

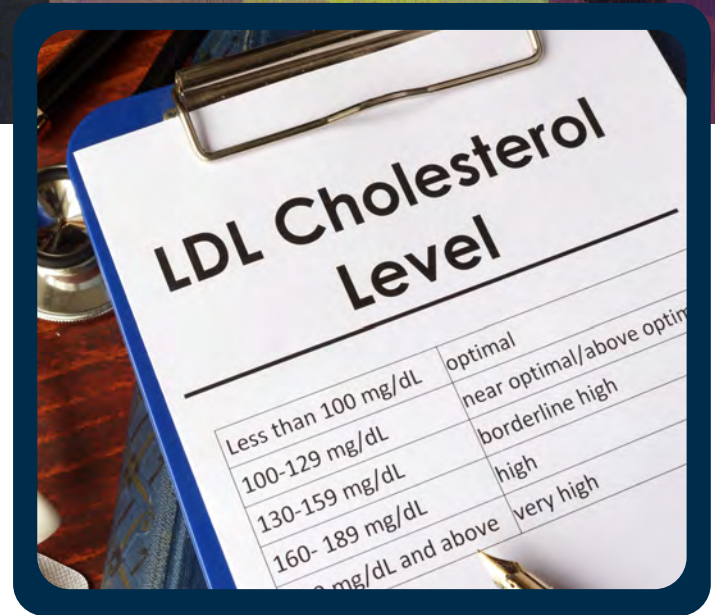
# CASE STUDY HIGHLIGHTS: PCSK9

How racial and ethnic diversity identified important genetic variants that aided drug discovery and development.

## BACKGROUND

Low-density lipoproteins (LDLs) are a well-studied risk factor associated with heart disease, mediated through “hardening of the arteries,” or atherosclerosis.

Research has shown that lowering the concentration of LDL in the blood can reduce the risk of cardiovascular diseases, specifically diseases related to coronary heart disease. There are many ways to achieve this, including diet modifications or cholesterol-lowering medications such as statins.



## RESEARCH

In 2002, research on families with high cholesterol (i.e., familial hypercholesterolemia) found that some 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.

Genetic sequencing identified gene mutations in individuals that affected the amount of PCSK9 in their blood – this resulted in individuals having either elevated or reduced levels of LDL.

Populations of self-reported Black participants had a higher frequency of two of the three most common mutations resulting in less PCSK9, while both of those variations were rare in White participants.



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## DISCOVERY

PCSK9 impacts the metabolism of LDL by degrading the LDL receptor on cells that would have otherwise bound to, digested, and reduced LDL.

In simple terms, this means that high levels of PCSK9 result in elevated levels of LDL- cholesterol and, in turn, a higher risk of heart disease.

This discovery and 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.



## CONCLUSION

While race is generally a weak marker for genetic differences, race has been associated with many biological differences (e.g., salt sensitivity, hypertension, renin activity, and nitric oxide response).

In this case, differences were associated with the likelihood of different genetic mutations of a protein.

Racial and ethnic diversity can, in some instances, serve as proxy indicators that may lead to identification of important genetic variants that may prove important in drug discovery and development.

For citations and more information on this case, please see the **MRCT Center toolkit**.