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Atherosclerosis newsletter

Simona Negrini and Arnold von Eckardstein

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Issues 349 and 350 of *Atherosclerosis* contain several articles on genetic dyslipidemias and genetically determined cardiovascular risk, as well as genetic methods to test causality between risk factors and manifest disease or identification of novel atherogenic pathways.

Prevalence and patient characteristics of familial hypercholesterolemia in a Chinese population aged 35–75 years: Results from China PEACE Million Persons Project

Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder causing premature coronary artery disease (CAD) due to lifelong elevated plasma low-density lipoprotein cholesterol (LDL-C) levels. According to the data from European studies, the prevalence of heterozygous FH is currently 0.2%–0.5% in Europe, while no such data has yet been published on the general population in China. Teng et al. aimed to investigate the prevalence and characteristics of FH in a Chinese population aged 35–75 years.

The authors obtained data from the China PEACE (Patient-centered Evaluative Assessment of Cardiac Events) MPP (Million Persons Project), a nationwide, population-based project that screened 3.7 million Chinese aged 35–75 years from 31 provinces in mainland China. The diagnosis of FH was based on 2 of the 3 diagnostic criteria from the Chinese expert consensus on diagnosis of FH (CEFH criteria). FH prevalence was estimated and clinical phenotypic characteristics were further analyzed.

The overall FH prevalence was 0.13% according to the CEFH criteria, and age and sex standardized FH prevalence was slightly lower. FH prevalence in female was twice as high as in male. Across different age groups, the prevalence also varied and peaked among 55 to 64-year-olds. Regarding geographical areas, the prevalence ranged from 0.19% in Eastern, to 0.11% in Central, and 0.08% in Western China. Participants living in rural areas had a lower prevalence than urban participants. The rate of coronary artery disease in FH patients was 5 folds higher than in the general population. The rate of FH patients receiving lipid-lowering medications was 18.1%. None of the treated patients achieved guideline recommended LDL-C targets.

The estimation of FH prevalence among 1.1 million Chinese population aged 35–75 years is 0.13%. FH patients ae surprisingly undertreated and uncontrolled even for those taking lipid-lowering

medication and statins. The prevalence of premature CAD and ischemic stroke is higher in FH patients, indicating the paramount importance of FH screening in China.

Quality of life and coping in Dutch homozygous familial hypercholesterolemia patients: A qualitative study

Homozygous familial hypercholesterolemia (HoFH) is characterized by severely elevated low-density lipoprotein cholesterol (LDL-C) levels leading to extremely premature atherosclerotic cardiovascular disease. Therefore, healthcare professionals consider HoFH to have major impact on patients' life. Remarkably, little is known on how patients deal with their condition. Mulder et al. investigated how Dutch patients experience and cope with HoFH in daily life.

Adult patients with genetically confirmed HoFH, treated at the 3 specialized HoFH-centers in the Netherlands, were interviewed in-depth. Interview transcripts were analyzed according to grounded theory. Health-related quality of life (QoL) and coping were measured with the EuroQol (EQ)-5D-5L questionnaire and the Threatening Medical Situations Inventory (TMSI), respectively.

20 Dutch HoFH patients were interviewed: 50% women, median age 38 years, 60% with cardiovascular disease, 10% on apheresis. Coding of the transcripts resulted in a conceptual model, with disease perception as the central theme. Individual TMSI-results corresponded to the interviews, with most patients showing both monitoring (information-seeking behavior) and blunting (distractive strategies) coping styles. The median EQ-5D-5L health utility score (0.839) was only 5% below the Dutch population. Transient anxiety was reported when confronted with the consequences of HoFH in daily life. Patients reported high confidence in treatment by a dedicated HoFH center, which helped them cope with their disease.

Dutch HoFH patients use a variety of effective coping mechanisms in such a way that their subjective QoL is only slightly affected. Healthcare professionals can use this knowledge to tailor their care to the specific needs of these patients.

Genetic variants associated with low-density lipoprotein cholesterol and systolic blood pressure and the risk of recurrent cardiovascular disease in patients with established vascular disease

Polygenic risk scores (PRSs) aggregate the modest effects of multiple single nucleotide polymorphism (SNPs) into a single score as a proxy for lifelong exposure to a given trait. As demonstrated earlier, including genetic information in risk models could potentially contribute to the improvement of personalized cardiovascular risk prediction or to the identification of high-risk patients, who might benefit from stricter treatment goals through treatments. In this context, PRSs can be used to quantify the effect of genetic contribution to low density lipoprotein cholesterol (LDL-C) and systolic blood pressure (SBP). Several PRSs for LDL-C and SBP have been shown to be associated

with cardiovascular disease (CVD) in the general population. Groenland et al. aimed to evaluate the effect of an LDL-C PRS and an SBP PRS on the risk of recurrent CVD in patients with CVD.

