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Low-Density Lipoprotein Cholesterol, Apolipoprotein B, and Risk of Coronary Heart Disease: From Familial Hyperlipidemia to Genomics

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Abstract

Coronary heart disease (CHD) affects 17 million people in the United States and accounts for over a million hospital stays each year. Technological advances, especially in genetics and genomics, have changed our understanding of the risk factors for developing CHD. The purpose of this paper is to review low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo B), and risk of CHD. The paper focuses on five topics: 1) a description of lipoprotein classes, normal lipoprotein metabolism, and the biological mechanism of atherosclerosis; 2) a review of selected epidemiologic and clinical trial studies examining the associations between elevated LDL-C and apo B with CHD; 3) a brief review of the familial forms of hyperlipidemia; 4) a description of variants in genes that have been associated with higher LDL-C levels in candidate gene studies and genome-wide association studies (GWAS); and 5) nursing implications, including a discussion on how genetic tests are evaluated and the current clinical utility and validity of genetic tests for CHD.

Keywords

Genetics; genomics; coronary heart disease (CHD); low-density lipoprotein cholesterol (LDL-C); apolipoprotein B (apo B)

Coronary heart disease (CHD), also known as coronary artery disease (CAD), is the narrowing, as a result of atherosclerosis, of the blood vessels that supply blood and oxygen to the heart (National Center for Biotechnology Information, 2010). CHD can lead to unstable angina, myocardial infarction (MI), and heart failure. In the United States, 17 million people have CHD (Lloyd-Jones et al., 2010). The prevalence of CHD in individuals older than 18 years ranges from 2.9% to 6.6%, depending on race and ethnicity, with Asians having the lowest prevalence and American Indians and Alaska natives having the highest. According to Russo and Andrews (2006), in 2004 it was estimated that CHD was

responsible for 1.2 million hospital stays. Treating these conditions resulted in more than \$44 billion in expenses. Acute MI alone resulted in 695,000 hospital stays and \$31 billion in inpatient hospital charges.

Recent advances, especially in genetics, have changed the way that we understand disease and its risk factors. It is known that some rare diseases, such as Huntington's disease, Tay-Sachs disease, and sickle cell anemia, are caused primarily by single gene mutations (Centers for Disease Control and Prevention, 2000). However, for many diseases, including CHD, genetic variants may not directly cause disease, but rather may affect an individual's susceptibility to certain environmental risk factors associated with the disease. The common disease/common variant (CD/CV) hypothesis, proposed in the late 1990s, suggests that common diseases are caused by increased susceptibility due to multiple genetic variants that are fairly common in the population, with an allele frequency greater than 5% (Reich & Lander, 2001). Such genetic variants, in the presence of infectious, chemical, physical, nutritional, or behavioral risk factors, are believed to trigger the physiological processes that result in most cases of CHD (Centers for Disease Control and Prevention, 2000).

Based on this paradigm, researchers have primarily used two methods to detect the genetic changes that may influence risk for common diseases: candidate gene studies and genome-wide association studies (GWAS). Candidate gene studies are hypothesis driven, based on the gene's structure or function (suggestive of being involved in disease etiology), and test the association between a disease or risk factor and a specific allele in a known gene (Seal, 2011). In contrast, GWAS require no prior hypothesis and can, in a single study, examine over a million genetic variants spanning the entire genome. However, GWAS can be challenging due to the large number of cases and controls needed (tens of thousands of each), the very large number of statistical tests being performed, and the potential for a significant number of false-positive results (Pearson & Manolio, 2008). Findings from candidate gene studies are often validated using GWAS and new findings from GWAS are often tested and validated using candidate gene studies. See the recent paper in *Biological Research for Nursing* by Seal for more details on candidate gene studies and GWAS (Seal, 2011).

A positive finding from genetic association studies, an association between an allele and a disease or risk factor, can be interpreted in one of three ways: as a true positive with a direct association, as an indirect association, or as a false positive. When there is a true, direct association the marker allele (the allele being tested in the study) is part of the pathologic process. In other words, the variant is functional and part of the causal pathway of the disease. When there is an indirect association, there is linkage disequilibrium (LD) between the marker allele and a presumed disease susceptibility allele. LD is the nonrandom association of alleles at different loci (Slatkin, 2008). The variant is not functional or is not likely to be part of the disease pathway. Finally, the association can be a false positive as a result of multiple comparisons, a lack of Hardy-Weinberg equilibrium, or confounding.

The purpose of this paper is to provide a review of low-density lipoprotein cholesterol (LDL-C) and apolipoprotein B (apo B) and the risk of CHD in the context of these genetic advances. We discuss five main topics: First, we describe lipoprotein classes, normal

lipoprotein metabolism, and the biological mechanism of atherosclerosis. Second, we review selected epidemiologic and clinical trial studies that have examined the association between LDL-C and CHD risk and, recently, the association between apo B and risk of CHD. Third, we provide a brief description of the familial forms of hyperlipidemia. The discovery of these familial diseases and their underlying genetic causes was pivotal in allowing us to achieve our current understanding of the role of genomics in common diseases. Fourth, we describe the genetic variants in eight genes that have been associated with higher LDL-C levels in candidate gene studies and GWAS. And fifth, we describe two methods used to evaluate the genetic tests and discuss the current state of genetic testing for CHD in terms of their implications for nursing.

Classes of Lipoproteins, Cholesterol Synthesis, and Lipoprotein Metabolism

Lipids, which are insoluble, are transported through the circulation in complexes with proteins known as lipoproteins (Lusis & Pajukanta, 2008). Lipoproteins have a hydrophobic core, consisting of cholesterol esters and triglycerides (TGs), and a hydrophilic coat, consisting of unesterified, or free, cholesterol, phospholipids, and apolipoproteins (Hegele, 2009). Apolipoproteins regulate and control lipoprotein metabolism and lipid transport. There are 13 different known apolipoproteins (Grundy, 1990). The primary TG-carrying lipoproteins are chylomicrons and very-low-density lipoproteins (VLDL). The primary cholesterol-carrying lipoproteins are LDL and high-density lipoproteins (HDL; Lusis & Pajukanta, 2008). Cholesterol is a component of cell membranes and a precursor for steroid hormones, bile acids and vitamin D and is required for the activation of neuronal signaling molecules (Hegele, 2009). TGs serve as a key energy source.

Classes of Lipoproteins

The following are the main classes of lipoproteins. See Table 1 for more detailed description.

- **Chylomicrons:** Chylomicrons are synthesized in the intestinal mucosal cells and are composed mainly of TGs derived from dietary fat. Dietary cholesterol is transported from the intestines to the liver by chylomicrons.
- **Very-low-density lipoproteins:** VLDLs are TG-rich lipoproteins synthesized by the liver. They are the primary lipoprotein produced by the liver and transport TGs, phospholipids, cholesterol, and cholesteryl esters.
- **Low-density lipoproteins:** LDLs are insoluble lipids containing a steroid-ring nucleus, a hydroxy group, and one double bond in the steroid nucleus (Grundy, 1990). They are the major cholesterol-carrying protein in plasma.
- **High-density lipoproteins:** HDLs are the smallest lipoproteins and also transport cholesterol. They contain apolipoprotein A-I (apo A-I) on their surface, which mediates reverse cholesterol transport, a process discussed below.
- **Lipoprotein(a):** Lipoprotein(a) consists of an LDL particle linked to apolipoprotein(a). Apolipoprotein(a) contains multiple copies of the plasminogen

kringle 4, resulting in 34 isoforms of different sizes (McCormick, 2004). Apolipoprotein(a) is synthesized by the liver and its linkage to LDL occurs extracellularly possibly on the surface of hepatocytes (Bennet et al., 2008; Marcovina & Koschinsky, 1998). The normal physiological functions of lipoprotein(a) remain unknown. However, recent studies suggest that lipoprotein(a) plays a role in acute inflammation as an acute-phase reactant and promoter, can contribute to foam cell formation (see *Biological Mechanism of Atherosclerosis* section) because it is prone to oxidative modification, and may have antifibrinolytic properties due to its similar structure to plasminogen (Maeda et al., 1989; Nordestgaard et al., 2010; Volpato et al., 2010).

Cholesterol Synthesis

There are two major sources of cholesterol, diet and endogenous synthesis. Approximately half of dietary cholesterol entering the intestines is absorbed; the rest is excreted in stool. The human body, through the process of cholesterol synthesis, produces about 500–1000 mg of cholesterol daily (Grundy, 1990). The majority (up to 70–80%) of circulating cholesterol is from endogenous synthesis (Hegele, 2009).

Specific mechanisms are required for the intestines to absorb cholesterol. In the intestinal lumen, cholesterol is mixed with lecithin, lysolecithin, and bile salts to become soluble. Then, the soluble mix, which also contains fatty acids and monoglycerides, crosses the intestinal lumen by monomolecular diffusion into the intestinal mucosal cell. Once in the intestines, the cholesterol is packaged into chylomicrons. Chylomicrons are secreted from the intestines into lymph and then enter systemic circulation through the thoracic duct (Hegele, 2009).

Once in the bloodstream, lipoprotein lipase (LPL), an enzyme that is activated by apo C-II on the surface of chylomicrons, causes the chylomicrons to release fatty acids from triglycerides (Hegele, 2009). LPL also causes the chylomicrons to release apo A-I, apo A-V, apo A-IV, apo C-II, and apo C-III, reducing them to chylomicron remnants. The chylomicron remnants are taken into the liver by either LDL receptors (LDLRs) or, in the absence of LDLRs, LDLR-related protein-1.

Endogenous cholesterol synthesis takes place mainly in the liver. All cholesterol is derived from acetate. Three molecules of acetate are condensed to produce 3-hydroxy 3-methylglutaryl coenzyme A (HMG CoA; Grundy, 1990). HMG CoA is converted to mevalonic acid by the enzyme HMG-CoA reductase (HMGCR). In normal cholesterol synthesis, this reaction is rate limiting (Hegele, 2009). Through a process of condensations and rearrangement, which takes approximately 20 steps, mevalonic acid is transformed into cholesterol. Apo B is synthesized in the liver by ribosomes of the rough endoplasmic reticulum. The apo B migrates to the smooth endoplasmic reticulum where the newly synthesized cholesterol is packaged with TG and apo B in the form of nascent VLDL particles. The nascent VLDL, also known as intermediate-density lipoprotein (IDL), is then released in the circulation.

