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Dr Malcolm Legget

Genetics, Genomics, and Coronary Artery Disease

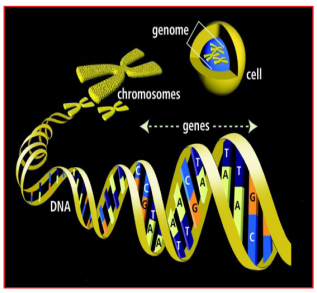
By Dr. Malcolm Legget

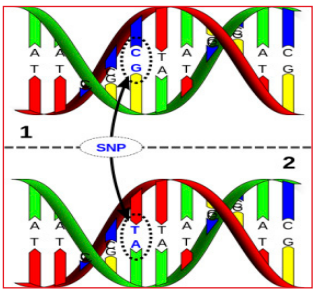
We have all been faced with the tragic situation of a distraught patient whose close family member has just dropped dead at a young age from a heart attack. We empathise but feel powerless to help. The conversation inevitably leads to the comment "well it's in the family of course". How much of coronary artery disease (CAD) is genetically determined, and how is the genomic revolution helping us to unravel the secrets of how our own DNA may predispose us to the world's biggest killer? Traditional risk factors such as elevated cholesterol, smoking, hypertension and diabetes have been used to predict cardiovascular risk and have been targeted to reduce the incidence of CAD, but it has been shown by twin and family studies that approximately 50% of the susceptibility to CAD is genetically based. This brief review will touch on aspects of genetics and heart disease, in terms of risk prediction, susceptibility to CAD, and insights into mechanisms and new treatment paradigms.

Genetic Sequencing

The first human genome was sequenced in 2000 at a cost of over $3 billion. Whole genome sequencing can now be performed for around $5000, and there have been parallel increases in the bioinformatic capability required to process and interpret the huge amount of data produced.

A human genome contains over 3 billion base pairs and over 15 million single nucleotide polymorphisms or SNPs (the substitution of a single base) which account for most of the genetic diversity of the human race. In the last few years genome wide association studies (GWAS) have identified thousands of disease susceptibility markers underpinning common "polygenic" disorders as well as single gene disorders in large case control studies. We are now moving into the era of whole genome and whole exome sequencing which will yield more detailed insights.

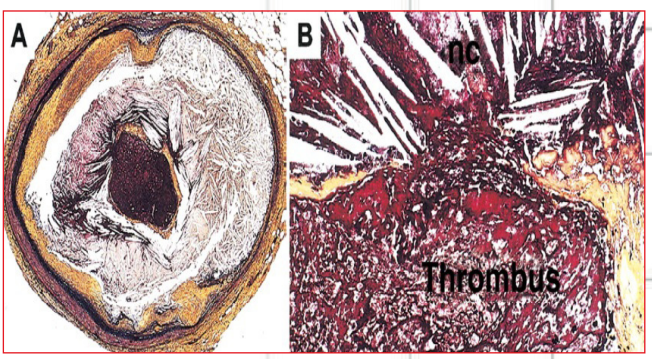




The Genetics of CAD

In contrast to single gene disorders, CAD is a polygenic disorder, where multiple genes with a small effect play a role on the ultimate phenotypic expression of disease in a given individual. The most significant study to inform us of the genetic predisposition to CAD is the CARDIoGRAMplus C4D(Coronary Artery Disease Genome-wide Replication and Meta Analysis) study [1] which is a massive collaboration now involving approximately 64,000 cases of CAD and 131,000 controls. There were 46 genetic variants detected for CAD, of which only 12 showed association with blood lipids and 5 with blood pressure. An example of this is the 9p21.3 locus risk allele which is carried by 75% the European population, with homozygotes (2 copies) having a 50% increased risk of CAD, and a twofold increased likelihood of developing premature CAD, which is equivalent to the risk from smoking. It is also associated with the extent of CAD, abdominal aortic aneurysm and stroke.

Interestingly none of the risk variants were associated with diabetes, and a large number are independent of known risk factors for CAD, and are located in DNA sequences that do not code for proteins. This is particularly exciting as there must therefore be other mechanisms contributing to the development of CAD that have not yet been discovered. These probably act through a few common molecular pathways, mainly related to lipid metabolism and inflammation, which may be able to be targeted with new therapies. It is estimated that only about 10% of the heritability of CAD can be explained by the variants that have been discovered so far. There are many possible reasons for this "heritability gap" which is the subject of intense research.[2]