Genotyping was performed in 4,416 patients included in the Utrecht Cardiovascular Cohort – Second Manifestations of Arterial Disease (UCC-SMART) study, an ongoing, single-center, prospective cohort at the tertiary referral center University Medical Center Utrecht (UMCU) in the Netherlands. Weighted LDL-C PRS (279 LDL-C-related SNPs) and SBP PRS (425 SBP-related SNPs) were calculated. Linear regression models were used to evaluate the relation between both PRSs and LDL-C and SBP. The effects of the LDL-C PRS and SBP PRS and its combination on the risk of recurrent CVD (stroke, myocardial infarction, and vascular death) were analyzed with Cox proportional-hazard models.

Per SD increase in LDL-C PRS, LDL-C increased by 0.18 mmol/L. Per SD increase in SBP PRS, SBP increased by 3.19 mmHg. During a follow-up of 11.7 years, 1,198 recurrent events occurred. Neither LDL-C nor SBP PRS were associated with recurrent CVD and HR 1.04 per SD increase in SBP PRS. The combination of both scores was not associated with recurrent CVD.

In patients with vascular disease, LDL-C PRS and SBP PRS, both separately and in combination, were not significantly associated with recurrent CVD. Genetically determined LDL-C and SBP do not explain residual cardiovascular risk in patients with CVD.

Prediction of incident atherosclerotic cardiovascular disease with polygenic risk of metabolic disease: Analysis of 3 prospective cohort studies in Korea

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death worldwide, but there are discrepancies in its incidence and patterns between ethnicities and populations, with a lower incidence in East Asians than in Caucasians. Studies have demonstrated that the risk of atherosclerotic cardiovascular disease (ASCVD) can be assessed by polygenic risk score (PRS) using common genetic variants. Because metabolic syndrome is a well-known, robust risk factor of ASCVD, Song et al. established PRS of metabolic disease and analyzed whether this PRS could predict incident ASCVD.

They constructed PRSs for eight quantifiable metabolic phenotypes—systolic/diastolic blood pressure, body mass index (BMI), four blood lipid components, and fasting blood glucose—by genome-wide association studies of two prospective Korean cohorts. Then they conducted a grid search of combinations of metabolic PRSs to identify the most optimal weighted score for incident ASCVD (PRSMetS-ASCVD). The utility of PRSMetS-ASCVD was validated in an independent prospective cohort.

The individuals in the highest PRS quintile demonstrated a 1.4–2.0-fold increased risk of incident hypertension, obesity, hyperlipidemia, and diabetes. Using the PRSMetS-ASCVD, the authors identified 6.7% of the population as a high risk group demonstrating a 3.3-fold higher risk for incident ASCVD. The model combining the PRSMetS-ASCVD demonstrated a better performance for predicting ASCVD than that consisting of only conventional risk factors, such as age, sex, BMI, smoking,

hypertension, diabetes and hyperlipidemia. The population with high PRSMetS-ASCVD minimally overlapped with that of high Framingham risk score, thus suggesting the additive independent benefits beyond the Framingham risk score, especially in younger individuals.

The polygenic risk of metabolic disease independently predicts those at an increased risk of ASCVD, identifying those at a genetically high risk of incident ASCVD. The performance of this model is equivalent to or higher than that of well-known cardiovascular risk factors and provides independent benefits beyond the Framingham risk score, especially in younger individuals.

Changes in adiposity modulate the *APOA5* genetic effect on blood lipids: A longitudinal cohort study

Apolipoprotein A5 (*APOA5*) gene has been widely reported to be related to triglyceride (TG) and high density lipoprotein cholesterol (HDL-c) metabolism by genome-wide association studies (GWAS). The *APOA5* rs662799 has been associated with elevated TG, decreased HDL-c, metabolic syndrome (MetS), and cardiovascular diseases. Whether dynamic changes of adiposity influence the effect of lipid loci on long-term blood lipid profile remains unclear. Lin et al. assessed interactions of 5-year body mass index (BMI) change and rs662799 genotypes with risk of incident dyslipidemia and longitudinal changes in serum lipids in a prospective cohort.

