Case Study: PCSK9

Key lessons learned
• In a number of large observational studies, reduced low-density lipoprotein (LDL) is associated with decreased coronary heart disease. • Early studies on families with very high cholesterol levels in the blood helped identify a link between LDL levels and PCSK9, a protein (proprotein convertase subtilisin kexin- type 9) that controls the number of receptors for LDL on the surface of cells. Genetic sequencing[1] was able to identify mutations expression of PCSK9 in individuals with very high and low levels of LDL. • While race is generally considered to be only a surrogate marker for genetic differences, race has been associated with a number of biological differences (e.g., salt sensitivity, hypertension, renin activity, and nitric oxide response). With regard to PCSK9, racial differences were associated with the likelihood of different genetic variants of the protein. • Racial and ethnic diversity can, in some instances, lead to identification of important genetic variants that may prove important in drug discovery and development.

Disease background

Low-density lipoproteins (LDL) are a well-studied risk factor associated with heart disease, mediated through “hardening of the arteries," or atherosclerosis. A number of studies have shown that lowering the concentration of LDL in the blood can reduce the risk of cardiovascular diseases, specifically those related to coronary heart disease (CHD).[2] There are a number of ways to lower LDL concentrations in the blood including modifying one’s diet by lowering saturated fat consumption or by using cholesterol-lowering therapies such as statins.

[1] There is a difference between genotyping, genetic sequencing, and genetic expression. Genotyping is the process of determining which genetic variants an individual has; genetic sequencing is the method used to determine the exact sequence the four chemical building blocks of DNA are within a certain cut of DNA; genetic expression is a result of how DNA is transcribed into different cells and therefore how genes may be expressed.
National Human Genome Research Institute. DNA Sequencing Fact Sheet [Internet]. National Institutes of Health. Dec. 18, 2015. Available online: https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Fact-Sheet (accessed May 8, 2020).

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In 2002, research on families with high cholesterol (i.e., familial hypercholesterolemia) found that certain individuals with high LDL levels also have an increased amount of a protein, termed PCSK9 (or proprotein convertase subtilisin kexin-type 9), in their blood.[3] PCSK9 impacts the metabolism of LDL by occupying and degrading the LDL receptor on cells that would have otherwise bound and digested LDL.[4] Therefore, high levels of PCSK9 result in elevated levels of LDL-cholesterol.

Discovery to genetic variation

Shortly after the initial findings from the familial high cholesterol studies,[5] a series of genetic analyses were done to investigate PCSK9 gene mutations; it was discovered that individuals may either express less (i.e., loss-of-function [LOF]) or more (i.e., gain-of-function [GOF]) of the protein PCSK9.[6,7,8] Research on gene expression found different variations of the gene in different individuals. Populations of self-reported Black participants had a higher frequency of two of the three most common PCSK9 loss-of-function mutations; both of these variations were rare in White participants.

The higher frequency of the LOF mutations in Black patients in earlier studies[9] correlated with the relationship that had been observed between reduced LDL-C and reduced CHD, leading to further study of the role and function of PCSK9. Discovery and the understanding of the function of PCSK9 led to the development of therapeutic PCSK9 inhibitors, thereby offering treatment for individuals with high cholesterol levels and heart disease.

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