Genetics and Molecular Biology : Identification of dyslpidemia genes

Editorial Comment

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Diabetes, hypertension and hypercholesterolemia are established risk factors associated with the development of atherosclerosis and cardiovascular disease (CVD) including myocardial infarction (MI) and stroke. Recently, a family history of adverse cardiovascular events has also been recognised as a significant independent risk factor. Despite evidence that 40 to 60 % of coronary artery disease (CAD) and myocardial infarction (MI) are associated with genetic heritability, the genetic basis of these diseases is not fully resolved **[1,2]**. Mendelian forms of hypertension and hypercholesterolemia have been well characterised **[3,4].** Most of our knowledge of lipoprotein genetics stems from monogenic familial disorders of lipoprotein metabolism with extreme phenotypes e.g. familial hypercholesterolemia is characterised by highly elevated serum levels of LDL-C **[4]**. Genome-wide linkage studies have reliably identified genes responsible for these conditions, however, they constitute only a minor proportion of total lipoprotein disorders. New approaches to determine which common genetic variants may be responsible for lipid disorders within the wider population have concentrated on the association between clinical phenotype and single nucleotide polymorphisms (SNPs) or genetic loci in multiple genes known to influence risk factors **[5,6•]**. These systematic genome-wide association studies (GWAS) have identified several new loci **[7,8]**.

Blood lipid levels are genetic phenotypes and are influenced by multiple genetic and environmental factors. Heritability for LDL-C, HDL-C and triglycerides is estimated to be in the region of 50 % **[5]**. Examples of sequence variants in individual genes linked to blood lipid phenotypes include *APOE/PCSK9* with LDL-C, *CETP/LIPC/LPL* with HDL-C, and *APOA5* with triglycerides. Much of this data has been derived from cohorts of white individuals of European ancestry. A new study by Keebler *et al*. **[9••]** is the first to investigate whether newly identified single-nucleotide polymorphisms (SNP) from GWA studies at 19 loci associated with blood lipids in individuals of European origin are also found in subjects of different ethnicities. Participants were from the National Health and Nutrition Examination Survey (NHANES) III cohort. Following exclusion for missing phenotype, age below 18 years and those on lipid-lowering drugs the group comprised 1627 non-Hispanic blacks, 1659 Mexican Americans and 2230 non-Hispanic whites. Blood levels of HDL-C and triglycerides were measured using standard enzymatic techniques, LDL-C was calculated using the Friedwald formula. DNA was isolated from cell lines derived from blood samples. Genotyping was carried out on the

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Sequenom platform. Ethnic-specific blood lipid levels were determined adjusting for age and gender and ethnic-specific linear regression was used to examine the association of genotype with blood lipids. A fixed-effects variance-weighted meta analysis was used to summarise the statistical data. $P \leq 0.05$ for the same allele at the same SNP for the same trait described in the original reports was deemed significant. At 5 loci the same SNP identified in whites was found to be significantly associated with blood lipids across all ethnic groups. At 1p13 near *PSRC1/CELSR2/SORT1*, rs646776 and at *HMGCR*, rs12654264 were associated with LDL-C. In all groups each copy of the minor G allele in polymorphism rs646776 lowered LDL-C. SNPs, r1800775 at *CETP* and rs328 at *LPL* were associated with HDL-C. Increases in minor allele copy number of r1800775 and rs328 resulted in decreases and increases in HDL-C respectively. At *APOA5*, an increase in minor allele copy number of rs3135506 was associated with increases in triglyceride levels. Variable results at the remaining loci suggest more work is required to study each locus in blacks and Mexican Americans. These data indicate that all 5 loci are important for controlling lipid profiles across ethnic/racial groups and highlight the relevance of the newly discovered locus at 1p13 near *PSRC1/CELSR2/SORT1*. This locus could be pivotally important in dyslipidaemias with phenotypic consequences in disease processes.

GWA studies have identified common variants in the fat mass and obesity (*FTO*) gene associated with body mass index (BMI) and increased risk of obesity **[10,11]**. Increases in body fat are well acknowledged to increase the risk of insulin resistant type 2 diabetes (T2D) and CVD. In a recent study Doney *et al*., **[12•]** examined the clinical impact of genetic variation of SNP rs9939609 in *FTO* at 16q10 on the risk of MI in 4897 patients with T2D from the prospective Genetics and Diabetes Audit and Research Study in Tayside Scotland (Go-Darts) Study. The rs9939609 A allele was found to be associated with increased BMI, lower plasma HDL-C levels, higher plasma triglycerides, greater atherogenic index of plasma and increased risk of MI during follow-up (mean 3.6 years) compared to TT homozygotes. Interestingly increased risk of MI was observed only in nonstatin users (predominantly TT homozygotes) and was abolished by statin use (predominantly carriers of the A allele) suggesting *FTO* genotype may provide a therapeutic target.

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This review outlines recent studies that have advanced our understanding of genes and gene regions responsible for controlling serum lipid levels and discusses the potential to generate a panel of clinically useful polymorphisms.

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The FTO rs9939609 A allele was shown to be associated with low HDL-C and high plasma triglyceride levels and increased risk of MI. Statins reduced deaths suggesting the FTO genotype may provide a therapeutic target.

Further recommended reading

- Pirruccello J & Kathiresan S. **Genetics of lipid disorders**. Curr Opin Cardiol 2010, 25: 238-242.
  This review outlines recent studies that have advanced our understanding of genes and gene regions responsible for controlling serum lipid levels and discusses the potential to generate a panel of clinically useful polymorphisms**.**

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  Oestrogen protects against CVD and acts by binding to receptors. Two types of receptor, have been identified, a G-protein coupled receptor and a ligand binding nuclear receptor or transcription factor (ER). ER exists in two forms, α and β, encoded by different genes *ESR1* (6q25.1) and *ESR2* (14q). This study confirms that 2 SNP, PvuII (rs2234693) and Xbal (rs9340799) of *ESR1*, previously identified in Western populations, are also associated with increased risk of hyperlipidemia in Chinese postmeopausal women. Risk was independent of age, estradiol levels. BMI and lifestyle.