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EDITORIAL COMMENT

Clinical use of polygenic risk scores in coronary artery disease – What can we expect?

Uso clínico dos *scores* de risco poligénicos na doença arterial coronária – o que podemos esperar deles?

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Due to our increasing knowledge of the human genome, paralleled by the availability of low-cost and high-throughput genotyping techniques, we have increased our insights into the genetic background and pathways that cause many common diseases. Genome-wide association studies (GWAS) on large cohorts, focused on identifying disease- or trait-associated genetic variants (characteristically single nucleotide polymorphisms (SNPs)) common in a given population, have identified thousands of loci associated with a range of complex human traits and diseases, including coronary artery disease (CAD).[1] Recently, interest has grown in the use of genetic information to assess risk prediction better and to individualize clinical decisions on disease prevention, diagnosis, therapeutics and prognosis.

The polygenic risk score (PRS) aggregates the effects of many genetic variants into a single value that estimates the risk of a certain disease or other clinically relevant outcome.[1,2] Typically, PRS are calculated by summing the number of risk alleles in an individual, weighted by per-allele effect sizes derived from GWAS, and normalized using a relevant population distribution.[2] The availability of large datasets of genetic information along with computational advances, has enabled the integration of thousands to millions of genetic variants, weighted by variant-level strength of association with a disease, and the information about the underlying interplay between variants.[3]

Coronary artery disease (CAD) is a leading cause of mortality and morbidity worldwide. Similar to most complex and multifactorial diseases, the individual's risk of developing CAD is determined by the interaction between genetic and environmental factors. As the heritability of CAD has been estimated to be 35–50%,[3–5] the knowledge of individual genetic susceptibility would be essential to identify high risk individuals that could benefit from early prevention strategies.

The publication of the first GWAS for CAD dates from 2007, when three independent groups identified common variants at the 9p21 locus that were associated with a 25–30% increase in the risk of CAD per risk allele.[5] Since then, knowledge in this field has grown and nowadays common genetic variants in >150 loci have been associated with CAD,[4] raising the hope for individualized risk prediction and personalized medicine. Although some of these genetic loci correspond to genes that interfere with CAD risk due to their association with traditional cardiovascular risk factors, for the majority of these variants, the pathophysiological link

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to CAD remains unknown,[1,3] evidencing the complexity in translating these findings into the clinical daily practice.

For risk assessment of CAD, traditional risk factors (such as age, blood pressure, cholesterol levels and smoking habits) are routinely used and sustain therapeutic decisions (e.g. statins prescription). However, in young patients, traditional risk factors may be imprecise to accurately estimate CAD risk,[6] since they could not identify those individuals that might have high risk genetic profile and that would benefit of early screening and primary prevention strategies. Several studies assessing the value of adding PRS, based on large number of SNPs, to traditional risk factors in CAD prediction, have demonstrated improvements in risk prediction and in the identification of different trajectories of lifetime CAD risk, highlighting the potential for early preventive interventions,[7,8] since PRS might be calculated early in life. However, other studies reported a relatively modest[9] or even absent[10] increment in the predictive accuracy of PRS versus a clinical risk score for CAD prediction. Indeed, a recent systematic review about genetic risk scores used in cardiovascular disease prediction models,[11] found that in most studies, genetic risk score was associated with the incidence of cardiovascular disease and clinical utility was improved, but this improvement was modest. Besides, this review highlighted the enormous methodological heterogeneity and differences in the genetic risk stratification models, which hampers the generalized use and clinical applicability of these scores. Additionally, the use of genetics in predicting recurring events in population with pre-existing CAD is less established. In fact, the well-studied 9p21 locus, strongly associated with CAD risk in GWAS, revealed there was no clear association with risk of subsequent acute events in individuals with CAD at baseline.[12] However, few small studies in the setting of secondary prevention and sub-analysis of pivotal outcome trials of PCSK9, found that PRS identified individuals with greater risk for cardiovascular events and identified individuals that would derive greatest benefit from therapy with PCSK9 inhibitors.[3]

