Preventive Treatment of Hypercholesterolemia and Atherosclerosis: A Genetic Approach

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Abstract

Hypercholesteremia is characterized by high levels of LDL-C, and leads to atherosclerosis. This is a largely preventable disease given the proper treatment. Historically, statins are the most widely used form of treatment in reducing cholesterol in those at-risk or already diagnosed with atherosclerosis. Recently, genetic risk factors have been identified, such as the PCKS9, LDLR and ANKS1A genes. Researchers have begun investigating their mechanisms and potential treatment options to lower risk for individuals at high-risk of developing atherosclerosis. This review outlines some of the major findings in the preventative treatment of hypercholesteremia and atherosclerosis and suggests future lines of research.

Background

High levels of cholesterol have been associated with increased risk of atherosclerosis and heart disease for decades. Atherosclerosis is a disease where deposits of plaques and fatty acids can build up within the artery walls, thereby impeding blood and oxygen flow and cause further conditions such as heart attacks, strokes, and peripheral vascular diseases. In general, atherosclerosis is the result of long-term, increased levels of low-density lipoproteins, or cholesterol, where the cholesterol builds up in the arteries as obstructing plaques. However, these coronary artery diseases are largely preventable (Roberts, 2014). Reducing risk factors, such as cholesterol, through preventative care have shown up to a 30% to 40% reduction in morbidity and mortality (Shepherd et al., 1995; Downs et al., 1998). Others argue that with time, we could prevent up to 90% of a coronary heart diseases (McGill, McMahan & Gidding, 2008).

McGill, McMahan & Gidding (2008) argue lowering risk factors in adolescence and young adults through preventative care and treatment will minimize the risk of atherosclerosis and further coronary heart disease later in life. Several studies provide evidence that slowing the effects of atherosclerosis earlier in life delay the onset of more severe medical issues (Lloyd, et al., 2006; Stamler et al., 1999; Cohen, Boerwinkle, Mosley, & Hobbs, 2006). Statins are the most widely used form of treatment in lowering cholesterol levels and lowering the risk of hypercholesterolemia and atherosclerosis. A statin is defined as any drug that inhibits

cholesterol synthesis. One study found statins administered to those at high risk of coronary heart disease significantly lowered the risk of a cardiovascular event (Thavendiranathan, Bagai, Brookhart, & Choudhry, 2006). However, the use of statins has only put a dent in the overall cases of atherosclerosis in at-risk individuals. One such study found that only 28% of individuals using statins achieved the recommended level of cholesterol (Seidah, 2003), suggesting that statins as the only means of preventative care is just not sufficient. Recently, researchers have begun focusing on the genetic risk factors of hypercholesterolemia and atherosclerosis as a means of potential treatment. As discussed below, they have found additional and complementary preventative treatments for those at risk of developing atherosclerosis and related diseases by determining genetic risk factors and investigating the mechanisms that lead to elevated cholesterol levels.

Methods

For this literature review, research articles were found using the online resources Google Scholar, The National Center for Biotechnology Information (NCBI), and PubMed. Key terms used for search results included “Genetics”, “Atherosclerosis”, “Hypercholesteremia”, “Prevention”, “Treatment”, “Risk Factors”, and others.

Wikipedia and WebMD were utilized for further understanding of biological and medical concepts relevant to this review.

Results

In a review article by Roberts (2014), GWAS identified single nucleotide polymorphism (SNP) variants of the genes LPA, APOB, SORT1, LDLR, APOE, ABCG5 – ABCG8, and PCSK9 were associated with high levels of low-density lipoprotein cholesterol (LDL-C) which lead to increased risk of atherosclerotic cardiovascular disease. Furthermore, he identified an SNP variant of the gene ANKS1A that is associated with low levels of high-density lipoprotein (HDL) which leads to increased risk of high cholesterol and atherosclerotic cardiovascular disease. Roberts (2014) points out that while statins are historically the only method of both prevention and treatment to high cholesterol and atherosclerosis, identification of these at-risk genes is leading to new forms of both prevention and treatment. For example, the PCSK9 gene creates the enzyme PCSK9 that increases degradation of LDL-C receptors, leading to excess LDL-C and hypercholesterolemia (Seidah, 2003). PCSK9 inhibitors can lead to lower levels of LDL-C, thus reducing risk of atherosclerotic cardiovascular disease (Roberts, 2014). Mutations of the LDLR receptor gene may lead in hypercholesterolemia as the receptors are a major mechanism for the removal of LDL-C. The ANSK1A gene produces high-density lipoproteins (HDL), which remove cholesterol from the blood. Mutations of this gene lead to increased cholesterol levels and increased risk of atherosclerosis. While unclear the connection to the ANSK1A gene, cholesteryl ester transfer protein (CETP) has recently been investigated as a source of increasing levels of HDL. However, in one such study, they found that a CEPT increased blood pressure and lowered serum potassium thereby increasing mortality rate of patients and forcing the trials to end prematurely (Barter et al., 2007; Feig, 2014). Other genes in this review have been implicated with hypercholesterolemia but their mechanisms are unclear. To date,

the best method of prevention and treatment are statins which inhibit cholesterol synthesis (Roberts, 2014).

