Computational geneticist Dr Ron Do constructs means of processing vast quantities of data to determine the contributions of genes and environment to risk factors for coronary artery disease and discover mutations underlying this common, complex disease.

What attracted you to the study of human genetics?

My interest in human genetics was first piqued during my undergraduate studies. At the time, there was much hype among scientists and the broader public about the recent completion of the Human Genome Project. I think everyone, especially young students of science, was deeply interested in the implications of this new genetics knowledge: what medical treatment options would genetic information open up? How would our understanding of human history and evolution expand and change? What new technological innovations might genetics studies spur?

Can you describe your role at the Center for Human Genetics Research, Massachusetts General Hospital?

I am an instructor in Medicine at Massachusetts General Hospital and an affiliate at the Broad Institute. My primary role is that of a computational geneticist. Most of my work involves programming and using a suite of software and computing tools to study the genetics of cardiovascular disease. Specifically, I look for differences in the frequencies of mutations in the genomes of individuals with high plasma cholesterol levels or with acute myocardial infarction (MI).

Why is investigating the effects of genetic variants on lipids and coronary artery disease (CAD) important?

CAD and MI are leading causes of morbidity and mortality worldwide. Statistics show that after the age of 40, half of all men and one-third of all women will suffer a coronary event during their lifetimes. A pressing public health goal is to reduce the number of these events.

Statins, a class of the most successful pharmacological therapeutics that reduce low-density lipoprotein cholesterol (LDL-C), have proven effective at lowering CAD and MI risk. However, even with the use of statins, some individuals continue to be at significant risk for CAD and MI. Furthermore, some people develop severe adverse effects to statin use. As such, we continue to have a great need to develop new pharmacological therapies to prevent CAD and MI. We also need to continue to advance our understanding of, and public messaging about, protective activities such as exercise and diet.

Has one area in particular shown promise?

An ongoing site of potential advancement is the use of human genetics approaches to identify gene targets for pharmacological therapies for CAD or MI. One area in human genetics that may prove promising is gene targets for plasma triglycerides. Until recently, there has been limited and conflicting evidence on the role of triglycerides in causing CAD or MI. Recently, I led a statistical genetics study that showed triglyceride-rich lipoproteins may causally influence risk for CAD. I discovered, using a model that accounted for effects on LDL-C and/or high-density lipoprotein cholesterol (HDL-C), that the strength of a polymorphism’s effect on triglyceride levels is correlated with the magnitude of its effect on CAD risk. These results provide evidence that triglyceride-rich lipoproteins may causally influence risk for CAD and suggest that scientists developing therapeutic targets for CAD should focus, in part, on plasma triglycerides.

Can you describe some key next steps in cardiovascular genetics?

Some important areas for future inquiry include the discovery of novel rare mutations conferring risk for CAD, examining the interactive role of genes and environment in conferring CAD risk, and follow-up of genes discovered from genome-wide association studies and sequencing studies for drug development and experimentation in animal models.

DO’S RESEARCH IS DRIVEN BY THREE KEY AIMS:

1. To study how both genetics and environment play a role in causing CAD or MI – dissecting the effects of genetic variants discovered in prior genome-wide association studies in the context of the environment.

2. To discover new genes causing CAD or MI. Do has used exome sequencing technology – sequencing of all of the protein-coding regions of the genome – to discover new genes related to blood lipids and CAD or MI.

3. To make causal inferences between biomarkers and risk factors with CAD or MI. Do uses an approach called Mendelian-Randomisation to study the causal relationship between plasma lipids and CAD which utilises estimates of the effect sizes of genetic variants obtained from meta-analyses of genome-wide association studies for plasma lipids and CAD.

In the genetic pipeline

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Lowering the odds of heart attack

Inquiries into massive, state-of-the-art genetic databases at the Center for Human Genetics Research, Massachusetts General Hospital, USA, reveal that some genetic mutations substantially raise the risk of coronary artery disease and heart attack.

**THE BUILD-UP OF** fatty deposits in the form of plaque leads to narrowing of the arteries and can cause heart attack, stroke and heart failure. This build-up can start in childhood and worsen with age as a consequence of the effects of stress, eating habits and lifestyle choices such as smoking. In terms of eating habits, it has long been known that a diet high in cholesterol and animal fats intensifies the likelihood of developing a chronic heart condition such as coronary artery disease (CAD) later in life. More recently, researchers have found that genetic factors also contribute to CAD and its risk factors, including blood lipids, blood pressure, obesity and diabetes, among others.

Research aimed at reducing CAD has shown that a Mediterranean diet of fresh vegetables, fruit, beans, nuts, fish and monounsaturated oils such as olive oil lowers CAD risk. While high levels of high-density lipoprotein cholesterol (HDL-C, ‘good cholesterol’) are associated with decreased risk of cardiovascular conditions, treatments that target HDL-C levels have so far shown little effect. Treatments aimed at reducing high levels of low-density lipoprotein cholesterol (LDL-C, ‘bad cholesterol’) have been shown, however, to lessen the incidence of CAD and heart attack.

**GENETIC VARIANTS/ENVIRONMENT INTERACTIONS**

During his doctoral research at McGill University, Montréal, Canada, Dr Ron Do investigated common genetic variation in the chromosome 9p21 region of the genome that predispose people to higher risk of CAD. Do, who is now based at the Center for Human Genetics Research at Massachusetts General Hospital, was seeking ways to mitigate or counteract genetic patterns linked to CAD. He found that people who consumed a ‘prudent’ diet high in raw fruits and vegetables mitigated the effects of their genetic risk factors for CAD. Those with specific risk alleles in the 9p21 genetic variant could reduce the burden of their natural heritage through diet.