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Genetic Profiling

Can genetic information be incorporated into current risk factor calculation? DNA variants do not change throughout life and are not altered by drugs or illness so it is conceivable that testing could be done in early adulthood or even at birth. Also, family history based on self reporting is notoriously inaccurate, and there is variable penetrance so that an individual's risk is difficult to estimate on the basis of family history alone. However, routine genetic testing is unlikely to be recommended until it can be proven that this will improve patient management. Given that each risk variant only increases the relative risk of developing CAD by about 15%, a genetic risk score has been developed incorporating a limited SNP panel, which showed an improved categorization of cases of CAD on top of standard risk factors, but it is not currently recommended for use in screening populations. It is likely that as more variants and pathways are identified, analysis of their utility in risk prediction and translation into therapy will result in incorporation of genetic testing into clinical practice, but this is not the case at present. The major challenge will be for the physician and patient to be able to interpret the information in a meaningful way that will lead to an improvement in cardiovascular health.

Genetics and Mechanisms of CAD

An important application of genetics has been the use of the "Mendelian randomization" approach to establish a link between key intermediate phenotypes (such as cholesterol level, glucose level and markers of inflammation) and complex traits. This is known as "nature's own randomised trial", and takes advantage of the fact that genes are randomly assorted and transferred to the offspring in an unbiased fashion at conception.[3] These studies have shown that CRP is in fact a marker and not a causative factor for CAD. [4] Conversely, the LPA gene has been shown to be strongly correlated with CAD, and the presence of certain risk variants which influence Lp(a) particle size and plasma levels were found to be strongly linked to CAD.[5] This has led to recommendations to routinely screen for Lp(a) levels in those at intermediate risk. [6]

Statins were developed by studying the gene encoding the LDL cholesterol receptor. New therapies that modulate LDL cholesterol by other pathways, for example the PCSK9 molecule are undergoing Phase III trials and were discovered by studying gain and loss of function variants in the PCSK9 gene which alters LDL receptor turnover. Monoclonal antibodies to PCSK9 are being developed which can dramatically lower cholesterol levels and may be an alternative or an adjunct to statin therapy.[7]

Pharmacogenetics

A major application of genomics has been in the ability to predict response to drug therapy. The prototype example of this is clopidogrel, where the (CYP) 2C19 loss of function variant carriers have a diminished response to the drug, whereas those with a gain of function variant have an increased risk of bleeding. This can result in important clinical endpoints such as stent thrombosis. Genetic tests can also predict the risk of bleeding and the maintenance dose of warfarin. A rare SNP in the LPA gene predicts those most likely to benefit from aspirin therapy. The SLCO1B1 polymorphism is highly predictive of a markedly increased risk of myopathy with statins. Although a more personalized approach to drug prescribing is desirable, widespread adoption of pharmacogenetics is not yet a reality.[8, 9]

Conclusion

A revolution of knowledge has occurred in the genetics of heart disease over the last few years. The challenge now facing clinicians and scientists is how these discoveries can be incorporated into clinical practice in a robust scientific manner. There is no doubt that a more individualised approach to risk prediction, monitoring and treatment of patients will be possible with the convergence of bioinformatics and an enhanced understanding of the secrets lying within our DNA. The patient coming in with their entire genome on a memory stick asking "what does it all mean Doc?" may not be that far away.

References

1. *CARDIoGRAMplusC4D consortium , Large-scale association analysis identifies new risk loci for coronary artery disease. Nat Genet, 2013. 45(1): p. 25-33.*
2. *Roberts, R. and A.F. Stewart, Genes and coronary artery disease: where are we? J Am Coll Cardiol, 2012. 60(18): p. 1715-21.*
3. *Burgess, S., et al., Use of Mendelian randomisation to assess potential benefit of clinical intervention. BMJ, 2012. 345: p. e7325.*
4. *Wensley, F., et al., Association between C reactive protein and coronary heart disease: mendelian randomisation analysis based on individual participant data. BMJ, 2011. 342: p. d548.*
5. *Kamstrup, P.R., et al., Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. JAMA, 2009. 301(22): p. 2331-9.*
6. *Nordestgaard, B.G., et al., Lipoprotein(a) as a cardiovascular risk factor: current status. Eur Heart J, 2010. 31(23): p. 2844-53.*
7. *Stein, E.A. and F.J. Raal, Insights into PCSK9, low-density lipoprotein receptor, and low-density lipoprotein cholesterol metabolism: of mice and man. Circulation,*
8. *Damani, S.B. and E.J. Topol, Emerging genomic applications in coronary artery disease. JACC Cardiovasc Interv, 2011. 4(5): p. 473-82.*
9. *Roberts, R., et al., Genomics in cardiovascular disease. J Am Coll Cardiol, 2013. 61(20): p. 2029-37.*