As nascent VLDLs circulate in the bloodstream, they are transformed into mature VLDL particles. The nascent VLDLs acquire additional cholesterol esters, apo C-II, apo C-III, and possibly more apo E. These additional cholesterol and apolipoproteins are transferred to the nascent VLDLs from HDLs (Grundy, 1990). The now mature VLDLs release fatty acids into the circulation and transfer phospholipids, apo C-II, apo C-III, and apo E back to LDL when it interacts with LPL, leaving a VLDL remnant. VLDL remnants can either be taken into the liver by LDLRs or they can remain in the circulation, where they are transformed into cholesterol-rich LDLs (Lusis & Pajukanta, 2008). Hepatic lipase, the enzyme responsible for transforming VLDL remnants into LDLs, hydrolyses the triglycerides and causes the release of apo C and apo E from the surface. Apo B is the remaining apolipoprotein on the surface of the LDLs (Benn, 2009). Normally, 60–70% of the VLDL remnants are taken into the liver (Grundy, 1990).

Approximately 75% of circulating LDLs are removed from the bloodstream by the liver. Extrahepatic tissues are responsible for the removal of the remaining 25% (Grundy, 1990). In both the liver and extrahepatic tissues, uptake of LDLs can be completed by either a receptor-mediated pathway or a non-receptor-mediated pathway. In the liver, it is estimated that receptor-mediated LDL uptake is responsible for 75% of LDL removal. In extrahepatic tissues, two-thirds of the LDL removal is completed by the receptor-mediated pathway.

During receptor-mediated LDL uptake in both hepatic and extrahepatic tissues, LDLRs are transported to the surface of the cell where they migrate to regions called coated pits. Apo B serves as the ligand on the LDL surface that binds to the LDLR. After LDLRs bind to circulating LDLs, the LDLs are internalized into lysosomes. LDLRs are then recycled and return to the cell surface. The cholesterol esters in the internalized LDLs are hydrolyzed into unesterified cholesterol and the apo B molecules on the surface of the LDLs are degraded into amino acids. The amount of unesterified cholesterol that enters the cell is regulated by 3-hydroxy 3-methylglutaryl coenzyme A reductase (HMGCR) and the rate of synthesis of LDLR (Grundy, 1990).

The number of LDLRs synthesized by a cell is regulated by the amount of cholesterol in the cell. Cholesterol derived from LDL acts at several levels. It suppresses the transcription of the *HMGCR* gene and regulates other processes that stabilize the cell's cholesterol content. The LDL-derived cholesterol activates acyl CoA cholesterol acyltransferase (ACAT), a cholesterol-esterifying enzyme, so excess cholesterol can be stored as cholesterol ester droplets in the cytoplasm (Goldstein & Brown, 2009). Additionally, LDL also suppresses transcription of the *LDLR* gene. Through these processes, cellular LDL content is maintained in its narrow optimal range.

Recent research suggests that plasma concentrations of lipoprotein(a) are determined mainly by the rate of hepatic synthesis of apolipoprotein(a) by the *APO(A)* gene. Although the site of lipoprotein(a) formation has not been identified, evidence suggests that apolipoprotein(a) covalently bonds to LDL outside of the liver, perhaps on or near hepatocytes (Bennet et al., 2008; Marcovina & Koschinsky, 1998). The apolipoprotein(a) genotype, which determines both the synthetic rate and isoform of the apolipoprotein(a) attached to the lipoprotein(a)

molecule, accounts for 90% of plasma concentrations of lipoprotein(a) in Caucasians and 78% in African Americans (Marcovina & Koschinsky, 1998; Nordestgaard et al., 2010).

HDL maturation involves a series of steps that begin in the liver and the small intestine where nascent HDLs are formed. Nascent HDLs are able to accept unesterified cholesterol from cell membranes of various tissues or from the surface coat of other lipoproteins. When this unesterified cholesterol reaches the surface of the nascent HDL, it is transformed by lecithin-cholesterol acyltransferase (LCAT), an enzyme, into cholesterol ester (Grundy, 1990). The apo A-I on the surface is an essential cofactor in this transformation.

Cholesterol can only be degraded and excreted by the liver (Grundy, 1990), and cholesterol must be transported to it in order to remove excess cholesterol from peripheral tissues. This process, known as reverse cholesterol transport, is accomplished through two mechanisms. In the first mechanism, apo A-I mediates the process through the adenosine triphosphate-cassette binding transporter (ABC) AI. Scavenger receptor B1 on hepatocytes allow the HDL particles to be taken into the liver (Natarajan, Ray, & Cannon, 2010). In the second mechanism, cholesterol esters on HDLs are transferred to VLDLs through the cholesterol ester transfer protein (CETP). The VLDLs are then taken into the liver by LDLRs. Any excessive cholesterol is converted into bile or removed from the body in stool as fecal acidic steroids (Grundy, 1990).

Biological Mechanism of Atherosclerosis

It is well established that cholesterol plays an important role in the development of atherosclerosis. The first step in the pathology of atherosclerosis is infiltration and entrapment of plasma LDLs, VLDLs, and VLDL remnants into the arterial wall. These particles leave the blood and filter through the endothelium into the intimal layer of the arteries where they accumulate (Insull, 2009). Once these particles are trapped, they are modified by enzymes into proinflammatory particles. These proinflammatory particles initiate an innate inflammatory response. This response causes the endothelial cells to express cellular adhesion molecules (Lawson & Wolf, 2009). In addition to cellular adhesion molecules, chemokines are secreted by smooth muscle, platelets, and adipose tissue, causing monocytes, lymphocytes, mast cells, and neutrophils to enter the arterial wall (Insull, 2009; Surmi & Hasty, 2010). At the same time, the smooth muscle cells secrete collagen and elastic fibers into the extracellular matrix (Insull, 2009). Once in the arterial wall, monocytes are transformed into macrophages producing oxidized foam cells (Hegele, 2009). These changes are microscopic and reversible and are not yet considered atherosclerosis (Insull, 2009). The continued accumulation of foam cells, from microscopic to grossly visible changes, results in fatty streak formation, which is considered the first stage of atherosclerosis.

During the second stage of atherosclerosis, the foam cells continue to accumulate along with other activated inflammatory cells. The extracellular lipids combine into pools causing cell necrosis (Insull, 2009). Eventually, these lipid-rich cores grow until they occupy 30–50% of the arterial wall volume. Next, fibrous tissue is added above the lipid-rich core, just underneath the endothelium, to form a fibrous cap.

The third, and final, stage of atherosclerosis is complex lesion development. In this stage, a thin-cap fibroatheroma develops and, possibly, ruptures. The fibrous cap becomes thin and weakened when enzymatic activity causes the fibrous tissue to dissolve (Insull, 2009). This lesion is called a vulnerable plaque because of its susceptibility to rupture. If it ruptures, the thrombogenic interior arterial wall is exposed, producing a potentially life-threatening occlusive clot (Hegele, 2009). However, many ruptures are clinically silent. They heal by forming fibrous tissue matrices of cells, collagen fibers, and extracellular space (Insull, 2009). These may rupture again causing a cycle of rupture-thrombosis-healing. Each of these steps results in calcium deposits. The increasing mass of the plaques can result in stenosis severe enough to cause lethal ischemia due to blood-flow restriction (Hegele, 2009).

LDL-C and Apo B as Risk Factors for Atherosclerosis and CHD

LDL-C and Risk of CHD

Numerous observational epidemiological studies, including the Framingham Heart Study, have found a relationship between elevated LDL-C levels and an increased incidence of CHD in both men and women (Stamler et al., 1999; Wilson et al., 1998). The relationship is similar for recurrent cardiovascular disease events among individuals with established CHD (Pekkanen et al., 1990; Wong, Wilson, & Kannel, 1991).

Although CHD in young and middle-age adults is uncommon (the average annual rates of first CHD events in men aged 35–44 years is 3 per 1000 men and even lower in women), it is actually a “pediatric problem” (Holman, 1961). The Bogalusa Heart Study, which included subjects between the ages of 2 and 39, found that both coronary and aortic fatty streaks and fibrous plaques increase with age. Among cardiovascular risk factors, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), and serum concentrations of cholesterol were strongly associated with the extent of lesions in the aorta and coronary arteries ($r = 0.70$; $p < .001$; Berenson et al., 1998). These findings indicate that, as the number of cardiovascular risk factors increases in young people, so does the severity of asymptomatic coronary and aortic atherosclerosis. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study confirmed that atherosclerosis has already started in a substantial number of people by the late teenage years (McGill, McMahan, & Gidding, 2008). In that study, American Heart Association Grade 4 and 5 lesions, lesions that are vulnerable to rupture resulting in a CHD or cerebrovascular event, were present in the left anterior descending (LAD) coronary artery of teenagers and young adults. The PDAY study also showed that risk factors measured early in life predict the severity of advanced lesions later in life.

Due to the extensive evidence for the association between elevated LDL-C levels and increased CHD risk, a normal LDL-C level is the goal of therapy to prevent or reduce the risk of CHD. According to the Adult Treatment Panel III guidelines (2002), LDL-C levels < 100 mg/dL (2.586 mmol/L) throughout life are associated with a very low risk for CHD in populations and are considered optimal. LDL-C levels > 100 mg/dL (2.586 mmol/L) lead to the development of atherosclerosis, which may result in CHD.

Multiple randomized controlled trials have demonstrated the benefits of lowering LDL-C by a class of drugs known as statins. Statin drugs are HMGCR inhibitors. As the amount of cholesterol in cells increase, the production of LDLRs decreases (Goldstein & Brown, 2009). When an individual takes a statin, the drug binds to and inhibits HMGCR in the liver, lowering endogenous cholesterol production. At the same time, through a pair of sterol-regulated, membrane-bound transcription factors called SREBPs, the number of LDLRs increases. The overall effect of the drug is that the amount of liver cholesterol is maintained at a safe, normal level while the level of LDL-C in blood is lowered.

Two of these studies are the Heart Protection Study and the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA), both published after the Adult Treatment Panel III final report was released. In the Heart Protection Study, 20,536 adults from the United Kingdom (aged 40–80 years) with coronary disease, other occlusive arterial disease, or diabetes were randomly allocated to receive 40 mg daily of the statin simvastatin or placebo. The primary study outcomes were mortality and fatal or nonfatal vascular events. During the 5-year treatment period, LDL-C decreased by an average of nearly 40 mg/dL (approximately 1 mmol/L) in the treatment group (Heart Protection Study Collaborative Group, 2002). All-cause mortality and rates of coronary death, first-event nonfatal MI, non-fatal or fatal stroke, and coronary revascularization all declined significantly in the intervention group versus the control group. These reductions were significant in each subcategory of participant studied, including those without diagnosed coronary disease who had cerebrovascular disease, peripheral artery disease or diabetes; men, women; and those who presented with LDL-C < 116 mg/dL (3.0mmol/L) or total cholesterol < 193 mg/dL (5.0mmol/L). The findings suggest that statin medications are effective and provide significant benefits to a wide range of high-risk patients regardless of their baseline cholesterol levels. Side effects of simvastatin included an increase in liver and muscles enzymes and muscle pain.

