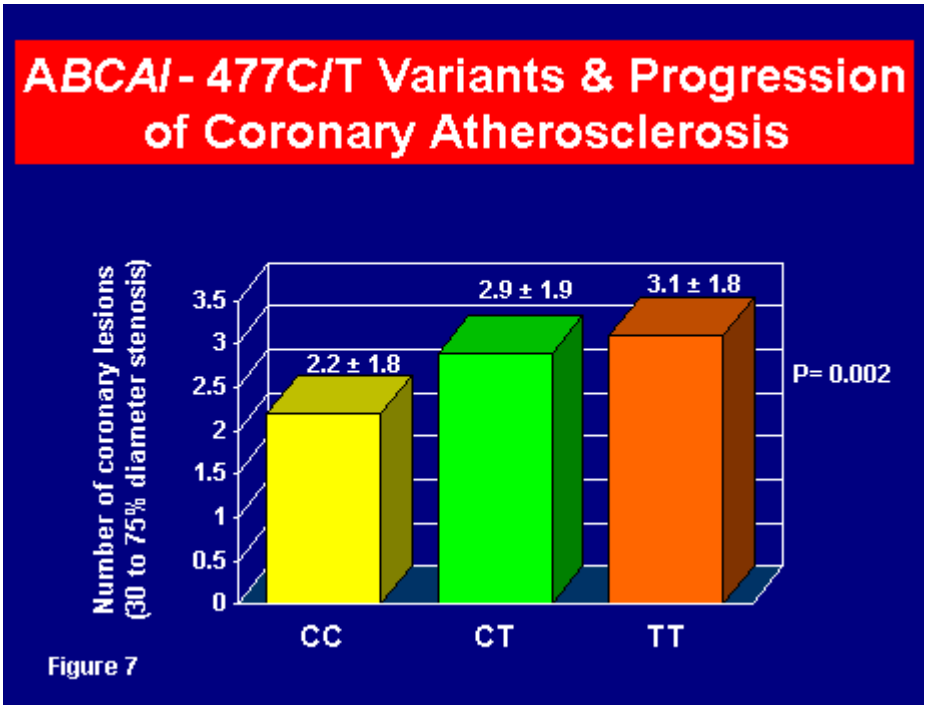
potential limitations of case-control studies, and the heterogeneity of populations, the results of these studies have been inconsistent. Therefore, the impact of these genetic factors in predisposition to CAD is not well defined yet. Large-scale well designed association studies or systematic genome wide search through robust genetic techniques are required to confirm the role of the candidate genes in susceptibility to CAD. The list of potential candidate genes for CAD is extensive and includes a variety of those involved in biology of smooth muscle cells, endothelial cells, lipid metabolism, and coagulation.

Increased plasma levels of pro-atherogenic lipoproteins are prerequisite for most forms of premature atherosclerosis. Approximately 1/2 of the total variance in plasma total cholesterol, high-density lipoprotein-cholesterol (HDL-C), and triglycerides levels could be attributed to genetic sources (21). Similarly, approximately half of the patients with angiographically documented premature CAD have underlying familial lipoprotein abnormalities (22). With the exception of a few rare Mendelian forms (Figure 3), multiple genes determine the plasma levels of lipoproteins. Genes encoding the key proteins are likely to play fundamental roles in determining plasma levels of cholesterol and fatty acid and thus, susceptibility to atherosclerosis. Therefore, SNPs in genes involved in lipid and lipoprotein metabolism are primary candidates as susceptibility genes for coronary atherosclerosis. Genes involved in inflammation, oxidative stress, lipid oxidation, endothelial cell function, and those involved in maintaining the integrity of extracellular matrix are primary candidates for susceptibility to coronary atherosclerosis.

The list of potential candidate genes for coronary atherosclerosis is expansive. Two examples, namely ABCA1 and CYBA are discussed briefly.

