A gene with a remarkable translational research story is leading the way in becoming potentially the next blockbuster drug in heart disease. This “gene of rare effect,” proprotein convertase subtilisin/kexin type 9 (PCSK9), was found to be a contributing factor to profoundly low cholesterol concentrations in some individuals and has made its way from unknown factor to headline grabber, as detailed in a recent Nature news feature (1).

In the postgenome era, the prevailing “common variant hypothesis” was that genetic variants present at approximately 5% frequencies were expected to contribute importantly to complex disease (such as heart disease). However, subsequent genome-wide association studies proved disappointing, finding that common variants actually have a very small effect on disease. On the contrary, a decade before the Human Genome Project, Helen Hobbs and Jonathan Cohen and their colleagues from the University of Texas Southwestern approached this problem in a divergent manner, by hypothesizing that many different rare variants were likely to have a big effect in complex disorders. They reasoned that common variants with a major impact on complex disorders would be weeded out by natural selection. The Dallas Heart Study (DHS) was a large multiethnic (>50% African American) population-based study designed in 1999 by Hobbs, Victor, and colleagues to identify these rare variants and obtain detailed physiological profiles. By sequencing 3 genes known to be key for the metabolism of HDL cholesterol [ATP-binding cassette, sub-family A (ABC1), member 1 (ABCA1), apolipoprotein A-I (APOA1), and lecithin-cholesterol acyltransferase (LCAT)] in DHS individuals with extremely low and high HDL concentrations, Hobbs and Victor found that the number of mutations was 5 times higher in the low-HDL group than in the high-HDL group. Their results confirmed that rare, clinically relevant mutations could be found in a population subdivided into extreme phenotypes.

Meanwhile, PCSK9, or proprotein convertase subtilisin/kexin type 9, was discovered in 2003 by Nabil Seidah, who then collaborated with Catherine Boileau and colleagues to find a link between the gene, PCSK9, and a group of French families with very high LDL cholesterol and gain-of-function PCSK9 mutations. PCSK9 normally circulates in the bloodstream and binds to the LDL receptor, whereby it assists in LDL-receptor internalization. Increased concentrations of PCSK9 lead to increased circulating concentrations of LDL cholesterol (owing to fewer LDL receptors on the cell surface), as observed in the French families. Based on these new PCSK9 findings, Hobbs theorized that loss-of-function variants could lead to low LDL cholesterol, and she and Cohen set out to study this hypothesis.

Hobbs and Cohen turned to their DHS cohort and sequenced PCSK9 in the individuals with very low LDL cholesterol concentrations. They found 7 African Americans with null mutations in PCSK9. These individuals were surprisingly healthy, with LDL cholesterol concentrations as low as 14 mg/dL (0.36 mmol/L). At first, only the effects of PCSK9 on low concentrations of LDL cholesterol were known; later, an association with the null mutations and an 88% lower risk of developing cardiovascular disease was found. It also was observed that individuals with a less severe PCSK9 mutation had a 15% reduction in LDL cholesterol and a 47% reduced risk of heart disease.

Although PCSK9 did not get a lot of attention from the genetics community at first, it immediately caught the attention of the pharmaceutical industry. Could PCSK9 be a target to compete with statins in the lipid-lowering drug market? While the quest to find a small molecule which inhibits PCSK9 that could be packaged into a pill was unsuccessful, the extracellular nature of PCSK9 enabled the development of a more costly monoclonal antibody approach. Results of phase II clinical trials published recently demonstrated that patients with high LDL cholesterol who had biweekly in-

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2 Human genes: PCSK9, proprotein convertase subtilisin/kexin type 9; ABCA1, ATP-binding cassette, sub-family A (ABC1), member 1; APOA1, apolipoprotein A-I; LCAT, lecithin-cholesterol acyltransferase.
jections of anti-PCSK9 paired with a high-dose statin had LDL cholesterol concentrations lowered by 73%, compared to an LDL cholesterol decrease of just 17% in patients taking only the high-dose statin. So far, side effects have been minor, and phase III trials are currently underway to determine the effect of these monoclonal antibody therapies on cardiovascular event outcomes.

If phase III clinical trials with PCSK9 inhibitors are successful, many questions remain. Will patients be compliant with subcutaneous injections of anti-PCSK9? Can therapy be tailored on the bases of response such that in a majority of individuals only monotherapy is needed? Individuals with PCSK9 null mutations have low LDL cholesterol concentrations from birth, thereby halting progression of atherosclerosis at a very early age. Thus, additional debate and thought are warranted toward starting these therapies in asymptomatic but high-risk individuals as early as postadolescence.

Although the larger genetics community failed at first to grasp the significance and impact of the PCSK9 findings, they are now heralding the uniqueness, beauty, and strength of the approach of Hobbs and Cohen. The discovery of PCSK9 and its medical potential was possible only because a group of researchers working apart from the prevailing scientific strategy of genome research applied a novel, contrary approach to a complex disease study design. The breakthrough has opened the door not only for a new potential blockbuster drug, but also for a novel application of the translation of genomic findings into clinical practice. By applying their rare variant theory to a well-characterized patient population, Hobbs and Cohen took the road less traveled, and that has made all the difference.

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