The ASCOT-LLA study, which also examined the effectiveness of a statin drug, had findings of similar reductions in LDL-C in the intervention group and a significant reduction in the incidences of fatal and nonfatal stroke, total cardiovascular events, and coronary events in the treatment group compared to the control group (Sever et al., 2003). Multiple other studies have demonstrated the effectiveness of statins in decreasing morbidity and mortality due to CHD (Nakamura et al., 2006; Scandinavian Simvastatin Survival Study Group, 1994; Shepherd et al., 2002).

Apo B and Risk of CHD

Plasma level of apolipoprotein B is a relatively new biomarker that may be a better measure of circulating LDL particle number concentration and a better indicator of risk than LDL-C (Benn, 2009; Contois et al., 2009). Apo B is a component of all atherogenic or potentially atherogenic particles, including VLDL, nascent VLDL/IDL, LDL, and lipoprotein(a). Therefore, apo B provides a direct measure of the number of atherogenic lipoprotein particles in the circulation. Apo B levels can be reduced through exercise and dietary changes (Dreon, Fernstrom, Miller, & Krauss, 1994; Holme, Hostmark, & Anderson, 2007; Matthan et al., 2004).

The Copenhagen City Heart Study examined prediction of ischemic heart disease and MI in a general population, both women and men, using apo B levels (Benn, Nordestgaard, Jensen, & Tybjaerg-Hansen, 2007). Women with high apo B levels, > 95 mg/dL, had a hazard ratio for ischemic heart disease of 1.8 (95% CI: 1.2–2.5) and for MI of 2.6 (95% CI: 1.4–4.7) versus women with low apo B levels, < 75 mg/dL. Men with high apo B levels, > 95 mg/dL, had a hazard ratio for ischemic heart disease of 1.9 (95% CI: 1.5–2.6) and for MI of 2.4 (95% CI: 1.5–3.6) versus men with low apo B levels, < 76 mg/dL. Additionally, apo B was superior to LDL-C in the prediction of ischemic heart disease and MI in both genders ($p < 0.001$ for prediction of ischemic heart disease and $p = 0.004$ for prediction of MI in females; $p = 0.01$ for ischemic heart disease and $p = 0.03$ for MI in males). Several other studies have reported similar results with respect to the predictive ability of apo B for ischemic heart disease (Chien et al., 2007; Ridker, Rifai, Cook, Bradwin, & Buring, 2005; St-Pierre, Cantin, Dagenais, Despres, & Lamarche, 2006).

Familial Forms of Hyperlipidemia

The effect of elevated LDL-C on increased CHD risk is most evident in individuals with familial forms of hyperlipidemia. In these individuals, significant atherosclerosis and early CHD are seen even in the absence of other risk factors such as obesity, hypertension, and smoking, providing strong evidence for LDL-C as a powerful atherogenic lipoprotein (Adult Treatment Panel III, 2002). These disorders, some of which have been studied for over 70 years, have helped us understand cholesterol synthesis and metabolism and led to the discovery of the statin drugs, which, as previously described, are effective at decreasing morbidity and CHD mortality in individuals with elevated LDL-C levels (Austin, Hutter, Zimmern, & Humphries, 2004). The study of these disorders, which result in extreme elevations in LDL-C and triglyceride levels, has helped researchers learn more about the genes involved in less severe but more common forms of hypercholesterolemia. These familial forms of hyperlipidemia are described briefly below and in more detail in Table 2.

Familial Hypercholesterolemia

In familial hypercholesterolemia (FH), individuals have elevated LDL levels and xanthomata (yellowish-orange, lipid-filled nodules on the skin) and suffer from early myocardial infarctions (Austin et al., 2004; Goldstein & Brown, 2009). Although it was initially believed that FH was caused by mutations in a single gene, it has since been discovered that it is caused by mutations in multiple genes, including *LDLR*, *APOB*, proprotein convertase subtilisin/kexin type 9 (*PCSK9*), and low-density lipoprotein receptor adaptor protein 1 (*LDLRAP1*).

The first gene found to be responsible for FH, *LDLR*, was discovered in the early 1970s by Goldstein and Brown (2009). Individuals with heterozygous FH have only one functional allele of the *LDLR* gene, resulting in half the normal number of functioning LDLRs (Grundy, 1990). As a result, patients with heterozygous FH have plasma LDL-C levels that are twice those of individuals with two normally functioning alleles. The frequency of heterozygous FH in Caucasian and Asian populations ranges from about 0.1 to 1.5% (see Table 2). Homozygous FH is rare, affecting about 1 in a million individuals (Austin et al., 2004). As of January 2011, researchers have found over 1100 unique deleterious mutations

in the *LDLR* gene (Leigh, Foster, Whittall, Hubbart, & Humphries, 2008). However, not all of the mutations cause a total lack of gene function resulting in FH.

In the 1980s, research demonstrated that mutations in the *APOB* gene resulted in the same clinical phenotype as FH. Over 100 variants in the *APOB* gene have been reported, but only one variant, R3500Q, is associated with severe hypercholesterolemia (Benn, 2009). This variant causes a mutation in the codon for amino acid 3500 that results in glutamine substitution for argine (Austin et al., 2004; Benn, 2009). Individuals with the R3500Q variant have a disorder known as familial defective apolipoprotein B (FDB). The mutation causes poor ligand binding to LDLRs resulting in less uptake into the liver and higher circulating LDL-C levels.

A third gene that can cause FH is *PCSK9*, located on the short arm of chromosome 1. Several mutations in the gene result in a “gain-of-function” that enhances the activity of the PCSK9 protein (Abifadel et al., 2009). The overactive PCSK9 protein reduces the number of LDLRs. It is believed that the altered protein causes the LDLRs to be broken down more quickly, resulting in elevated LDL-C levels.

Additionally, researchers have identified a gene responsible for a form of autosomal recessive hypercholesterolemia (ARH). Individuals with ARH usually have LDL-C levels between 500 and 700 mg/dL (13 to 18.3 mmol/L). Mutations in the *LDLRAP1* gene, located on the short arm of chromosome 1, are responsible for ARH (*LDLRAP1*—low density lipoprotein receptor adaptor protein 1, n.d.). More than 10 mutations in the *LDLRAP1* gene lead to the production of an abnormally small, nonfunctional version of the *LDLRAP1* protein. Without the functioning protein, LDL receptors are unable to effectively remove LDL particles from the circulation, resulting in excessive LDL-C levels.

Familial Hypertriglyceridemia

Familial hypertriglyceridemia (FHTG) is inherited in an autosomal dominant fashion (Kolovou, Anagnostopoulou, Kostakou, Bilianou, & Mikhailidis, 2009). In FHTG, plasma triglycerides and VLDLs are moderately-to-markedly elevated; whereas LDL-C and HDL-C are usually normal or slightly elevated (Genest, 2003; Kolovou et al., 2009). Total cholesterol is normal or slightly elevated, with a typical value of less than 240 mg/dL (6.2 mmol/L). Fasting plasma concentrations of triglycerides are usually 200–500 mg/dL (2.3–5.7 mmol/L). However, after a meal, plasma triglycerides may exceed 1000 mg/dL (11.3 mmol/L; Genest, 2003). FHTG is often not expressed in childhood and can remain asymptomatic until other factors, such as moderate-to-excessive alcohol consumption, obesity, type II diabetes, or hypothyroidism, are present (Kolovou et al., 2009). FHTG is caused by a variant or variants in the apolipoprotein A-V (*APOA5*) gene, which results in an overproduction of VLDL and decreased VLDL uptake (*APOA5*—apolipoprotein A-V, n.d.). See table 2 for additional information about FHTG.

Familial Combined Hyperlipidemia

Familial combined hyperlipidemia (FCHL) is the most common familial lipoprotein disorder, with a prevalence of 1–2% in Western populations (Genest, 2003; Shoulders,

Jones, & Naoumova, 2004). Families with FCHL have multiple patterns of hyperlipidemia including hypercholesterolemia, hypertriglyceridemia, and elevated apo B levels (Grundy, 1990; Kolovou et al., 2009). FCHL is present in 10-20% of individuals with early CAD and is associated with peripheral artery disease. Additionally, Austin and colleagues (2000) compared individuals with FCHL to spouse controls and found an increased 20-year CVD mortality rate (relative risk [RR] = 1.7, 95% CI: 1.1–2.7, $p = 0.02$).

Some debate exists over whether FCHL is truly a monogenetic disorder or if it is polygenic. Studies have suggested linkage or association between FCHL and a number of genes. These include the tumor necrosis factor receptor 1B (*TNFRSF1B*) gene located on the short arm of chromosome 1; the *APOA2* and upstream stimulatory factor-1 (*USF1*) genes on the long arm of chromosome 1; the *SOD2* locus on the short arm of chromosome 6; the lipoprotein lipase (*LPL*) gene on the short arm of chromosome 8; the *APOA1/C3/A4/A5* genomic region and fatty acid desaturase locus (*FAD*) locus on the long arm of chromosome 11; the *CETP/LCAT* region, winged helix/forkhead transcription factor (*FOXC2*) gene and the WW-domain-containing oxidoreductase (*WWOX*) gene on the long arm of chromosome 16; and the peroxisome proliferators-activated receptor α (*PPARA*) gene on the long arm of chromosome 22 (See Table 2; Hyperlipidemia, Familial Combined, n.d.; Naukkarinen, Ehnholm, & Peltonen, 2006; Plaisier et al., 2009; Sáez et al., 2010; Shoulders et al., 2004).

Familial Dysbetalipoproteinemia (Type III Dyslipidemia)

Familial dysbetalipoproteinemia, or type III dyslipidemia, is an autosomal recessive disorder that predisposes affected individuals to the premature development of atherosclerosis and CAD (Kolovou et al., 2009; Mahley, Huang, & Rall, 1999). Individuals with the disorder have elevated cholesterol and TG levels of approximately 300 mg/dL (cholesterol of 7.8 mmol/L; TG of 3.4 mmol/L) to 1000 mg/dL (cholesterol of 25.9 mmol/L; TG of 11.3 mmol/L), reduced HDL-C, and the presence of β -VLDLs, which are cholesterol-enriched VLDL remnants. β -VLDL is the result of defective clearance of VLDL due to the $\epsilon 2/\epsilon 2$ genotype of the *APOE* gene. However, less than 10% of apo E $\epsilon 2$ homozygotes develop this type of hyperlipidemia, despite the presence of β -VLDL (Mahley et al., 1999). Additional genetic, hormonal, or environmental factors, such as obesity, diabetes mellitus, hypothyroidism, or estrogen status, are required for the hyperlipidemia to manifest itself.

Overall, these four familial forms of hyperlipidemia are relatively rare and present with significantly elevated LDL-C and/or triglyceride levels resulting in increased risk for developing early CHD. The discovery and continued investigation into the genetic causes of these disorders have provided insight into the genetic causes of elevated LDL-C beyond the familial hyperlipidemias in the general population.

