How Hobbs found a way to fight bad cholesterol

Geneticist and her team discovered a rare mutation that protects against heart disease

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The discovery of cholesterol-lowering mutations in a human gene called PCSK9 led to the development of the most promising new drugs against heart disease since statins.

At the Hyderabad edition of the TNQ’s Distinguished Lectures in Life Sciences, geneticist Helen Hobbs told an audience of scientists and lay persons the story of this discovery. Ms. Hobbs and her colleague at Dallas’ UT Southwestern Medical Center, geneticist Jonathan Cohen, found that when people had a mutation in PCSK9, they ended up with lower levels of low-density lipoprotein (LDL) or bad cholesterol. Through this mechanism, the mutation protected people against heart disease, seemingly without side effects. In 2016, Ms. Hobbs was awarded the Breakthrough Prize in Life Sciences for her work.

Ms. Hobbs’ research journey was unusual in many ways. When she began working on cholesterol in the early 2000s, the prevailing strategy among researchers looking for the genetic basis of disease was to search for common gene variants (present in around 5% of the population). However, this strategy hasn’t gone very far in understanding complex illnesses like heart disease; most common variants only have small effects on traits like cholesterol. Ms. Hobbs reasoned that it would be more fruitful to look for rare gene variants with large impacts. Large impacts would also mean such findings would translate more quickly into treatments, she said.

The question Ms. Hobbs and Mr. Cohen wanted to answer was how necessary high LDL was to causing coronary artery disease (CAD). From Mendelian, or single-gene disorders, the researchers already knew that elevated LDL made people sick. People with Mendelian heart disease often have no other risk factor, such as obesity or smoking. LDL seems sufficient to make them ill.

Ms. Hobbs wanted to test if the opposite was true. In other words, she was looking for a gene that protected against LDL and promoted health. To do this, the team set up the Dallas Heart Study, a cohort of around 3,500 people, comprising blacks, hispanics and whites. The idea was that more racial diversity would make it more likely to find rare variants.

**PCSK-9 gene mutation**

The cue for which gene to focus on in the Dallas Heart Study came from a French study which found that people with familial hypercholesteremia - a genetic disorder leading to high LDL - tended to have a mutation in the PCSK-9 gene. Could a mutation with the opposite effect protect people against CAD then? To answer this, Ms. Hobbs et al. sequenced the genes of people at both extremes of the Dallas Heart Study - those with the highest LDL levels and lowest. Sure enough, they found a mutation that protected against LDL, the opposite of the French study. The findings led to the development of the PCSK9 inhibitors Alirocumab and Evolocumab within 10 years, an unusually rapid example of drug development. The average time between the discovery of a drug target to commercialisation is typically 15 years.

Today, Ms. Hobbs has turned her attention to fatty liver disease.

Here, too, her efforts led to the identification of two gene mutations which promote the disease through different pathways. Both mutations increase triglycerides in blood through different mechanisms, while also making people susceptible to liver cirrhosis and cancer.

This finding shows that a condition called hepatic steatosis, in which fat builds up in the liver is not as benign as clinicians currently think, according to Ms. Hobbs. When hepatic steatosis is not accompanied by inflammation, clinicians call it “bland” and believe it has a good prognosis. Ms. Hobbs’ research shows that such fat build-up, which results from high triglycerides, can lead to cirrhosis and cancer without help from any other factors. “I question whether [steatosis] really is bland,” she said.