Sun et al. (2018) investigated genetic variants associated with familial hypercholesterolemia (a genetic disorder) which causes lifelong levels of increased LDL-C and enhances risk of atherosclerotic cardiovascular disease. They found additional specific variants or SNPs of genes to be significantly associated with high levels of LDL-C. One variant of the gene PCSK9, two variants of the gene APOB, and 5 variants of the gene LDLR.

In a study on the prevention and treatment of ischemic heart disease (IHD) which is generally caused by atherosclerosis, Gerloni et al. (2017) examined several preventive treatments as a means of coping with atherosclerosis. β-blockers reduce blood pressure by altering heart rhythm. Calcium channel blockers reduce peripheral vascular resistance by inducing vasodilation. And nitrates allow for coronary arteriolar and venous vasodilation (Gerloni et al., 2017). However, no clear link was given between medication and genetic interaction.

A summary of the review findings can be found in the table below.

Gene	**Variant (SNP ID)**	**Gene Products**	**Phenotypic Expression**	**Preventative Treatment**
PCSK9	rs11206510 rs141502002	PCSK9 Enzyme	Hypercholesterolemia	PCSK9 Inhibitors Statins
APOB	rs12713559 rs5742904 rs515135	-	Hypercholesterolemia	Statins

LDLR	rs768563000 rs151207122 rs121908030 rs201573863 rs137853964	LDL Receptor	Hypercholesterolemia	Statins
LPA	rs3798220	-	Hypercholesterolemia	Statins
APOE	rs2075650	-	Hypercholesterolemia	Statins
SORT1	rs599839	-	Hypercholesterolemia	Statins
ABCG5-ABCG8	rs6544713	-	Hypercholesterolemia	Statins
ANKS1A	rs12205331	HDL	Hypercholesterolemia	CETP

Table 1: Identified genes variations associated with risk of hypercholesterolemia.

Discussion

One of the most studied genetic links to hypercholesteremia and atherosclerosis has been the PCKS9 gene. Studies have led to innovative solutions using PCKS9 inhibitors to lower levels of LDL-C. However, preventative treatments such as this used with individuals at high risk of developing atherosclerosis are not meant to be used as a sole treatment, but a complement to other treatments. Stein et al. (2012) found that treatment of at-risk individuals with statins alone results in a 17% reduction of LDL-C, while treatment of a statin paired with the PCSK9 antibody results in a LDL-C reduction of 72%. While many of the genes and gene mutations associated with high risk of hypercholesteremia and atherosclerosis have no developed preventative treatments, the research and development of the PCKS9 gene should be used as a model case for the development of treatments associated with these genes and their gene products.

For the LDLR gene, where the receptors are a major mechanism for the removal of LDL-C, future research should focus on restoring the functionality of these receptors. Much like in the PCKS9 gene where the PCKS9 inhibitors complement the use of statins, so to for the LDL-C receptors would treatment focused on restoring the functionality of these receptors be complemented by the use of statins. Looking to the ANKS1A gene, it is unique among the other gene variations as it produces HDLs that remove cholesterol from the blood. While CEPT is used to combat mutations of this gene by increasing the HDL levels, the side effects of increased blood pressure and lowered serum potassium are counterproductive. One solution is pair CEPTs with other medications to address the side effects. Though, adding additional medications may not lead to optimal results. Further treatment options should be researched that would restore functionality to mutated genes or replace the functionality of HDL with an alternative treatment, aside from the use of statins alone.

Conclusions

The identification of genes that lead to high risk of hypercholesteremia and atherosclerosis is an open door for researchers to find new methods of treatment against this disease. While statins alone have improved overall patient care in those at-risk or already diagnosed with hypercholesteremia and atherosclerosis, future advances in preventative care and treatment could lead to up to 90% prevention of coronary heart disease as McGill, McMahan & Gidding (2008) suggest. Future work should include identifying the gene products and mechanisms at the cellular and molecular level of these identified genes and their associations with hypercholesteremia and atherosclerosis.

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