Genetic Variants and Elevated LDL-C in the General Population

Most individuals with moderate-to-severe hypercholesterolemia do not have a form of familial hyperlipidemia (Grundy, 1990). However, genetic factors often influence an individual's susceptibility to environmental risk factors and contribute to elevated LDL-C. Perhaps the most studied type of genetic variants are single nucleotide polymorphisms (SNPs), DNA sequence variations that occur when a single nucleotide (A, T, C, or G) in the

genome sequence is altered (U.S. Department of Energy, 2008). Many SNPs have no apparent effect on cell function, but others can predispose people to disease by altering encoded proteins and gene expression (Hindorff et al., n.d.). When an SNP is discovered and added to the National Center for Biotechnology SNP Database (dbSNP), it is assigned a refSNP number (rs), which is used for reference but does not provide information about the location or type of the SNP in the genome sequence (National Center for Biotechnology Information, n.d.).

There are multiple types of SNPs with an allele frequency of 1% or greater in the population (Tabor, Risch, & Myers, 2002). Major types of SNPs in this category include nonsense, missense or nonsynonymous; sense or synonymous; promoter or regulatory; splice-site or intron–exon boundary; intronic; and intergenic. Nonsense SNPs occur in an exon, or protein coding region, of a gene and result in the premature termination of an amino-acid sequence. Nonsynonymous SNPs also occur in an exon and result in a codon change that then codes for a different amino acid with different biochemical properties. In contrast, a synonymous SNP occurs in an exon and results in a codon change but codes for the same amino acid with similar properties due to the redundancy of the genetic code. Even though the same amino acid is translated, protein function can be affected (Defesche, Schuurman, Klaaijsen, Khoo, Wiegman, & Stalenhoef, 2008). Promoter, or regulatory, SNPs occur in a promoter, 5′ untranslated region (UTR), or 3′ UTR. Although they do not change the amino acid, they may affect gene expression (Tabor et al., 2002). Splice site, or intron–exon boundary, SNPs occur within 10 base-pairs (bp) of the exon and may affect the splicing pattern or efficiency of introns. Intronic SNPs occur within an intron, or nonprotein-coding region. These regions have no apparent function but may affect the stability of messenger RNA or gene expression. Finally, intergenic SNPs occur in the noncoding regions between genes, which also have no apparent function but may affect expression through enhancer or other mechanisms.

Table 3a lists the SNPs that have been confirmed to be associated with increased LDL-C in two or more candidate gene studies or GWASs. Table 3b includes other variants in the same genes associated with increased LDL-C that have been identified in a single candidate gene study or GWAS because future studies may validate these associations. The presence of each variant is associated with small, but statistically significant, increases (effect size) in LDL-C levels and accounts for a small percentage of the variance in LDL-C levels. For an individual to have hyperlipidemia, he or she most likely carries multiple risk alleles that together result in increased LDL-C levels.

The G allele of the intronic SNP rs6511720 in the *LDLR* gene has been associated with hypercholesterolemia in Europeans/Caucasians (Kathiresan et al., 2009; Sabatti et al., 2009; Willer et al. 2008). This susceptibility allele is associated with slightly higher levels of LDL-C, 0.26 (0.04 SEM) mmol/L, and higher rates of CAD (OR = 1.29, 95% CI: 1.10–1.52) for each copy of the G allele (Sabatti et al., 2009; Willer et al., 2008). As previously discussed, *LDLR* encodes for LDLRs that bind to LDLs in the blood and take them into the liver, where they are degraded.

A variant in the *APOB* gene has been associated with hypercholesterolemia in Europeans/Caucasians. The association between the A allele of the synonymous SNP rs693 with hypercholesterolemia has been replicated in five GWASs, four involving Europeans/Caucasians and one involving a Japanese sample (Aulchenko et al., 2009; Kathiresan et al., 2008; Nakayama et al., 2009; Sabatti et al., 2009; Willer et al., 2008). Presence of the A allele is associated with an increase in levels of LDL-C of 0.123 (0.018 SEM) mmol/L and with an increase in risk for CAD (OR = 1.07, 95% CI: 1.00–1.14) for each copy of the risk allele (Sabatti et al., 2009; Willer et al., 2008). Although the SNP does not result in an amino acid change, in vivo turnover studies have shown that presence of the A allele does result in an increased LDL-C production rate compared to noncarriers (Benn, 2009).

The association between the functional intronic G allele at SNP rs3846662 in the *HMGCR* gene and elevated LDL-C levels has been replicated in GWASs of European/Caucasians, Japanese, and Micronesians (Burkhardt et al., 2008; Hiura et al., 2010; Kathiresan et al., 2008; Kathiresan et al., 2009). The intronic SNP is in LD ($r > 0.80$) with rs3846663 (the SNP reported in Kathiresan et al., 2009) and rs12654264 (the SNP reported in Kathiresan et al., 2008). It is located 47 bp downstream of exon 13 and is associated with the alternative splicing for exon 13 (Burkhardt et al., 2008). The allele is associated with a slight increase in LDL-C levels and with an increase in MI risk (OR = 1.15, 95% CI: 1.04–1.28) per copy of the susceptibility allele, after adjusting for age, sex, diabetes, hypertension, and smoking status (Hiura et al., 2010).

The G allele at SNP rs4420638 in the *APOE-CI-CII* gene cluster has been associated with elevated LDL-C levels of 0.29 (0.06 SEM) mmol/L per allele (Kathiresan et al., 2009). The SNP is located ~300 bp downstream from *APOCI*. The association between the risk allele and elevated LDL-C levels has been replicated in multiple GWASs with a European/Caucasian sample (Kathiresan et al., 2009; Sabatti et al., 2009; Waterworth et al., 2010; Willer et al., 2008). It is also associated with increased CAD risk (OR = 1.17, 95% CI: 1.08–1.28) per copy of the G allele (Willer et al., 2008). This SNP is in LD with rs7412 ($r^2 = 1$) and rs429358 ($r^2 = 0.62$), which are responsible for the $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$ alleles of the *APOE* gene (Bhatia, Davies, & McPherson, 2009; Ken-Dor, Talmud, Humphries, & Drenos, 2010). The $\epsilon 2/\epsilon 2$ genotype of the *APOE* gene results in β -VLDL from defective clearance of VLDL in some individuals, and the $\epsilon 3/\epsilon 4$ and $\epsilon 4/\epsilon 4$ genotypes are associated with elevated LDL-C levels (Kolovou et al., 2009; Mahley et al., 1999). Apo C (also known as apo CI) is present on the surface of VLDLs and HDLs (Table 1) and inhibits the binding of VLDLs to LDL-related proteins and apo E-mediated binding of VLDLs to LDLRs, resulting in reduced LDL-C levels (Ken-Dor et al., 2010). Apo C-II is an essential cofactor for LPL, which is the rate-limiting enzyme for the hydrolysis and removal of triglycerides in chylomicrons and VLDLs. It is not known if the intergenic SNP is affecting *APOCI*, *APOCII*, *APOE*, or another gene altogether through LD.

The association between the intergenic T allele at SNP rs11206510 near *PCSK9* and increased LDL-C has been replicated in three GWASs with European/Caucasian samples (Kathiresan et al., 2009; Waterworth et al., 2010; Willer et al., 2008). The susceptibility allele is associated with an LDL-C increase of 0.09 (0.02 SEM) mmol/L and an increase in CAD risk (OR = 1.13, 95% CI: 1.03–1.23) per copy of the T allele (Kathiresan et al., 2009;

Willer et al., 2008). As with FH, the SNP may enhance the expression of the PCSK9 protein, reducing the number of LDLRs, resulting in elevated LDL-C levels (Abifadel et al., 2009).

Alleles in the neurocan (*NCAN*)/cartilage intermediate layer protein (*CILP2*)/pre-B-cell leukemia transcription factor 4 (*PBX4*) region on chromosome 19 have been associated with slightly elevated LDL-C levels. Little is known about the function of the genes in this region. The *NCAN* gene is a nervous system—specific proteoglycan involved in neuronal pattern formation, remodeling of neuronal networks and regulation of synaptic plasticity (Nakayama et al., 2009). None of the genes have an obvious biological relation to LDL-C (Willer et al., 2008). The associations between the G allele at the intergenic SNP rs16996148 and the C allele at the intronic SNP rs10401969 with elevated LDL-C levels were replicated in two GWASs with a European/Caucasian sample (Kathiresan et al., 2009; Sabatti et al., 2009; Waterworth et al., 2010; Willer et al., 2008).

The A allele at the intergenic SNP rs17321515 in the tribbles homolog 1 (*TRIB1*) gene on chromosome 8 was associated with elevated LDL-C in two GWASs with Asian populations (Nakayama et al., 2009; Tai et al., 2009). However, Tai and colleagues (2009) found an association between the allele and total cholesterol and LDL-C levels, whereas Nakayama and colleagues (2009) found an association between the allele and TG and LDL-C levels. Tribble 1 is one of a family of proteins that act as secondary messengers in mitogen-activated protein kinases-related signaling cascades known to regulate vascular smooth-muscle cell proliferation and chemotaxis, which may play a role in atherosclerosis formation (Aulchenko et al., 2009; Kathiresan et al., 2009; Tai et al., 2009). The gene's role in cholesterol synthesis and metabolism is currently unclear.

Additional SNPs associated with elevated LDL-C levels are listed in Table 3b. These SNPs have been reported in a single candidate gene study or GWAS only. All but one of the SNPs in Table 3b occurs in genes already discussed in this section. The T allele of the intronic SNP rs6544713 in the adenosine triphosphate-cassette binding transporter G8 (*ABCG8*) gene has been associated with elevated LDL-C (Kathiresan et al., 2009; Table 3b). The susceptibility allele is associated with a LDL-C increase of 0.15 (0.02 SEM) per allele. *ABCG8* is a member of the adenosine triphosphate (ATP)-binding cassette (ABC) transporter family and is required for efficient secretion of cholesterol into bile. Disruption of these genes increases the responsiveness of plasma and hepatic cholesterol levels to changes in dietary cholesterol content (ATP-binding cassette, subfamily G, member 5, n.d.).

The associations we reviewed in this section serve as an example of the complex nature of the genomics of hyperlipidemia. None of the SNPs we mentioned are nonsynonymous, but most occur in or near genes that play a role in cholesterol synthesis or metabolism. This observation suggests that the true causal variants behind the biological mechanisms that increase an individual's LDL-C and their CHD susceptibility have yet to be discovered. As Manolio recently discussed (2010), only 12% of SNPs associated with traits are located in, or are in tight LD with, the protein-coding regions of genes. Approximately 40% of trait-associated SNPs are intergenic and another 40% are intronic. These findings highlight the potential roles of intronic and intergenic regions in gene expression. Also, the variants described in this section represent both allelic heterogeneity, different variants in the same

gene causing the same disorder, and genetic locus heterogeneity, variants in different genes causing the same disorder.