In preparation for the project, Do and his collaborators genotyped four chromosome 9p21 single nucleotide polymorphisms associated with CAD risk, using DNA data from the global INTERHEART database. On analysing the combined data from INTERHEART and another database, FINRISK, which together held the DNA information of 27,000 people of Arabian, Latin American, South Asian, European and Chinese ethnicities, Do found that the odds of experiencing heart attack were significantly lower for those with a diet high in raw fruit and vegetables, even if they had two of the high-risk gene mutations, compared to those with a diet low in raw fruit and vegetables.

Do believes further analysis of the nature of genetic links to coronary artery disease and heart attack is required, both in terms of disease aetiology and with respect to diet, lifestyle and other environmental factors.
INTELLIGENCE

THE GENETICS OF CORONARY ARTERY DISEASE

OBJECTIVES

• To study how both genetics and environment play a role in causing and protecting against coronary artery disease or myocardial infarction
• To discover new genes causing coronary artery disease or myocardial infarction using exome sequencing technology
• To make causal inferences between biomarkers and risk factors with coronary artery disease or myocardial infarction

KEY COLLABORATORS

Professor James Engert, PhD, McGill University Health Centre, USA • Professor Sonia Anand, MD, PhD, McMaster University, USA • Professor Benjamin Neale, PhD; Professor Mark Daly, PhD; Professor Sekar Kathiresan, MD, Massachusetts General Hospital, USA

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DR RON DO is an instructor in Medicine at Massachusetts General Hospital, and an affiliate at the Broad Institute. He completed his MSc in Epidemiology at the University of British Colombia and his PhD in Human Genetics at McGill University, both in Canada. During his PhD, he studied the effects of genetic variants on lipids and cardiovascular disease using a variety of approaches including fine-mapping, gene-environment interaction and meta-analysis methods in gene association studies. Do is currently investigating the role of low frequency variants and rare mutations in whole exome resequencing datasets of families with extreme lipid disorders and population-based samples with early onset myocardial infarction. He is also integrating genetic findings from genome-wide association studies for lipid traits with findings for coronary disease.

The finding that genetic risk for CAD and heart attack can be countered by environmental factors, such as diet, was one of the most robust associations of its kind. Do went on to further analyse the INTERHEART and FINRISK data. The results were found to be consistent across all five ethnicities. However, the data indicated that South Asians with certain genetic variations in the 9p21 region were more at risk of CAD and heart attack than people of other ethnicities. Researchers do not yet know what explains this difference in effect of diet on CAD risk across population groups. “An important area for future study is the physiological mechanisms by which a prudent diet influences 9p21 genetic variants on CAD risk, why the effect is stronger among certain ethnic groups, and whether other genetic loci interact similarly not just with diet, but with other known protective factors such as physical activity,” Do states.

AN UNFORTUNATE INHERITANCE

Do has recently investigated the bases for certain genetically-inherited conditions related to CAD, including familial combined hypolipidemia (FCH), a condition that results in markedly decreased levels of LDL-C, HDL-C and triglycerides in the blood. “I led the construction of one of the first robust statistical pipelines for analysing exome sequencing data in families with Mendelian lipid disorders,” Do explains. “We discovered that compound heterozygote nonsense mutations in the Angiopoietin-like 3 (ANGPTL3) gene were a cause of FCH.” Do subsequently extended this statistical pipeline to cover 2,000 heart attack cases and controls; in analysing this expanded dataset, he identified mutations in two lipid genes that significantly increase the risk of early-onset heart attack.

His use of computation and statistics to unravel genetic mutations that lead to coronary disease has revealed both common and rare genetic factors that raise the risk of CAD and heart attack. In his view, this approach has been clearly validated. The main challenge is to design ways to deal with the ever-growing and vast quantities of genetic data now available, as groups all over the world contribute more and more information to genomic databases: “I am fortunate to be able to work on some of the largest and most cutting-edge genetic datasets,” enthuses Do. “Working out how to best construct computational pipelines and analyse the large amount of sequencing data available, typically gigabytes to terabytes, is a challenge I have managed to overcome through collaboration.”

PLASMA TRIGLYCERIDES

Epidemiological studies have shown correlations between plasma lipids and CAD. As Do explains, “the best-established associations for heart attack are blood concentration of increased triglycerides, decreased HDL-C and increased LDL-C. Epidemiological studies, however, have limitations in distinguishing causality in the pathological process”. Though the role of plasma triglycerides in raising the risk of CAD has been the subject of some recent trials testing the triglyceride-lowering effects of fish oils and fibrate therapeutics on CAD, the results of these studies have been inconclusive. These trials may have failed to establish a relationship between fish oil or fibrates intake and CAD because these studies were statistically underpowered or the methodology applied in the trial was inchoate.

Do has studied the causal relationship of plasma triglycerides and CAD using novel methods and approaches in statistical genetics. Using 185 genetic variants associated with plasma blood lipids, Do discovered that in a model accounting for effects on LDL-C and/or HDL-C, the degree to which a genetic variant affects triglycerides is correlated with the strength of its effect on CAD risk. “This result provided evidence that triglyceride-rich lipoproteins may causally influence risk for CAD. It therefore suggests that scientists developing therapeutic targets for CAD should focus in part on plasma triglycerides,” he asserts.

Do believes that further analysis of genetic links to CAD and heart attack is required, both in terms of disease aetiology and with respect to diet, lifestyle and other environmental factors. He intends to pursue his search for new and rare genetic mutations that confer greater risk of developing CAD, and to examine the interactions of genes and environment in elevating or mitigating such risk. He aims to contribute to public health knowledge about the importance of environmental factors on cardiovascular health and find opportunities in the form of genetic markers that will serve as targets for new therapeutic drugs in the future.