More than 1,200 clinical and research scientists from over 50 countries are attending ISA 2012, the premier conference into atherosclerosis and cardiovascular disease, held every 3 years. Highlights of ISA2012 include genetics of cardiovascular disease, identification of cardiovascular risk factors, therapeutic advances, epidemiology, imaging, biomarker identification, dyslipidaemias, abdominal obesity, diabetes, lipoprotein metabolism and vascular biology.

Opening ISA 2012, Professor Kerry Anne Rye, ISA2012 Chair highlighted the ‘sea change’ in the organisation of such meetings; the current meeting includes 15 plenary session, 42 workshops and over 400 poster presentations. Professor W. Virgil Brown, President of the International Atherosclerosis Society, said that the International Symposium on Atherosclerosis was indeed the precursor to the International Atherosclerosis Society, given that the first meeting preceded the inauguration of the society.

Plenary 1: NEW AND EMERGING APPROACHES FOR IDENTIFYING AND TREATING CARDIOVASCULAR DISEASE: Genetic approaches

A rare view of coding mutations and risk for myocardial infarction

Dr S Kathiresan, Director of Preventive Cardiology, Massachusetts General Hospital Heart Center and Assistant Professor, Harvard Medical School, Boston, USA overviewed recent developments in understanding the genes and specific DNA sequence variants responsible for the heritability of coronary artery disease (CAD). Recent technological approaches, including the use of systematic genome-wide association studies (GWAS), have helped in genetic mapping.

First approaches have been directed to identifying common variants (allele frequency >1:20). To date, more than 30 loci have been mapped to CAD; 7 of these also map to LDL cholesterol and one to blood pressure. However, 22 variants do not map to any known risk factors. Previous Mendelian randomisation studies targeting the extremes of the distribution together with exome sequencing (i.e. sequencing the protein-coding regions of the genome) were used to identify nonsense mutations in ANGPTL3 variants that are associated with very low LDL cholesterol levels. ‘However, there remain questions regarding the underlying molecular mechanisms, and whether loss of ANGPTL3 function translates to reduction in risk for MI.’

There is evolving interest in GWAS of rare variants (a term encompassing alleles with frequency <1:100 for very rare and >1:100 and <1:20 for rare), given suggestions that these may be more likely to be functional than common variants. Advances in DNA sequencing and genotyping technology, which allow for the identification of rare variants through direct sequencing, together with bioinformatics, has permitted such analysis. However, a major limitation is inclusion of non-causal and missense non-functional variants. Estimates suggest that only 1/5 are deleterious as nonsense
mutations. Collapsing genotypes across variants and multivariate analysis are robust approaches to counteract this. Using this approach, Dr Kathiresan and coworkers investigated rare variants associated with early onset MI (<50 years in males and <60 years in females), in about 1,100 individuals and compared this with data obtained from controls (1,335 individuals without MI). Excluding missense non-functional mutations (~75% of variants), and using symptomatic deflation identified LDLR variants that were associated with 4-fold increase in effect size contributing to increased MI risk.

Sequencing-based replication studies have also investigated whether rare variants of APOA5 are linked with increased MI risk. In a meta-analysis of more than 7,000 individuals, variants were identified in 58 cases that were associated with a 2-fold increase in MI risk compared with controls. However there are statistical issues when dealing with DNA variants only evident in a single person, which cannot therefore be tested for association with phenotype. Instead, they need to be aggregated with similar rare variants to be tested collectively for association. ‘Such association signals the burden of very rare variants.’

In conclusion, Dr Kathiresan emphasised that while advances in gene technology and bioinformatics have permitted such analyses, functional translation is the next priority. ‘The ongoing challenge will be understanding the underlying mechanisms implicated in CAD.’

Journal of Lipid Research Lectureship: Coronary Artery Disease, Genetics and Genomics.

Professor Ruth McPherson, University of Ottawa Heart Institute, Canada

As previously highlighted by Dr Kathiresan, CAD is a complex trait resulting from an interplay between environmental and genetic factors. While the age-specific incidence of CAD is increased 2-fold in subjects with a family history of premature disease, the contribution of family history cannot be fully explained by known CAD risk factors.

In the last 2 years, considerable progress has been made in understanding the genetic basis of CAD. GWAS has led to the identification of over 40 novel loci associated with CAD. GWAS was instrumental in identifying the first genetic variant for CAD on chromosome 9p21. This association was independent of established CAD risk factors such as plasma lipoproteins, hypertension, or diabetes. This variant is extremely common with one or two copies occurring in 75% of the population. Homozygotes have about 2-fold increased risk in CAD. ‘However, this risk allele was also associated with increased risk of other cardiovascular complications, including stroke, peripheral arterial disease and abdominal aortic aneurysm, as well as periodontal disease.’

Beyond 9p21, there has been a concerted drive to further characterise loci associated with CAD risk. The CARDIOGRAM (Coronary ARtery Disease Genome wide Replication And Meta Analysis) programme has identified 23 genetic variants showing increased risk for CAD of which 13 were novel and 10 confirmatory. However, only a few of these display significant association with traditional CAD risk factors and most are in gene regions not previously implicated in the pathogenesis of CAD. Many DNA variants are in or near genes known to cause Mendelian dyslipidemias (LDLR, APOB, and PCSK9) or established molecular targets for LDL cholesterol lowering therapies (HMGCR), yet several of the LDL loci contain genes not previously implicated in lipoprotein metabolism. Furthermore,
novel CAD risk loci appear to have pleiotropic effects, showing strong association with various other human diseases or traits. Therefore, alternative approaches are required to identify causative genetic variants by deep resequencing and translate these findings to functional effects using cellular and in vivo approaches. Pathway based analyses can be useful in uncovering pathways consisting of genes for which no individual SNP satisfies a traditional genome wide significant p-value threshold, but for which there exists an excess of variants with low to moderate effect on the disease.

GWAS have also identified a strong signal for triglyceride-associated loci and CAD, providing support for a role for triglyceride-rich lipoproteins and impaired lipolysis in the aetiology of CAD. For HDL, there are genetic inconsistencies, which is not surprising given the heterogeneity of the HDL particle population and complexity of HDL metabolism.

There remain many unanswered questions surrounding the heritability of CAD. It is still unclear how 9p21 relates to atherosclerosis development, although recent research has identified that the 9p21 risk allele contains a functional enhancer, which is altered in carriers. Current evidence suggests that 9p21 may promote atherosclerosis by regulating expression of ANRIL, which in turn is associated with altered expression of genes controlling cellular proliferation pathways.

GWAS have implicated $SORT1$ as the causal gene at the 1p13 locus for LDL cholesterol and MI, suggesting a promising new target for therapeutic intervention to prevent MI. However, this only accounts for about 10% of heritability of MI. ‘Clearly there is much to do to elucidate the genetics of CAD. Genetic approaches investigating the heritability of CAD is a numbers game. Increasing sample sizes will increase the likelihood of identifying more rare DNA variants relevant to the complex genetic architecture of CAD.’ Identification of genetic variants contributing to CAD may provide insight into novel biological pathways affecting atherosclerosis initiation or progression and ultimately assist in risk assessment information and personalised therapeutic approaches customised on the basis of the individual’s genetic signature.

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