Overall, GWASs have revealed that 1) for almost any disease that has been studied, there are common SNPs, SNPs with a minor allele frequency of >5%, associated with the disease; 2) most of these variants are in genes that were previously not known to be functional in the pathway of disease or are not near a known protein-coding gene; 3) the effect sizes of associated SNPs are usually small; and 4) for any particular disease, the accumulated effects of many different SNPs associated with a disease usually explain only a small fraction of the familial risk or heritability (Visscher & Montgomery, 2009). These concepts are certainly true about the variants associated with increased LDL-C and CHD. Finally, it has been suggested that genes with common variants may also contain rare variants with large effects that cannot be found using GWASs (Manolio et al., 2009).

Nursing Implications

Should the findings of associations between the SNPs discussed above and elevated LDL-C levels and CHD lead to increased genetic testing for CHD? Genetic tests are generally evaluated based on three criteria: analytic validity, clinical utility, and clinical validity (Burke & Zimmern, 2004). Analytic validity is the accuracy with which a given laboratory test can identify a particular genetic characteristic, such as a SNP. Clinical utility describes the risks and benefits of test use. Finally, clinical validity is the accuracy with which a test identifies or predicts a patient's clinical status.

Another way to evaluate a genetic test is to examine it in the context of its ethical, legal, and social implications (ELSI). Burke, Pinsky, and Press (2001) developed a two-by-two table to categorize a genetic test based on its clinical validity, high or low, and the presence or absence of effective treatment for the condition or disease the test is designed to detect (Table 4). A genetic test can fit into one of four categories: high clinical validity with effective treatment available, high clinical validity without effective treatment available, low clinical validity with effective treatment available, and low clinical validity without effective treatment available.

For a genetic test with high clinical validity and effective treatment available, the primary ELSI concern is ensuring that eligible individuals are tested and have access to treatment (Burke et al., 2001). When a genetic test has high clinical validity but effective treatment is unavailable, geneticists, genetic counselors, and nurses involved in genetics are most concerned with providing adequate nondirective counseling to ensure an informed, autonomous decision. If a genetic test has low clinical validity but effective treatment is available (which is the case for genetic testing for CHD), there are many factors, including the nature of the condition, its potential for stigma, and the nature and effectiveness of the treatment, that need to be examined to balance the potential for adverse effects of labeling against that for improved health outcomes. Despite the low predictive value, testing may be acceptable when the label carries little emotional weight. Finally, when a genetic test has low clinical validity and no effective treatment is available, testing is difficult to justify.

Currently, the clinical validity of genetic tests for CHD is low due to the complex nature of the disease, the multitude of variants in different genes, the clinically small effect sizes of each variant, and the interaction between the genetic variants and the environment. Additionally, the results of the genetic tests for CHD have the potential to result in false reassurance or a sense of hopelessness or lack of personal control (McPherson, 2006). Nonetheless, nurses should know how to respond to patients when they ask about genetic tests for CHD and should focus on available biomarkers (LDL-C, apo B) and family history for determining CHD risk. Nurses should also be prepared to provide counseling regarding lifestyle changes and possibly medications to reduce CHD risk. For example, exercise, dietary changes, and specific medications such as the statin drugs, as well as smoking cessation, have been shown to reduce the risk for developing CHD (Adult Treatment Panel III, 2002; Delaney et al., 2007; Schaefer, 2002; Toborek, Lee, Garrido, Kaiser, & Hennig, 2002).

However, with new advances in genomics, individualized risk stratification and targeted therapy may become feasible (Kullo & Cooper, 2010). By using a multimarker approach, in which an individual is assessed with a panel of genetic or genomic tests and specific biomarkers, it may become possible to identify exactly which physiological pathway, or pathways, are altered to result in atherosclerosis and increased CHD risk. In the future, this approach may allow for development of the best preventative and therapeutic interventions for each individual and take us one step closer the personalized medicine promised by the genomic era. Future studies examining biomarkers, environment factors, and whole genome sequencing will continue to advance our knowledge and our ability to apply that knowledge to prevent or reduce CHD in the future.

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References

- Abifadel M, Rabes JP, Devillers M, Munnich A, Erlich D, Junien C, Boileau C. Mutations and polymorphisms in the proprotein convertase subtilisin kexin 9 (PCSK9) gene in cholesterol metabolism and disease. *Human Mutation*. 2009; 30(4):520–529.10.1002/humu.20882 [PubMed: 19191301]
- Adult Treatment Panel III. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults final report. *Circulation*. 2002; 106(25):3143–3421. Retrieved from <http://circ.ahajournals.org/cgi/content/full/106/25/3143>. [PubMed: 12485966]
- APOA5—apolipoprotein A-V. n.d. Retrieved from the U. S. National Library of Medicine's Genetics Home Reference website at <http://ghr.nlm.nih.gov/gene/APOA5>
- ATP-binding cassette, subfamily G, member 5. n.d Retrieved from Online Mendelian Inheritance in Man at <http://omim.org/entry/605459>
- Aulchenko YS, Ripatti S, Lindqvist I, Boomsma D, Heid IM, Pramstaller PP, Peltonen L. Loci influencing lipid levels and coronary heart disease risk in 16 European population cohorts. *Nature Genetics*. 2009; 41(1):47–55.10.1038/ng.269 [PubMed: 19060911]
- Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia: A HuGE prevalence review. *American Journal of Epidemiology*. 2004; 160(5):407–420.10.1093/aje/kwh23610.1093/aje/kwh236 [PubMed: 15321837]

- Austin MA, McKnight B, Edwards KL, Bradley CM, McNeely MJ, Psaty BM, Motulsky AG. Cardiovascular disease mortality in familial forms of hypertriglyceridemia: A 20-year prospective study. *Circulation*. 2000; 101(24):2777–2782.10.1161/01.CIR.101.24.2777 [PubMed: 10859281]
- Benn M. Apolipoprotein B levels, APOB alleles, and risk of ischemic cardiovascular disease in the general population, a review. *Atherosclerosis*. 2009; 206(1):17–30.10.1016/j.atherosclerosis.2009.01.004 [PubMed: 19200547]
- Benn M, Nordestgaard BG, Jensen GB, Tybjaerg-Hansen A. Improving prediction of ischemic cardiovascular disease in the general population using apolipoprotein B. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2007; 27(3):661–670.10.1161/01.ATV.0000255580.73689.8e
- Bennet A, Di Angelantonio E, Erqou S, Eiriksdottir G, Sigurdsson G, Woodward M, Gudnason V. Lipoprotein(a) levels and risk of future coronary heart disease: Large-scale prospective data. *Archives of Internal Medicine*. 2008; 168(6):598–608.10.1001/archinte.168.6.598 [PubMed: 18362252]
- Berenson GS, Srinivasan SR, Bao W, Newman WP 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. *New England Journal of Medicine*. 1998; 338(23):1650–1656. [PubMed: 9614255]
- Bhatia, SS.; Davies, RW.; McPherson, R. Relationship of rs4420638 in the APOE/C1/C4/C2 locus to coronary artery disease; Paper presented at the 59th Annual Meeting of the American Society of Human Genetics; Honolulu, HI. 2009. Abstract retrieved from <http://www.ashg.org/2009meeting/abstracts/fulltext/f10745.htm>
- Burke W, Pinsky LE, Press NA. Categorizing genetic tests to identify their ethical, legal, and social implications. *American Journal of Medical Genetics*. 2001; 106(3):233–240.10.1002/ajmg.10011 [PubMed: 11778984]
- Burke W, Zimmern RL. Ensuring the appropriate use of genetic tests. *Nature Reviews Genetics*. 2004; 5(12):955–959.10.1038/nrg1495
- Burkhardt R, Kenny EE, Lowe JK, Birkeland A, Josowitz R, Noel M, Breslow JL. Common SNPs in HMGCR in Micronesians and Whites associated with LDL-cholesterol levels affect alternative splicing of exon13. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2008; 28(11):2078–2084.10.1161/ATVBAHA.108.172288
- Centers for Disease Control and Prevention, Office of Genetics and Disease Prevention. Gene-environment interaction fact sheet, August 2000. Atlanta, GA: Author; 2000. Retrieved from <http://www.ashg.org/pdf/CDC%20Gene-Environment%20Interaction%20Fact%20Sheet.pdf>
- Chien KL, Hsu HC, Su TC, Chen MF, Lee YT, Hu FB. Apolipoprotein B and non-high density lipoprotein cholesterol and the risk of coronary heart disease in Chinese. *Journal of Lipid Research*. 2007; 48(11):2499–2505.10.1194/jlr.M700213-JLR200 [PubMed: 17698856]
- Contois JH, McConnell JP, Sethi AA, Csako G, Devaraj S, Hoefner DM, Warnick GR. Apolipoprotein B and cardiovascular disease risk: Position statement from the AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices. *Clinical Chemistry*. 2009; 55(3):407–419.10.1373/clinchem.2008.118356 [PubMed: 19168552]
- Defesche JC, Schuurman EJ, Klaaijsen LN, Khoo KL, Wiegman A, Stalenhoef AF. Silent exonic mutations in the low-density lipoprotein receptor gene that cause familial hypercholesterolemia by affecting mRNA splicing. *Clinical Genetics*. 2008; 73(6):573–578.10.1111/j.1399-0004.2008.00999.x [PubMed: 18400033]
- Delaney JA, Daskalopoulou SS, Brophy JM, Steele RJ, Opatrny L, Suissa S. Lifestyle variables and the risk of myocardial infarction in the general practice research database. *BMC Cardiovascular Disorders*. 2007; 7:38.10.1186/1471-2261-7-38 [PubMed: 18088433]
- Dreon DM, Fernstrom HA, Miller B, Krauss RM. Low-density lipoprotein subclass patterns and lipoprotein response to a reduced-fat diet in men. *FASEB Journal*. 1994; 8(1):121–126. Retrieved from <http://www.fasebj.org/content/8/1/121.long>. [PubMed: 8299884]
- Genest J. Lipoprotein disorders and cardiovascular risk. *Journal of Inherited Metabolic Disease*. 2003; 26(2-3):267–287.10.1023/A:1024449603891 [PubMed: 12889666]
- Goldstein JL, Brown MS. History of discovery: The LDL receptor. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2009; 29(4):431–438.10.1161/ATVBAHA.108.179564

