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Progress in genetics of coronary artery disease

To the Editor

Coronary Heart Disease (CHD) is the leading cause of mortality and morbidity worldwide [1] and it is a result of coronary artery disease (CAD). Coronary artery disease refers to the build-up of atherosclerotic plaque in the blood vessels that supply oxygen and nutrients to the heart. Progressive infiltration of the vessel wall by lipoprotein particles carrying cholesterol propagates an inflammatory response by cholesterol-loaded macrophage 'foam cells'. Smooth muscle cells underlying the vessel wall proliferate and lead to remodeling of the vessel that can ultimately lead to a narrowing of the vessel that obstructs blood flow. A myocardial infarction is typically caused when a blood clot is incited by a rupture in the surface of the plaque; this process deprives the heart muscle downstream of the blood clot of adequate blood flow and leads to cell death [2].

The development of the CHD depends on a complex interaction between environmental and genetic factors [3]. The heritability of CAD has been estimated between 40% and 60%, on the basis of family and twin studies, a method that yields high precision despite potential bias [4].

Recent progress in understanding the genetics of CAD has been driven by technological advances, including high-throughput DNA microarray technology using chips containing up to a million DNA markers consisting of single-nucleotide polymorphisms (SNPs). Genome-wide association studies (GWAS) using hundreds of thousands of markers and targeted gene-based resequencing have facilitated the gene discovery for CHD [5,6]. In genome-wide association studies, a susceptibility locus for CHD has been mapped to chromosome 9p21 [7]. The region of chromosome 9p21 contained the coding sequences of a gene for 2 cyclin-dependent kinase inhibitors, CDKN2A and CDKN2B, which played an important role in the regulation of the cell cycle and would be implicated, through their role in transforming growth factor (TGF) induced growth inhibition, in the pathogenesis of atherosclerosis [8]. Helgadottir et al., found that the variant rs2383207 was associated with myocardial infarction (MI) [7]. McPherson et al., found that the homozygotes of the risk alleles of rs2383206 were associated with an increased risk of CHD [9]. A recent report by Qi et al., genotyped 12 CHD susceptibility loci in 3 nested case – control studies of CHD. As expected, the chromosome 9p21 CHD risk locus showed a strong association with CHD risk, whereas 4 other loci [PHACTR1 (phosphatase and actin regulator 1), HNF1A (HNF1 homeobox A), PCSK9 (proprotein convertase subtilisin/kexin type 9), and SORT1 (sortilin 1)] demonstrated associations consistent with those seen in previous GWAS reports [10]. The authors then constructed a simple unweighted genetic risk score (GRS) based on the number of risk alleles carried (each individual will carry 0, 1, or 2 risk alleles at each locus) and assessed the performance of the GRS in predicting CHD.

Progressively larger sample sizes have been used to interrogate the genetic architecture of CAD, yielding ~60 distinct genetic loci for CAD [11]. The vast majority of these variants have a minor allele frequency of >5% in the population, are associated with modest increases in CAD risk and cumulatively explain 30–40% of CAD heritability [12]. By contrast, 15 low-frequency variants identified using a false-discovery rate threshold explained only 2% of CAD heritability [12].

Most of the variants identified to date are located outside protein-coding regions. 5–10% of the loci relate to blood pressure, a known and modifiable causal risk factor for CAD. For example, guanylate cyclase 1, soluble, alpha 3 (GUCY1A3) and nitric oxide synthase 3 (NOS3) are key regulators of vascular tone and platelet aggregation. Common DNA sequence variants at the GUCY1A3 and NOS3 loci have been associated with both blood pressure and CAD [13]. Approximately 20% of the loci are located near genes with known roles in metabolism of low-density lipoprotein (LDL), triglyceride-rich lipoproteins (TRLs) or lipoprotein (a), reinforcing key roles for these pathways in the development of CAD and providing internal validation of common variant association studies findings. Studies to date have identified at least nine genes for which an aggregation of rare mutations alters the risk of CAD [14]. The strongest signal was noted for damaging mutations in low density lipoprotein receptor. A second finding was related to inactivating mutations in PCSK9. Gene sequencing revealed two damaging PCSK9 mutations with an aggregate frequency of 2% of individuals with African ancestry [15]. Carriers of either of these two mutations had substantially lower LDL cholesterol and risk of CAD [15]. Most recently, a whole-genome sequencing study of Icelandic individuals identified a 12 bp deletion that leads to inactivation of ASGR1 (which encodes asialoglycoprotein receptor) [16]. Heterozygous carriers of this mutation had decreased levels of LDL cholesterol and triglycerides, translating into a decreased risk of CAD.

Rare variant association studies have also provided evidence linking genes related to the metabolism of TRLs, in particular those in the lipoprotein lipase (LPL) pathway, with risk of CAD. Individuals harbouring a heterozygous damaging mutation in LPL have increased levels of circulating triglycerides as well as risk of CAD

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[17]. The activity of LPL is regulated by the protein products of multiple additional genes, several of which have been similarly associated with CAD. Damaging mutations in apolipoprotein A5 (APOA5), which encodes a protein that enhances LPL activity, are associated with increased CAD risk [18]. By contrast, rare mutations in APOC3 and ANGPTL4, the protein products of which inhibit LPL, are associated with decreased CAD risk [19].

The study of the genetic architecture of human CAD has led to substantial progress in gene discovery, informing drug development.