They included in the study 4329 non-dyslipidemia participants aged ≥ 40 years at baseline from a well-defined community-based cohort and followed up for an average of 5 years. BMI and blood lipids were measured at both time points.

The association of each rs662799 A-allele with risk of incident dyslipidemia was stronger along with the increase in BMI change levels, with odds ratios (OR) increasing from 1.03 in the lowest tertile of BMI change to 1.17 in the second, and 1.46 in the highest tertile. Associations of each 1-unit of BMI increase with incident dyslipidemia were more prominent in the AA carriers, while much weaker in the GA or GG carriers. Similar results were found for the risk of incident higher triglyceridesand lower high-density lipoprotein cholesterol, or the longitudinal changes in $\log_{10}$-TG.

BMI changes significantly modulate rs662799 genetic contribution to dyslipidemia and long-term lipid profile, which provide new evidence for personalized clinical management of lipids according to individual genetic background.

Self-reported and genetically predicted coffee consumption and smoking in dementia: A Mendelian randomization study

Due to a steady increase in the number of elderly people, dementia has become one of the greatest global health challenges. Dementia is not an inevitable consequence of aging, but its risk is influenced by several lifestyle factors early in life. Coffee consumption and smoking are important modifiable lifestyle factors. Studies of self-reported coffee consumption and smoking on risk of

dementia have shown results conflicting with two-sample Mendelian randomization studies. Nordestgaard et al. tested the hypotheses that coffee consumption and smoking influence risk of dementia using observational and one-sample Mendelian randomization designs with individual level data.

The authors included in their study 114,551 individuals from two Danish general population cohorts (median age 58 years). First, they tested whether high self-reported coffee consumption/smoking were associated with risk of dementia. Second, whether genetically predicted high coffee consumption/smoking due to variation near CYP1A1/AHR/CHRNA3 genes were associated with risk of dementia.

3,784 dementia events were observed. Moderate self-reported coffee consumption was associated with low risk of all dementia and non-Alzheimer's dementia, with a similar trend for Alzheimer's disease. Genetically predicted high coffee consumption was associated with high risk of all dementia, with a similar trend for non-Alzheimer's dementia. High self-reported smoking was associated with high risk of non-Alzheimer's dementia. High genetically predicted smoking was associated with a trend towards high risk of all dementia and Alzheimer's disease.

Moderate self-reported coffee consumption was associated with low risk of all and non-Alzheimer's dementia, while high genetically predicted coffee consumption was associated with a trend towards the opposite. High self-reported smoking was associated with high risk of non-Alzheimer's dementia, with a similar trend for genetically predicted smoking on all dementia and Alzheimer's disease.

A novel anti-inflammatory role links the *CARS2* locus to protection from coronary artery disease

Genome-wide association studies (GWAS) identified a coronary artery disease (CAD) risk locus on 13.q34 tagged by rs61969072 (T/G). This variant lies in an intergenic region, proximal to inhibitor of growth family member (*ING1*), carbohydrate kinase domain containing protein (*CARKD*) and cysteine--tRNA ligase (*CARS2)* but its causal relationship to CAD is unknown.

Dang et al. demonstrated that rs61969072 and tightly linked single nucleotide polymorphisms (SNPs) associate with CARS2 but not ING1 or CARKD expression in carotid endarterectomy samples, with reduced CARS2 abundance in carriers of the CAD risk allele (G). THP-1 monocytes were differentiated and polarized to proinflammatory (M1) and anti-inflammatory (M2) macrophages. CARS2 gene expression decreased in M1 and increased in M2 macrophages, consistent with a role for CARS2 in inflammation. Gene expression profiling revealed an increase in pro-inflammatory markers in response to *CARS2* siRNA knockdown in THP-1 derived macrophages, accompanied by an increased abundance of inflammatory cytokines in the cell supernatant. Functional enrichment analysis of impacted transcripts identified the anti-inflammatory IL10 signalling pathway. Western blot analysis

of CARS2 silenced macrophages revealed reduced STAT3 phosphorylation in response to IL-10 and increased expression of LPS-induced genes that are repressed by IL-10, indicating a role for CARS2 in anti-inflammatory signalling. Finally, to simulate vessel wall conditions, macrophages, and smooth muscle cells (SMC) were maintained in co-culture. Significantly, *CARS2* silencing in macrophages altered the SMC phenotype, decreasing expression of contractile genes and increasing expression of inflammatory genes.

These data highlight a novel anti-inflammatory novel role for CARS2 in human macrophages and SMCs that may underlie the protective effect of a common GWAS-identified variant.