- Grundey, SM. Cholesterol and atherosclerosis: Diagnosis and treatment. Philadelphia: J. B. Lippincott Company; 1990.
- Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: A randomised placebo-controlled trial. *Lancet*. 2002; 360(9326):7–22.10.1016/S0140-6736(02)09327-3 [PubMed: 12114036]
- Hegele RA. Plasma lipoproteins: Genetic influences and clinical implications. *Nature Reviews Genetics*. 2009; 10(2):109–121.10.1038/nrg2481
- Hindorf, LA.; MacArthur, J.; European Bioinformatics Institute. Wise, A.; Junkins, HA.; Hall, PN.; Klemm, AK.; Manolio, TA. A catalog of published genome-wide association studies. n.d.Retrieved from the National Human Genome Research Institute website at <http://www.genome.gov/gwastudies>
- Hiura Y, Tabara Y, Kokubo Y, Okamura T, Goto Y, Nonogi H, Iwai N. Association of the functional variant in the 3-hydroxy-3-methylglutaryl-coenzyme a reductase gene with low-density lipoprotein-cholesterol in Japanese. *Circulation Journal*. 2010; 74(3):518–522.10.1253/circj.CJ-09-0790 [PubMed: 20145341]
- Holman RL. Atherosclerosis--a pediatric nutrition problem? *American Journal of Clinical Nutrition*. 1961; 9(5):565–569. [PubMed: 13715441]
- Holme I, Hostmark AT, Anderson SA. ApoB but not LDL-cholesterol is reduced by exercise training in overweight healthy men. Results from the 1-year randomized Oslo Diet and Exercise Study. *Journal of Internal Medicine*. 2007; 262(2):235–243.10.1111/j.1365-2796.2007.01806.x [PubMed: 17645591]
- Hyperlipidemia, Familial Combined. n.d. Retrieved from Online Mendelian Inheritance in Man at <http://omim.org/entry/144250>
- Inull W Jr. The pathology of atherosclerosis: Plaque development and plaque responses to medical treatment. *American Journal of Medicine*. 2009; 122(1 Suppl):S3–S14.10.1016/j.amjmed.2008.10.013 [PubMed: 19110086]
- Kathiresan S, Melander O, Anevski D, Guiducci C, Burt NP, Roos C, Orho-Melander M. Polymorphisms associated with cholesterol and risk of cardiovascular events. *New England Journal of Medicine*. 2008; 358(12):1240–1249.10.1056/NEJMoa0706728 [PubMed: 18354102]
- Kathiresan S, Willer CJ, Peloso GM, Demissie S, Musunuru K, Schadt EE, Cupples LA. Common variants at 30 loci contribute to polygenic dyslipidemia. *Nature Genetics*. 2009; 41(1):56–65.10.1038/ng.291 [PubMed: 19060906]
- Ken-Dror G, Talmud PJ, Humphries SE, Drenos F. APOE/C1/C4/C2 gene cluster genotypes, haplotypes and lipid levels in prospective coronary heart disease risk among UK healthy men. *Molecular Medicine*. 2010; 16(9-10):389–399.10.2119/molmed.2010.00044 [PubMed: 20498921]
- Kolovou GD, Anagnostopoulou KK, Kostakou PM, Biliou H, Mikhailidis DP. Primary and secondary hypertriglyceridaemia. *Current Drug Targets*. 2009; 10(4):336–343. [PubMed: 19355858]
- Kullo IJ, Cooper LT. Early identification of cardiovascular risk using genomics and proteomics. *Nature Reviews Cardiology*. 2010; 7(6):309–317.10.1038/nrcardio.2010.53
- Lawson C, Wolf S. ICAM-1 signaling in endothelial cells. *Pharmacological Reports*. 2009; 61(1):22–32. Retrieved from http://www.if-pan.krakow.pl/pjp/pdf/2009/1_22.pdf. [PubMed: 19307690]
- LDLRAP1—low density lipoprotein receptor adaptor protein 1. n.d. Retrieved from the U. S. National Library of Medicine's Genetics Home Reference website at <http://ghr.nlm.nih.gov/gene/LDLRAP1>
- Leigh SE, Foster AH, Whittall RA, Hubbart CS, Humphries SE. Update and analysis of the University College London low density lipoprotein receptor familial hypercholesterolemia database. *Annals of Human Genetics*. 2008; 72(Pt 4):485–498.10.1111/j.1469-1809.2008.00436.x [PubMed: 18325082]
- Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Wylie-Rosett J. Heart disease and stroke statistics--2010 update: A report from the American Heart Association. *Circulation*. 2010; 121(7):e46–e215.10.1161/CIRCULATIONAHA.109.192667 [PubMed: 20019324]
- Lusis AJ, Pajukanta P. A treasure trove for lipoprotein biology. *Nature Genetics*. 2008; 40(2):129–130.10.1038/ng0208-129 [PubMed: 18227868]

- Maeda S, Abe A, Seishima M, Makino K, Noma A, Kawade M. Transient changes of serum lipoprotein(a) as an acute phase protein. *Atherosclerosis*. 1989; 78(2-3) Retrieved from <http://www.atherosclerosis-journal.com/article/0021-9150%2889%2990218-9/abstract>.
- Mahley RW, Huang Y, Rall SC Jr. Pathogenesis of type III hyperlipoproteinemia (dysbetalipoproteinemia). Questions, quandaries, and paradoxes. *Journal of Lipid Research*. 1999; 40(11):1933–1949. Retrieved from <http://www.jlr.org/content/40/11/1933.long>. [PubMed: 10552997]
- Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorff LA, Hunter DJ, Visscher PM. Finding the missing heritability of complex diseases. *Nature*. 2009; 461(7265):747–753.10.1038/nature08494 [PubMed: 19812666]
- Manolio TA. Genomewide association studies and assessment of the risk of disease. *New England Journal of Medicine*. 2010; 363(2):166–176.10.1056/NEJMra0905980 [PubMed: 20647212]
- Marcovina SM, Koschinsky ML. Lipoprotein(a) as a risk factor for coronary artery disease. *American Journal of Cardiology*. 1998; 82(12A):57U–66U. discussion 86U. 10.1016/S0002-9149(98)00954-0
- Matthan NR, Welty FK, Barrett HR, Harausz C, Dolnikowski GG, Parks JS, Lichtenstein AH. Dietary hydrogenated fat increase high-density lipoprotein apoA-I catabolism and decreases low-density lipoprotein apoB-100 catabolism in hypercholesterolemic women. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2004; 24(6):1092–1097.10.1161/01.ATV.0000128410.23161.be
- McCormick SP. Lipoprotein(a): Biology and clinical importance. *Clinical Biochemist: Reviews*. 2004; 25(1):69–80. Retrieved from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1853362/>.
- McGill HC Jr, McMahan CA, Gidding SS. Preventing heart disease in the 21st century: Implications of the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study. *Circulation*. 2008; 117(9):1216–1227.10.1161/CIRCULATIONAHA.107.717033 [PubMed: 18316498]
- McPherson E. Genetic diagnosis and testing in clinical practice. *Clinical Medicine & Research*. 2006; 4(2):123–129.10.3121/cmr.4.2.123 [PubMed: 16809405]
- Nakamura H, Arakawa K, Itakura H, Kitabatake A, Goto Y, Toyota T, Ohashi Y. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): A prospective randomised controlled trial. *Lancet*. 2006; 368(9542):1155–1163.10.1016/S0140-6736(06)69472-5 [PubMed: 17011942]
- Nakayama K, Bayasgalan T, Yamanaka K, Kumada M, Gotoh T, Utsumi N, Iwamoto S. Large scale replication analysis of loci associated with lipid concentrations in a Japanese population. *Journal of Medical Genetics*. 2009; 46(6):370–374.10.1136/jmg.2008.064063 [PubMed: 19487539]
- Natarajan P, Ray KK, Cannon CP. High-density lipoprotein and coronary heart disease. *Journal of the American College of Cardiology*. 2010; 55(13):1283–1299.10.1016/j.jacc.2010.01.008 [PubMed: 20338488]
- National Center for Biotechnology Information. Coronary heart disease. 2010. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0004449/>
- National Center for Biotechnology Information. n.d. Submission and assignment of submitted SNP(ss)/refSNP(rs) numbers. Retrieved from <http://www.ncbi.nlm.nih.gov/books/NBK44391/>
- Naukkarinen J, Ehnholm C, Peltonen L. Genetics of familial combined hyperlipidemia. *Current Opinion in Lipidology*. 2006; 17(3):285–290.10.1097/01.mol.0000226121.27931.3f [PubMed: 16680034]
- Nordestgaard BG, Chapman MJ, Ray K, Boren J, Andreotti F, Watts GF, Tybjaerg-Hansen A. Lipoprotein(a) as a cardiovascular risk factor: Current status. *European Heart Journal*. 2010; 31(23):2844–2853.10.1093/eurheartj/ehq386 [PubMed: 20965889]
- Pearson TA, Manolio TA. How to interpret a genome-wide association study. *JAMA*. 2008; 299(11):1335–1344.10.1001/jama.299.11.1335 [PubMed: 18349094]
- Pekkanen J, Linn S, Heiss G, Suchindran CM, Leon A, Rifkind BM, Tryolier HA. Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. *New England Journal of Medicine*. 1990; 322(24):1700–1707. Retrieved from <http://www.nejm.org/doi/full/10.1056/NEJM199006143222403>. [PubMed: 2342536]