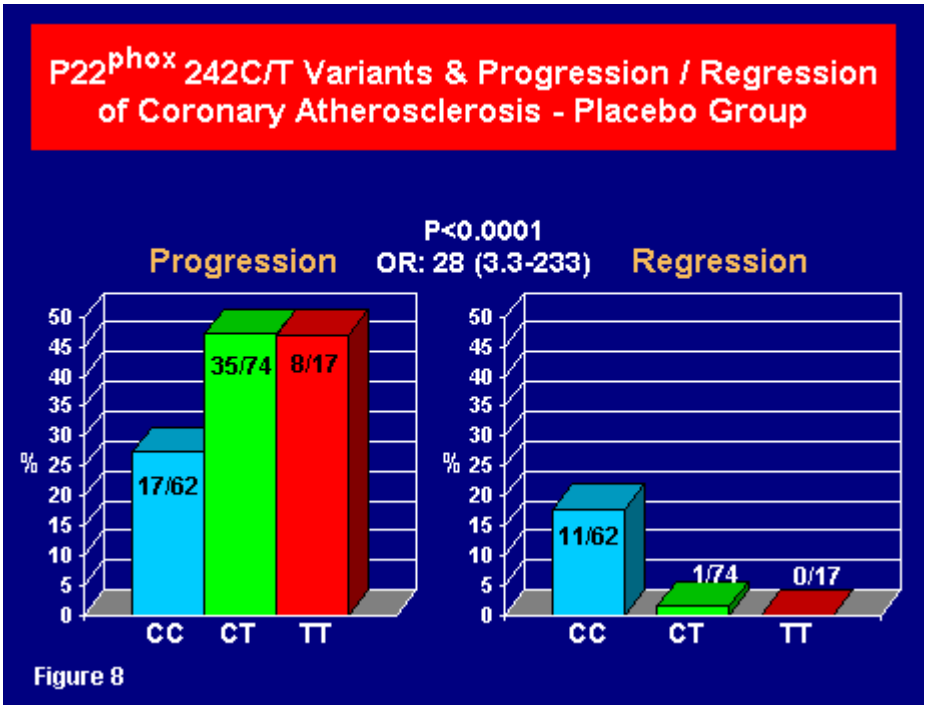
-477C/T SNP and coronary atherosclerosis: Plasma levels of HDL-C and its apolipoprotein apoA1 are under tight control of genetic factors, which are largely unknown. Recent Identification of mutations in the ATP binding cassette transporter (ABCA1) gene in patients with Tangier disease (14-16), who also have very low plasma levels of HDL-C and apoA1 and an increased risk of coronary atherosclerosis, suggests a major role for the ABCA1 protein in regulating plasma HDL-C and apoA1 levels and thus the risk of atherosclerosis. This notion is further supported by a recent observation of increased frequency of coronary artery disease in members of families with Tangier or familial hypoalphalipoproteinemia who are heterozygous for mutations in the ABCA1 gene (23).

Recent studies have implicated variants of ABCA1 in susceptibility to coronary atherosclerosis in the general population (20;23). We recently reported that an SNP located in the promoter region of ABCA1 was associated with severity and progression of coronary atherosclerosis (20). Subjects with the TT variants, which is associated with reduced promoter activity, had more severe coronary atherosclerosis than subjects with CC genotype and those with the CT genotypes were in between (Figure 7).



A second example is the CYBA gene, which is involved in maintaining the delicate balance between oxidation and reduction (redox) state in the vessel wall. CYBA codes for $p22^{phox}$ protein, which is a component of the plasma membrane-associated enzyme NADPH oxidase. NADPH oxidase is the most important source of superoxide anion, the precursor to a variety of potent oxidants, in intact vessel walls. $p22^{phox}$ in conjunction with gp91 forms a membrane-bound heterodimeric protein referred to as flavocytochrome b_{558}. The latter is considered the redox center of the NADPH oxidase. The $p22^{phox}$ protein is essential for the assembly and activation of the NADPH oxidase and plays a major role in NADPH-dependent O_2^- production in the vessel wall.

CYBA is located on chromosome 16q24 and has several allelic variants, including a 242C/T transition that results in replacement of histidine by tyrosine at amino acid position 72 (H72Y), a potential heme-binding site. We determined the association for the 242C/T variants with severity and progression of coronary atherosclerosis and response to treatment with a statin in a well-characterized cohort of LCAS population (24). We showed that in the placebo group, subjects with the mutation had 3-5 fold greater loss in mean minimum lumen diameter (MLD) and lesion-specific MLD than those without (Figure 8). Progression was also more and regression less common in those with the mutation. These results suggest that variants of $p22^{phox}$ are involved in progression of coronary atherosclerosis.



Genetically engineered mouse models could provide insight into the pathogenesis of atherosclerosis: Orthologous genes frequently contribute to a trait in rodents and humans. Mice, the most useful mammals for genetic studies, have common variations in many traits relevant to atherosclerosis. Animal models of atherosclerosis will not be discussed. Suffice it to say that ApoE$^{-/-}$ (25;26) and LDLR$^{-/-}$ (27) mice have proven to be extremely powerful tools in understanding the pathogenesis of atherosclerosis in humans. Similarly, over-expression of SREBPs in transgenic mice has provided significant insight into the pathogenesis of atherosclerosis (28-30). Thus, mouse models are potentially powerful tools to characterize the role of specific candidate genes in susceptibility to coronary atherosclerosis.

Potential impact of understanding the genetics basis of Coronary Atherosclerosis: Elucidation of the molecular genetic basis of coronary atherosclerosis is an important task that is very much in its early stages. Development of new molecular genetic techniques, SNPs maps of human genome, and informatics and their application to identify the susceptibility genes for coronary atherosclerosis could provide for an early genetic diagnosis, and risk stratification, independent and prior to the development of coronary atherosclerosis. It also could provide for the opportunity to prevent the disease through intervention aimed at specific targets involved in the pathogenesis of atherosclerosis. Finally, it will provide the opportunity for individualized therapy based on genetic information.

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