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ORIGINAL INVESTIGATIONS

Genomic Risk Prediction of Coronary Artery Disease in 480,000 Adults

Implications for Primary Prevention

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ABSTRACT

BACKGROUND Coronary artery disease (CAD) has substantial heritability and a polygenic architecture. However, the potential of genomic risk scores to help predict CAD outcomes has not been evaluated comprehensively, because available studies have involved limited genomic scope and limited sample sizes.

OBJECTIVES This study sought to construct a genomic risk score for CAD and to estimate its potential as a screening tool for primary prevention.

METHODS Using a meta-analytic approach to combine large-scale, genome-wide, and targeted genetic association data, we developed a new genomic risk score for CAD (metaGRS) consisting of 1.7 million genetic variants. We externally tested metaGRS, both by itself and in combination with available data on conventional risk factors, in 22,242 CAD cases and 460,387 noncases from the UK Biobank.

RESULTS The hazard ratio (HR) for CAD was 1.71 (95% confidence interval [CI]: 1.68 to 1.73) per SD increase in metaGRS, an association larger than any other externally tested genetic risk score previously published. The metaGRS stratified individuals into significantly different life course trajectories of CAD risk, with those in the top 20% of metaGRS distribution having an HR of 4.17 (95% CI: 3.97 to 4.38) compared with those in the bottom 20%. The corresponding HR was 2.83 (95% CI: 2.61 to 3.07) among individuals on lipid-lowering or antihypertensive medications. The metaGRS had a higher C-index (C = 0.623; 95% CI: 0.615 to 0.631) for incident CAD than any of 6 conventional factors (smoking, diabetes, hypertension, body mass index, self-reported high cholesterol, and family history). For men in the top 20% of metaGRS with >2 conventional factors, 10% cumulative risk of CAD was reached by 48 years of age.

CONCLUSIONS The genomic score developed and evaluated here substantially advances the concept of using genomic information to stratify individuals with different trajectories of CAD risk and highlights the potential for genomic screening in early life to complement conventional risk prediction. (J Am Coll Cardiol 2018;72:1883–93)

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CAD = coronary artery disease

CI = confidence interval

GRS = genomic risk score(s)

HR = hazard ratio

As coronary artery disease (CAD) is the leading cause of morbidity and mortality worldwide, early identification of individuals who are at high risk of CAD is essential for primary prevention. As the heritability of CAD has been estimated to be 40% to 60%, comprehensive information on genetic susceptibility could contribute importantly to CAD risk stratification (1,2).

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Although family history has long been identified as a risk factor for CAD, elucidation of the genetic architecture of CAD has advanced substantially only during the past decade with the advent of genome-wide association studies. Results from these assumption-free surveys across the genome have laid foundations for developing genomic risk scores (GRS) in the estimation of an individual's underlying genomic risk (3–9). Furthermore, because GRS are based on germline DNA, they are quantifiable in early life, at or before birth. Hence, they offer the potential for early risk screening and primary prevention before other conventional risk factors become informative.

Due to several inter-related factors, however, previous GRS for CAD have been unable to provide comprehensive assessment of the potential of using genomic information in CAD risk prediction. First, because previously published GRS have utilized only genetic variants of genome-wide significance (4,5,8) or involved genotyping arrays that focused only on pre-selected loci (3), they have not fully utilized genome-wide variation, preventing accurate estimation of the relative contribution of each genetic variant to CAD risk. Second, because previous studies of GRS have tended to have moderate statistical power, they have been unable to provide precise effect size estimates (10–12). Third, because previous studies of GRS have largely lacked external testing in large-scale cohorts that represent a diversity of ancestries (3) and typically have involved only a narrow spectrum of CAD burden (e.g., inclusion of myocardial infarction only) (13,14), their generalizability has been limited.

Here, we report a more powerful and generalizable genome-wide GRS for CAD to provide a more comprehensive evaluation. We utilized a meta-analytic strategy to construct a GRS for CAD (metaGRS) that captures the totality of information from the largest previous genome-wide association studies, and then investigated the external performance of this metaGRS in stratifying CAD risk in >480,000 individuals from the UK Biobank (UKB) (15). Furthermore, we assessed the effects of 6 conventional risk factors (smoking, blood pressure, body

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