- Pisciotta L, Priore Oliva C, Pes GM, Di Scala L, Bellocchio A, Fresa R, Bertolini S. Autosomal recessive hypercholesterolemia (ARH) and homozygous familial hypercholesterolemia (FH): A phenotypic comparison. *Atherosclerosis*. 2006; 188(2):398–405.10.1016/j.atherosclerosis.2005.11.016 [PubMed: 16343504]
- Plaisier CL, Horvath S, Huertas-Vazquez A, Cruz-Bautista I, Herrera MF, Tusie-Luna T, Pajukanta P. A systems genetics approach implicates USF1, FADS3, and other causal candidate genes for familial combined hyperlipidemia. *PLoS Genetics*. 2009; 5(9):e1000642.10.1371/journal.pgen.1000642 [PubMed: 19750004]
- Reich DE, Lander ES. On the allelic spectrum of human disease. *Trends in Genetics*. 2001; 17(9):502–510.10.1016/S0168-9525(01)02410-6 [PubMed: 11525833]
- Ridker PM, Rifai N, Cook NR, Bradwin G, Buring JE. Non-HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. *JAMA*. 2005; 294(3):326–333.10.1001/jama.294.3.326 [PubMed: 16030277]
- Russo, CA.; Andrews, RM. The national hospital bill: The most expensive conditions, by payer, 2004. Rockville, MD: Agency for Healthcare Research and Quality; 2006 Sep. HCUP Statistical Brief no. 13Retrieved from <http://www.hcup-us.ahrq.gov/reports/statbriefs/sb13.pdf>
- Sabatti C, Service SK, Hartikainen AL, Pouta A, Ripatti S, Brodsky J, Peltonen L. Genome-wide association analysis of metabolic traits in a birth cohort from a founder population. *Nature Genetics*. 2009; 41(1):35–46.10.1038/ng.271 [PubMed: 19060910]
- Sáez ME, González-Pérez A, Martínez-Larrad MT, Gayán J, Real LM, Serrano-Ríos M, Ruiz A. WWOX gene is associated with HDL cholesterol and triglyceride levels. *BMC Medical Genetics*. 2010; 11:148.10.1186/1471-2350-11-148 [PubMed: 20942981]
- Schaefer EJ. Lipoproteins, nutrition, and heart disease. *American Journal of Clinical Nutrition*. 2002; 75(2):191–212. Retrieved from <http://www.ajcn.org/content/75/2/191.full>. [PubMed: 11815309]
- Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994; 344(8934):1383–1389.10.1016/S0140-6736(94)90566-5 [PubMed: 7968073]
- Seal N. Introduction to genetics and childhood obesity: Relevance to nursing practice. *Biological Research for Nursing*. 2011; 13(1):61–69.10.1177/1099800410381424 [PubMed: 20798151]
- Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, Ostergren J. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): A multicentre randomised controlled trial. *Lancet*. 2003; 361(9364):1149–1158.10.1016/S0140-6736(03)12948-0 [PubMed: 12686036]
- Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Westendorp RG. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): A randomised controlled trial. *Lancet*. 2002; 360(9346):1623–1630.10.1016/S0140-6736(02)11600-X [PubMed: 12457784]
- Shoulders CC, Jones EL, Naoumova RP. Genetics of familial combined hyperlipidemia and risk of coronary heart disease. *Human Molecular Genetics*. 2004; 13(suppl. 1):R149–160.10.1093/hmg/ddh069 [PubMed: 14764618]
- Slatkin M. Linkage disequilibrium--understanding the evolutionary past and mapping the medical future. *Nature Reviews Genetics*. 2008; 9(6):477–485.10.1038/nrg2361
- Stamler J, Stamler R, Neaton JD, Wentworth D, Daviglus ML, Garside D, Greenland P. Low risk-factor profile and long-term cardiovascular and noncardiovascular mortality and life expectancy: Findings for 5 large cohorts of young adult and middle-aged men and women. *JAMA*. 1999; 282(21):2012–2018.10.1001/jama.282.21.2012 [PubMed: 10591383]
- St-Pierre AC, Cantin B, Dagenais GR, Despres JP, Lamarche B. Apolipoprotein-B, low-density lipoprotein cholesterol, and the long-term risk of coronary heart disease in men. *American Journal of Cardiology*. 2006; 97(7):997–1001.10.1016/j.amjcard.2005.10.060 [PubMed: 16563904]
- Surmi BK, Hasty AH. The role of chemokines in recruitment of immune cells to the artery wall and adipose tissue. *Vascular Pharmacology*. 2010; 52(1-2):27–36.10.1016/j.vph.2009.12.004 [PubMed: 20026286]
- Tabor HK, Risch NJ, Myers RM. Candidate-gene approaches for studying complex genetic traits: Practical considerations. *Nature Reviews Genetics*. 2002; 3(5):391–397.10.1038/nrg796

- Tai ES, Sim XL, Ong TH, Wong TY, Saw SM, Aung T, Seielstad M. Polymorphisms at newly identified lipid-associated loci are associated with blood lipids and cardiovascular disease in an Asian Malay population. *Journal of Lipid Research*. 2009; 50(3):514–520.10.1194/jlr.M800456-JLR200 [PubMed: 18987386]
- Toborek M, Lee YW, Garrido R, Kaiser S, Hennig B. Unsaturated fatty acids selectively induce an inflammatory environment in human endothelial cells. *American Journal of Clinical Nutrition*. 2002; 75(1):119–125. Retrieved from <http://www.ajcn.org/content/75/1/119.full>. [PubMed: 11756069]
- U. S. Department of Energy. Human genome project information. 2008. SNP fact sheet. Retrieved from http://www.ornl.gov/sci/techresources/Human_Genome/faq/snps.shtml
- Visser PM, Montgomery GW. Genome-wide association studies and human disease: From trickle to flood. *JAMA*. 2009; 302(18):2028–2029.10.1001/jama.2009.1643 [PubMed: 19903925]
- Volpato S, Vigna GB, McDermott MM, Cavalieri M, Maraldi C, Lauretani F, Ferrucci L. Lipoprotein(a), inflammation, and peripheral arterial disease in a community-based sample of older men and women (the InCHIANTI study). *American Journal of Cardiology*. 2010; 105(12):1825–1830.10.1016/j.amjcard.2010.01.370 [PubMed: 20538138]
- Waterworth DM, Ricketts SL, Song K, Chen L, Zhao JH, Ripatti S, Sandhu MS. Genetic variants influencing circulating lipid levels and risk of coronary artery disease. *Arteriosclerosis, Thrombosis, Vascular Biology*. 2010; 30(11):2264–2276.10.1161/ATVBAHA.109.201020
- Willer CJ, Sanna S, Jackson AU, Scuteri A, Bonnycastle LL, Clarke R, Abecasis GR. Newly identified loci that influence lipid concentrations and risk of coronary artery disease. *Nature Genetics*. 2008; 40(2):161–169.10.1038/ng.76 [PubMed: 18193043]
- Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998; 97(18):1837–1847. Retrieved from <http://circ.ahajournals.org/cgi/content/full/97/18/1837>. [PubMed: 9603539]
- Wong ND, Wilson PW, Kannel WB. Serum cholesterol as a prognostic factor after myocardial infarction: The Framingham Study. *Annals of Internal Medicine*. 1991; 115(9):687–693. [PubMed: 1929036]

Table 1

Characteristics of Classes of Lipoproteins

Class	Function	Location of Synthesis	Composition of Core	Apos Present on Surface	Diameter of Particles	Density
Chylomicron	Transportation of dietary cholesterol from the intestines to the liver	Intestinal mucosal cells	TG from dietary fat	apo A-I, apo A-V, apo A-IV, apo B-48, apo C-II, apo C-III, apo E	1000–4000 Å	~ 0.98 g/ml
Very-low-density lipoprotein (VLDL)	Transports TGs, phospholipids, cholesterol, and cholesterol esters	Liver	Primarily TG with a small amount of cholesterol	apo B (primary), apo A-V, apo C, apo C-II, apo C-III, apo E	400–700 Å	~ 1.006 g/ml
Low-density lipoprotein (LDL)	Primary cholesterol-carrying lipoprotein	Derived from VLDL in the circulation	Lipid core containing approximately 1500 cholesterol esters	A single apo B protein	225–275 Å	~ 1.019–1.063 g/ml
High-density lipoprotein (HDL)	Reverse cholesterol transport	Liver, intestine	Primarily cholesterol esters	apo A-I, apo A-II, apo A-V, apo C, apo E	75–100 Å	~ 1.063–1.21 g/ml
Lipoprotein(a)	Unknown; plays a role in acute inflammation and may have antifibrinolytic properties	Extracellular	Lipid core containing cholesterol esters	Single apo B and apo(a) proteins	Varies depending on apo(a) isoform	Varies depending on apo(a) isoform

Note. Apos = apolipoproteins; TG = triglyceride.

Table 2
Characteristic of Familial Forms of Hyperlipidemia

Hyperlipidemia Form	Frequency	Clinical Signs and Symptoms	Clinical Significance	Genetic Cause(s)
Familial hypercholesterolemia (FH) ^a				
Low-density lipoprotein receptor (<i>LDLR</i>)	Heterozygous FH	<ul style="list-style-type: none"> Heterozygous FH, LDL-C levels are > 300 mg/dL (7.78 mmol/L; Grundy, 1990) Homozygous FH, LDL-C levels in the range 700–1,000 mg/dL (18.3–25.9 mmol/L; Grundy, 1990) Xanthomata (Austin et al., 2004; Goldstein & Brown, 2009) 	Higher risk for early CAD (Austin et al., 2004; Goldstein & Brown, 2009)	Over 1100 unique deleterious variants in the <i>LDLR</i> gene (Leigh et al., 2008)
	<ul style="list-style-type: none"> 0.1–0.2% in Caucasian and Asian populations May be as high as 1.5% in Afrikaners, Ashkenazi Jews, and Christian Lebanese (Austin et al., 2004) 			
	Heterozygous FH	<ul style="list-style-type: none"> Rare, affecting about 1 in a million individuals (Austin et al., 2004; Goldstein & Brown, 2009) 		
Apolipoprotein B (<i>APOB</i>); also known as familial defective apolipoprotein B (FDB)	0.14–0.41% in several North American and European populations (Austin et al., 2004)	<ul style="list-style-type: none"> Increases in total cholesterol, LDL-C, and apo B levels (Benn, 2009) 	Higher risk for early CAD (Benn, 2009)	<ul style="list-style-type: none"> Caused by R3500Q variant (Benn, 2009) Mutation causes poor ligand binding to LDLRs resulting in less uptake (Austin et al., 2004; Benn, 2009)
Proprotein convertase subtilisin/kexin type 9 (<i>PCSK9</i>) also known as autosomal dominant hypercholesterolemia (ADH)	Exact frequency still unknown; found in American, French, German, Italian, New Zealand, Norwegian, and South African families with elevated LDL-C levels (Abifadel et al., 2009)	<ul style="list-style-type: none"> LDL-C levels 200–500 mg/dL (5.2–13 mmol/L) Tendon xanthomas (Abifadel et al., 2009) 	Increased risk for early CAD (Abifadel et al., 2009)	<ul style="list-style-type: none"> Several mutations result in a “gain-of-function” (Abifadel et al., 2009) Enhanced activity of protein reduces the number of LDLRs (Abifadel et al., 2009)
Low-density lipoprotein receptor adaptor protein 1 (<i>LDLRAP1</i>) also known as autosomal recessive hypercholesterolemia (ARH)	Extremely rare; known frequency is 0.003% on Sardinia (Pisciotta et al., 2006)	<ul style="list-style-type: none"> LDL-C levels 500–700 mg/dL (13–18.3 mmol/L) (<i>LDLRAP1</i>, n.d.) Tendon xanthomas (Pisciotta et al., 2006) 	Higher CAD risk (Pisciotta et al., 2006)	<ul style="list-style-type: none"> More than 10 mutations lead to the production of an abnormally small, nonfunctional version of protein LDLRs are unable to effectively remove LDL particles from the circulation (<i>LDLRAP1</i>, n.d.)
Familial hypertriglyceridemia (FHTG)	Approximately 1% (Genest, 2003)	<ul style="list-style-type: none"> Fasting plasma concentrations of TGs of 200–500 mg/dL (2.3–5.7 	Higher CAD risk (Austin et al., 2000)	<ul style="list-style-type: none"> Inherited in an autosomal-dominant fashion