Rare genetic mutations in several genes have been noted to confer lifelong resistance to the development of CAD without detectable toxicity. A gene editing-based therapeutic that introduced such mutations via a one-time injection could extend these protective effects into the population [20]. This approach would leverage one of the most significant scientific advances in recent decades, namely use of a clustered regularly interspaced short palindromic repeats (CRISPR) RNA-guided endonuclease system to cleave sequences of the human genome in a highly specific fashion [21]. A single injection of a viral vector designed to target hepatic proprotein convertase subtilisin/kexin type 9 using CRISPR–Cas9 led to mutations in ~50% of hepatocytes and a 40% reduction in cholesterol levels in a mouse model [22]. Similar therapeutics could be designed to decrease circulating TRLs, lipoprotein (a) or other causal risk factors for CAD identified in coming years. For genes in which damaging mutations confer increased risk of CAD (for example, low density lipoprotein receptor), future advances may enable upregulation or potentiation of gene activity [23].

One new therapy targeting APOC3 is showing promise: an antisense oligonucleotide, which is a small stretch of DNA that binds to the APOC3 RNAs to block the protein from being made. This antisense drug has shown substantial reductions in triglyceride levels in humans.

Therapeutic antibodies are an established way to inhibit circulating proteins to treat disease. The recently approved antibody to the PCSK9 protein is one example of this approach for lowering LDL and reducing heart disease [24].

References

[1] Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the global burden of disease study 2010. Lancet 2013;380(9859):2095–128.

[2] P. Libby, in Braunwald's Heart Disease: a Textbook of Cardiovascular Medicine, 10th edn, (eds R.O. Bonow, D.L. Mann, D.P. Zipes, P. Libby), pp. 873–890, Saunders, 2014.

[3] World Health Organization. The 10 leading causes of death in the world, 2000 and 2012. Available at: http://www.who.int/mediacentre/factsheets/fs310/en/. Accessed December 30, 2015.

[4] Vinkhuyzen AA, Wray NR, Yang J, Goddard ME, Visscher PM. Estimation and partition of heritability in human populations using whole genome analysis methods. Annu Rev Genet 2013;47:75–95.

[5] Abecasis G, Tam PK, Bustamante CD, Ostrander EA, Scherer SW, Chanock SJ, et al. Human genome variation 2006: emerging views on structural variation and large-scale SNP analysis. Nat Genet 2007;39(2):153–5.

[6] Roberts R et al. Genetics of coronary artery disease in the 21st century. Clin Cardiol 2012;35(9):536–40.

[7] Helgadottir A, Thorleifsson G, Manolescu A, et al. A common variant on chromosome 9p21 affects the risk of myocardial infarction. Science 2007;316 (5830):1491–3.

[8] Kalinina N, Agrotis A, Antropova Y, et al. Smad expression in human atherosclerotic lesions: evidence for impaired TGF-beta/Smad signaling in smooth muscle cells of fibrofatty lesions. Arterioscler Thromb Vasc Biol 2004;24:1391–6.

[9] McPherson R, Pertsemlidis A, Kavaslar N, et al. A common allele on chromosome 9 associated with coronary heart disease. Science 2007;316:1488–91.

[10] Kalea AZ. Genetic susceptibility for coronary heart disease and Type 2 diabetes complications. Clin Chem 2012;58(5):818–20.

[11] Myocardial Infarction Genetics Consortium. Genome-wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants. Nat Genet 2010;41:334–41.

[12] Nikpay M et al. A comprehensive 1,000 genomes-based genome-wide association meta-analysis of coronary artery disease. Nat Genet 2015;47 (10):1121–30.

[13] Ehret GB et al. The genetics of blood pressure regulation and its target organs from association studies in 342,415 individuals. Nat Genet 2016;48:1171–84.

[14] Khera AV, Kathiresan S. Genetics of coronary artery disease: discovery, biology and clinical translation. Nat Rev Genet 2017;18(6):331–44.

[15] Cohen J et al. Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9. Nat Genet 2005;37(2):161–5.

[16] Nioi P et al. Variant ASGR1 associated with a reduced risk of coronary artery disease. N Engl J Med 2016;374:2131–41.

[17] Khera AV et al. Association of rare and common variation in the lipoprotein lipase gene with coronary artery disease. JAMA 2017;317(9):937–46.

[18] Do R et al. Exome sequencing identifies rare LDLR and APOA5 alleles conferring risk for myocardial infarction. Nature 2015;518(7537):102–6.

[19] Dewey FE et al. Inactivating variants in ANGPTL4 and risk of coronary artery disease. N Engl J Med 2016;374:1123–33.

[20] Choudhry NK et al. Full coverage for preventive medications after myocardial infarction. N Engl J Med 2011;365:2088–97.

[21] Mali P et al. RNA-guided human genome engineering via Cas9. Science 2013;339(6121):823–6.

[22] Ding Q et al. Permanent alteration of PCSK9 with in vivo CRISPR–Cas9 genome editing. Circ Res 2014;115(5):488–92.

[23] Blendon RJ, Gorski MT, Benson JM. The public and the gene-editing revolution. N Engl J Med 2016;374(15):1406–11.

[24] Khetarpal SA et al. A human APOC3 missense variant and monoclonal antibody accelerate apoC-3 clearance and lower triglyceride- rich lipoprotein levels. Nat Med 2017;23:1086–94.

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