atherosclerosis

Atherosclerosis newsletter

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The two January issues contain several articles on the genetics of dyslipidemia and risks of cardiovascular disease and diabetes

Genetic mutations, regression of Achilles tendon thickness, and cardiovascular events among patients with familial hypercholesterolemia

Familial hypercholesterolemia (FH) is a genetic disorder characterized by very high levels of low-density lipoprotein (LDL). Several types of FH clinical diagnostic criteria exist. The Dutch Lipid Clinical Network and Japan Atherosclerosis Society clinical diagnostic elements include assessment of hyper LDL cholesterolemia, family history, and Achilles tendon thickness (ATT). In FH patients, ATT can be regressed through LDL-lowering, similar to the regression of coronary atherosclerotic plaque. Tada et al. aimed to determine factors associated with regression of ATT and its role in development of major adverse cardiovascular events (MACE).

Patients with clinically diagnosed FH were retrospectively assessed. FH-related gene mutations and ATT data using X-ray were collected. Factors associated with deterioration of ATT were assessed by multivariable linear regression analysis while Cox proportional hazards models were used to determine factors associated with MACE, including cardiovascular death and acute coronary events.

The median follow-up period was 12.6 years. FH-linked mutations were identified in 777 patients. During the follow-up period, 113 MACEs were observed, and median ATT regressed from 8.7 to 8.5 mm. In addition, there was a more significant positive correlation between cholesterol-year score and ATT among patients with FH-related gene mutations. Multivariable linear regression analyses revealed that age, hypertension, and diabetes were positively correlated with changes in ATT (progression). Baseline ATT and FH-related mutations were negatively correlated with changes in ATT (regression). Considering these confounding factors, regression of ATT was significantly associated with reduced MACE.

In FH patients, assessment of ATT and the presence of FH-linked gene mutations have a diagnostic value and provide risk stratification information.

Assessment of practical applicability and clinical relevance of a commonly used LDL-C polygenic score in patients with severe hypercholesterolemia

Low-density lipoprotein cholesterol (LDL-C) levels vary in patients with familial hypercholesterolemia (FH) and can be explained by a single deleterious genetic variant or by the aggregate effect of multiple, common small-effect variants that can be captured in a polygenic score (PS). Tromp et al. investigated the contribution of a previously published PS to the inter-individual LDL-C variation and coronary artery disease (CAD) risk in patients with a clinical FH phenotype.

In a cohort of 628 patients referred for genetic FH testing, they evaluated the distribution of a PS for LDL-C comprising 12 genetic variants. Next, they determined its association with coronary artery disease (CAD) risk using UK Biobank data.

The mean PS was higher in 533 FH-variant-negative patients (FH/M-) compared with 95 FH-variant carriers. 39% of all patients had a PS equal to the top 20% from a population-based reference cohort and these patients were less likely to carry an FH variant compared with patients in the lowest 20%. In UK Biobank data, the PS explained 7.4% of variance in LDL-C levels and was associated with incident CAD. Addition of PS to a prediction model using age and sex and LDL-C did not increase the c-statistic for predicting CAD risk.

This 12-variant PS was higher in FH/M- patients and associated with incident CAD in UK Biobank data. However, the PS did not improve predictive accuracy when added to the readily available characteristics age, sex and LDL-C, suggesting little clinical benefit.

Polygenic architecture and cardiovascular risk of familial combined hyperlipidemia

Familial combined hyperlipidemia (FCHL) is one of the most common inherited lipid phenotypes, characterized by elevated plasma concentrations of apolipoprotein B-100 and triglycerides. The genetic architecture of FCHL remains incompletely understood, because of the heterogeneous clinical definitions used to identify it, and the presumed complex genetic inheritance. It has been suggested that most cases of FCHL may arise from the interaction between polygenic susceptibility, co-morbidities, and environmental factors. However, there is limited data to directly support this hypothesis from genome-wide association studies of FCHL in large population studies. Trinder et al. aimed to investigate the polygenetic architecture and cardiovascular risk associated with FCHL.

Individuals with an FCHL phenotype were identified among 349,222 unrelated participants of European ancestry in the UK Biobank using modified versions of 5 different diagnostic criteria.

The prevalence of the FCHL phenotype was 11.44%, 5.01%, 1.48%, 1.10%, and 0.48% according to modified versions of the Consensus Conference, Dutch, Mexico, Brunzell, and Goldstein criteria, respectively. Discovery, case-control genome-wide association studies for these different FCHL criteria

identified 175 independent loci associated with FCHL at genome-wide significance. The association of genetic and clinical risk with FCHL was assessed and it was found that polygenic susceptibility to hypercholesterolemia or hypertriglyceridemia and features of metabolic syndrome were associated with greater prevalence of FCHL. Participants with an FCHL phenotype had a similar risk of incident coronary artery disease compared to participants with monogenic familial hypercholesterolemia.

These results suggest that, rather than being a single genetic entity, the FCHL phenotype represents a polygenic susceptibility to dyslipidemia in combination with metabolic abnormalities. The cardiovascular risk associated with an FCHL phenotype is similar to that of monogenic familial hypercholesterolemia, despite being ~5x more common.

Role of mitochondrial DNA copy number in incident cardiovascular diseases and the association between cardiovascular disease and type 2 diabetes: A follow-up study on middle-aged women

The mitochondrial genome is a non-chromosomal DNA, which plays an important role in a variety of homeostatic and signalling processes. Due to its close proximity with high concentrations of reactive oxygen species (ROS), mitochondrial DNA (mtDNA) is highly susceptible to oxidative stress; this may lead to mitochondrial dysfunction, characterized by a loss of efficiency in the electron transport chain and reduction in energy production. Moreover, mtDNA-CN is associated with type 2 diabetes (T2D) and cardiovascular disease (CVD). However, its role in the association between T2D and CVD is unknown. Sundquist et al. investigated whether baseline mtDNA-CN is associated with CVD incidence and has a role as a mediator between T2D and CVD.

Absolute mtDNA-CN was quantified by droplet digital PCR method in a population-based follow-up study of middle-age women. The median follow-up period was 17 years.

The results show that low baseline levels of mtDNA-CN (<111 copies/µL) were associated with an increased risk of CVD, as well as with specific CVDs: coronary heart disease, stroke and abdominal aortic aneurysm. The associations decreased but persisted even after adjustment for potential confounders. Furthermore, the total effect of T2D on future risk of CVD was reduced after controlling for mtDNA-CN and the proportion mediated by mtDNA-CN was estimated to be 4.9%.

Lower baseline mtDNA-CN is associated with incident CVD and may have a mediating effect on the association between T2D and CVD. If this novel observation is confirmed, mtDNA-CN has the potential to identify individuals with higher risk of CVD for early clinical intervention.