Hyperlipidemia Form	Frequency	Clinical Signs and Symptoms	Clinical Significance	Genetic Cause(s)
		<ul style="list-style-type: none"> mmol/L) (Genest, 2003) After a meal, TGs may exceed 1000 mg/dL (11.3 mmol/L) (Genest, 2003) Total cholesterol is normal or slightly elevated, typically < 240 mg/dL (6.2 mmol/L; Genest, 2003; Kolovou et al., 2009) Often not expressed in childhood and can remain asymptomatic until other factors, such as moderate-to-excessive alcohol consumption, obesity, type II diabetes, or hypothyroidism, are present (Kolovou et al., 2009) 		<ul style="list-style-type: none"> Apolipoprotein A-V (APOA5) (Kolovou et al., 2009) <ul style="list-style-type: none"> Apo A-V is an important determinant of TG levels by both being a potent stimulator of LPL and an inhibitor of the hepatic TG and VLDL production The variant(s) in the APOA5 gene results in an overproduction of VLDL and decreased VLDL uptake, resulting in elevated TG and VLDL (APOA5-apolipoprotein A-V, n.d.)
Familial combined hyperlipidemia (FCHL)	1–2% in Western populations (Genest, 2003; Shoulders et al., 2004)	<ul style="list-style-type: none"> Families with FCHL have multiple patterns of hyperlipidemia including hypercholesterolemia, hypertriglyceridemia, and elevated apo B levels (Grundy, 1990; Kolovou et al., 2009) Individuals with FCHL usually have elevated serum cholesterol and/or TG levels, elevated apo B levels, and increased numbers of small, dense LDL particles (Austin et al., 2000; Shoulders et al., 2004) 	<ul style="list-style-type: none"> Increased risk for early CAD (Genest, 2003; Shoulders et al., 2004) Increased CVD mortality (Austin et al., 2000) 	<p>Debate exists over whether FCHL is truly a monogenetic disorder or if it is polygenic. Studies have suggested linkage between FCHL and multiple genes:</p> <ul style="list-style-type: none"> Tumor necrosis factor receptor 1B (<i>TNFRSF1B</i>; Naukkarinen et al., 2006; Hyperlipidemia, Familial Combined, n.d.) Apolipoprotein A-II (<i>APOA2</i>; Hyperlipidemia, Familial Combined, n.d.) Upstream stimulatory factor-1 (<i>USF1</i>; Naukkarinen et al., 2006; Plaisier et al., 2009) Superoxide dismutase 2, mitochondrial (<i>SOD2</i>; Hyperlipidemia, Familial Combined, n.d.) Lipoprotein lipase (<i>LPL</i>; Naukkarinen et al., 2006) Apolipoprotein A1/C-III/A-IV/A-V (<i>APOA1/C3/A4/A5</i>) genomic region (Naukkarinen et al., 2006; Hyperlipidemia, Familial Combined, n.d.) Fatty acid desaturaselocus (<i>FAD</i>) locus (Plaisier et al., 2009) Cholesteryl ester transfer protein (<i>CETP</i>)/Lecithin-cholesterol acyltransferase (<i>LCAT</i>) region

Hyperlipidemia Form	Frequency	Clinical Signs and Symptoms	Clinical Significance	Genetic Cause(s)
				(Naukkarinen et al., 2006; Hyperlipidemia, Familial Combined, n.d.)
				<ul style="list-style-type: none"> Winged helix/forkhead transcription factor (<i>FOXC2</i>; Shoulders et al., 2004; Hyperlipidemia, Familial Combined, n.d.) WW-domain-containing oxidoreductase (<i>WWOX</i>; Sáez et al., 2010) Peroxisome proliferators-activated receptor α (<i>PPARA</i>; Naukkarinen et al., 2006)
Familial dysbetalipoproteinemia (Type III dyslipidemia)	1% of the general population is apo E ϵ 2 homozygous; < 10% of apo E ϵ 2 homozygotes develop hyperlipidemia (Kolovou et al., 2009)	<ul style="list-style-type: none"> Elevated cholesterol, 300–1000 mg/dL (7.8–25.9 mmol/L) Elevated TG, 300–1000 mg/dL (3.4–11.3 mmol/L) Reduced HDL level The presence of β-VLDL (cholesterol-enriched VLDL remnants; Kolovou et al., 2009; Mahley et al., 1999) 	Premature development of atherosclerosis; increased CAD risk (Kolovou et al., 2009; Mahley et al., 1999)	<ul style="list-style-type: none"> Autosomal recessive disorder Apolipoprotein E (<i>APOE</i>) <ul style="list-style-type: none"> β-VLDLs are the result of defective clearance of VLDLs due to the ϵ2/ϵ2 genotype of the <i>APOE</i> gene (Kolovou et al., 2009; Mahley et al., 1999) Additional genetic, hormonal, or environmental factors, such as obesity, diabetes mellitus, hypothyroidism, or estrogen status, are required (Kolovou et al., 2009; Mahley et al., 1999)

Note. apo B = apolipoprotein B; CAD = coronary heart disease; CVD = cardiovascular disease; HDL = high-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; LDLR = low-density lipoprotein receptor; LPL = lipoprotein lipase; TG = triglyceride; VLDL = very-low-density lipoprotein.

^aFH is divided in subcategories based on genetic cause.

Table 3a
Variants Associated with Elevated Low-Density Lipoprotein Cholesterol (LDL-C) Levels Based on Two or More Candidate Gene Studies or Genome-wide Association Studies

Gene Name	SNP rs #	Chromosome Location	Susceptibility Allele	SNP Type	Frequency of Susceptibility Allele per Population	Effect Size for Susceptibility Allele (SEM) ^a	References
Low-density lipoprotein receptor (<i>LDLR</i>)	rs6511720	19p13.2	G	Intronic	0.90 in European/Caucasians	0.26 (0.04) mmol/L	Kathiresan et al., 2009; Sabatti et al., 2009; Willer et al., 2008
Apolipoprotein B (<i>APOB</i>)	rs693	2p24.1	A	Coding-synonymous	0.48 in European/Caucasians 0.04 in Japanese	0.123 (0.018) mmol/L N/A	Aulchenko et al., 2009; Kathiresan et al., 2008; Sabatti et al., 2009; Nakayama et al., 2009; Willer et al., 2008
3-hydroxy 3-methylglutaryl coenzyme A reductase (<i>HMGCR</i>)	rs3846662	5q13.3	G	Intronic	0.39 in European/Caucasians 0.52 in Japanese ~0.40 in Micronesians	0.07 (0.02) mmol/L N/A N/A	Burkhardt et al., 2008; Hiura et al., 2010; Kathiresan et al., 2008; Kathiresan et al., 2009
Apolipoprotein E – apolipoprotein C – apolipoprotein CII (<i>APOE-C1-CII</i>) cluster	rs4420638	19q13.2	G	Intergenic (~300 bp downstream from <i>APOC1</i>)	0.20 in European/Caucasians	0.29 (0.06) mmol/L	Kathiresan et al., 2008; Kathiresan et al., 2009; Sabatti et al., 2009; Waterworth et al., 2010; Willer et al., 2008
Proprotein convertase subtilisin/kexin type 9 (<i>PCSK9</i>)	rs11206510	1p32.2	T	Intergenic	0.81 in European/Caucasians	0.09 (0.02) mmol/L	Kathiresan et al., 2009; Waterworth et al., 2010; Willer et al., 2008
Neurocan (<i>NCAN</i>)/cartilage intermediate layer protein (<i>CILP2</i>)/pre-B-cell	1) rs16996148	19p13.11	G	Intergenic	0.90 European/Caucasians	0.01 (0.037) mmol/L	Sabatti et al., 2009; Willer et al., 2008

Gene Name	SNP rs #	Chromosome Location	Susceptibility Allele	SNP Type	Frequency of Susceptibility Allele per Population	Effect Size for Susceptibility Allele (SEM) ^a	References
leukemia transcription factor 4 (<i>PBX4</i>) cluster	2) rs10401969	19p13	C	Intronic	0.06-0.09 in European/Caucasians	0.05 (0.04) mmol/L	Kathiresan et al., 2009; Watervorth et al., 2010
Tribbles homolog 1 (<i>TRIB1</i>)	rs17321515	8q24.13	A	Intergenic	0.48 in Asians	0.04 (0.01) mmol/L	Nakayama et al., 2009; Tai et al., 2009

Note. bp = base pairs; N/A = not available; rs # = refSNP number; SEM = standard error of the mean; SNP = single nucleotide polymorphism.

^aEffect size on increase in LDL-C levels for each copy of the susceptibility allele.

Table 3b
Variants Associated with Elevated Low-Density Lipoprotein Cholesterol (LDL-C) Levels Reported in Only One Candidate Gene Study or Genome-wide Association Studies

Gene Name	SNP rs #	Chromosome	Susceptibility Allele	SNP Type	Frequency of Susceptibility Allele per Population	P-value	References
Low-density lipoprotein receptor (<i>LDLR</i>)	rs2738459	19p13.2	A	Intronic	0.52 in European/Caucasians	6.6×10^{-6}	Waterworth et al., 2010
Apolipoprotein B (<i>APOB</i>)	1) rs1367117	2p24.1	A	Nonsynonymous (missense)	0.27 in European/Caucasians	$< 0.001^a$	Benn, 2009
	2) rs3791980	2p24.1	T	Intronic	0.73 in European/Caucasians	$< 0.001^a$	Benn, 2009
	3) rs562338	2p24.1	A	Intergenic	0.23 in European/Caucasians	5.6×10^{-22}	Willer et al., 2008
	4) rs754523	2p24.1	G	Intergenic	0.29 in European/Caucasians	8.3×10^{-12}	Willer et al., 2008
	5) rs7575840	2p24.1	T	Intergenic	0.35 in European/Caucasians	8×10^{-7}	Kathiresan et al., 2008
	6) rs515135	2p24.1	T	Intergenic	0.20 in European/Caucasians	5×10^{-29}	Kathiresan et al., 2009
Proteinase subtilisin/kexin type 9 (<i>PCSK9</i>)	rs11591147	1p32.2	G	Nonsynonymous (Missense)	0.99 in European/Caucasians	7×10^{-7}	Kathiresan et al., 2008
Neurocan (<i>NCAN</i>)/cartilage intermediate layer protein (<i>CILP2</i>)/pre-B-cell leukemia transcription factor 4 (<i>PBX4</i>)	rs2304130	19p13.11	A	Intronic	0.93 in European/Caucasians	1.5×10^{-7}	Aulchenko et al., 2009
Adenosine triphosphate-cassette binding transporter G8 (<i>ABCG8</i>)	rs6544713	2p21	T	Intronic	0.32 in European/Caucasians	2×10^{-20}	Kathiresan et al., 2009

Note. rs # = refSNP number, SNP = single nucleotide polymorphism.

^a Bonferroni-corrected significance level $p < 0.008$.

Table 4
Genetic Test Categories Based on Clinical Validity and Availability of Treatment in the Context of Ethical, Legal, and Social Implications (ELSI)

Clinical Validity	Effective Treatment Available	
	Yes	No
High	Primary ELSI concern is ensuring that eligible individuals are tested and have access to treatment	Predominant ELSI concerns are adverse labeling, psychological distress, and potential for discrimination
Low	Goal is to balance the potential for adverse effects of labeling and the potential for improved health outcome	Genetic testing is difficult to justify

Source. Burke et al., 2001.