In this issue of the Journal, Mendonça et al. report the results of the GENEMACOR (GENEs in Madeira and CORonary Disease) study, designed previously to understand better the main environmental and genetic risk factors for CAD development in the Madeira population, and in particular, the influence of genetic information on CAD risk.[13]

GENEMACOR is a case-control study that included 1723 consecutive patients recruited from the Cardiology Department of the Funchal Hospital Center at least six months after the acute event and 1416 controls, matched for age and gender. All participants were between 30 and 65 years of age and were born and had been residents in the archipelago for at least two generations. For clinical risk stratification, patient demographics and data on traditional risk factors (age, gender, smoking and alcohol habits, body mass index, diabetes mellitus, dyslipidemia, physical inactivity and arterial hypertension) as well as clinical characteristics (e.g., heart rate, creatinine clearance and pulse wave Doppler) were collected. For genetic risk assessment, the authors included SNPs previously associated with CAD or its main risk factors, derived from GWAS or candidate gene association studies, in a total of 33 variants, distributed according to five major potential physiopathological pathways for CAD development (lipid metabolism; diabetes/obesity; hypertension; oxidative process; cell cycle, cellular migration and inflammation). After multivariate analysis, the main traditional risk factors were all strong and independent predictors of CAD, with smoking presenting the highest impact on CAD incidence (OR 3.40; 95% CI: 2.83–4.09; p<0.0001). For genetic variants, after adjusting for all the significant variants derived from a first bivariate analysis, nine remained independent predictors of CAD and eight maintained that association after adjustment for significant traditional risk factors (for these variants, authors provide brief data regarding the potential mechanism of action). *LPA* rs3798220 presented the strongest association (odds ratio (OR) 1.51; 95% confidence index (CI): 1.21–1.87; p<0.0001), followed by *APOE* rs7412/rs429358 (OR 1.25; 95% CI: 1.06–1.47; p<0.007) and *CDKN2B-AS1* rs4977574 (OR 1.19; 95% CI: 1.07–1.32; p<0.002). By integrating the available data, the authors created a multiplicative genetic risk score (mGRS), that could predict CAD likelihood in this population more accurately than dyslipidemia and hypertension, presenting an AUC of 0.60, identical to diabetes. Individuals in the fourth mGRS quartile presented an increase in CAD probability by 136% (p<0.0001). The addition of the mGRS to the traditional model was associated with a statistically significant, yet modest, increment in the predictive accuracy for CAD (area under curve (AUC)=0.75 for traditional risk factors+mGRS versus AUC=0.73 for traditional risk factors, p<0.0001) and improved risk reclassification, particularly in the intermediate-risk categories.

The results of the GENEMACOR study, a pioneer in Portugal, are in line with previous studies performed in this field and re-enforce the potential for improved risk prediction for CAD and early implementation of preventive strategies. Although these findings are very promising, some considerations should be kept in mind.

This study was performed in a homogenous, isolated, population with no genetic admixtures, limiting the extrapolation of the results to other group of people, including individuals from mainland. Likewise, the PRS was derived from the comparison of patients with previous CAD disease and controls. Although the capability of predicting recurring events in CAD patients has already been demonstrated in another paper from the authors,[14] whether the use of this genetic score in persons without established CAD, even those natural from the Archipelago, would perform equally, cannot be assumed and would be very interesting to investigate. Also, it would be important to explore the potential of the mGRS in identifying those patients that would benefit the most, from more aggressive secondary prevention strategies (e.g., PCSK9 inhibitors) in an extended follow-up. On the other hand, a restricted number and type of SNPs was used in this study, which could have limited the predictive accuracy of the mGRS, considering the modest improvement when mGRS was added to the traditional risk factors model. Nevertheless, one might think that this modest improvement could have meaningful clinical benefit if applied to large population, considering the elevated prevalence/incidence of CAD. Future studies are needed to evaluate the cost-effectiveness of PRS in CAD and to define the target population for the use of these tools.

In summary, there is growing evidence for the potential use of PRS in predicting CAD risk, enabling more personalized medicine, however further clinical studies are warranted to

define a more appropriate genetic risk prediction model and the specific context for its use.

Conflicts of interest

The author has no conflicts of interest to declare regarding this manuscript.

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