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Rare and common genetic variations responsible for high triglyceride levels in blood

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It can make blood look like cream of tomato soup. Patients with high levels of triglycerides in their blood, a disease called hypertriglyceridemia (HTG) face an increased risk for heart disease and stroke. HTG affects one in 20 people in North America and is also associated with obesity, diabetes and pancreatitis. Most people now understand the importance of LDL, the bad cholesterol and HDL, the good cholesterol, to their overall health. But high triglycerides are like the Rodney Dangerfield of the lipid world: they get less respect and notoriety compared to their cholesterol cousins. Doctors are often uncertain about how best to treat patients with this condition. Understanding the genes that make patients susceptible to HTG could provide clues to newer, better treatments.

In a new study published online in *Nature Genetics*, Dr. Robert Hegele of the Robarts Research Institute, Schulich School of Medicine & Dentistry at The University of Western Ontario (London, Canada) has shown that it's a combination of both common and rare variants or 'misprints' in several genes that add up and put a patient at risk of developing HTG. Working with graduate student Christopher Johansen, Dr. Hegele used two different methods to uncover the complex genetic basis of HTG in more than 500 patients.

First, using DNA microarrays (also called gene chips) the researchers found that commonplace variants in four different genes are strongly

related to having HTG. Next, using detailed DNA sequence analysis, they found that patients with HTG also had an excess of rare variants - ones only found in one or two people - in these same four genes. Cumulatively, the rare variants were found in 28 per cent of HTG patients, about twice the rate seen in healthy controls.

"This is one of the first studies that combined gene chips with DNA sequencing to examine the genomes of patients", explains Dr. Hegele, an endocrinologist and professor in the Departments of Biochemistry and Medicine at Western. "It was fortunate that we used both methods. Gene chip studies are popular nowadays and are effective at finding relationships between common genetic variants and disease. But gene chips cannot detect rare variants. For that, you need to do the more expensive and time-consuming method of DNA sequencing."

Scientists have long suspected that both common and rare genetic variants contribute to many diseases, but the study from the Robarts group now definitively shows that this is the case.

"It's also instructive that one single gene is not solely responsible for high triglyceride levels but rather a mosaic of both common and rare variations in several genes." Dr. Hegele adds that these rare variants now help explain the missing heritability of lipid traits. "It means that to get a full picture of a patient's genetic risk, you need to consider both common and rare variants in many genes simultaneously, and to use methods that will detect both types of variation."

Provided by University of Western Ontario