Perspective

Genetic Susceptibility for Coronary Heart Disease and Type 2 Diabetes Complications

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Type II diabetes (T2D)[3] represents a major public health challenge, with the WHO having estimated a current prevalence of 346 million worldwide. Cardiovascular disease, including coronary heart disease (CHD), stroke, and peripheral vascular disease, is one of the major complications of T2D, and the development of new strategies to tackle this problem is undoubtedly necessary. Although the association between diabetes and cardiovascular risk is well established, the pathologic basis of CHD in patients with T2D may differ from that in the general population. Whether this relationship has a genetic component is not fully understood.

With regard to understanding the genetic basis of complex diseases, genomewide association studies (GWASs) have led to an unprecedented number of well-validated variants associated with complex diseases. There is now considerable interest in understanding both the mechanism by which these variants confer risk and whether the variants identified will be useful for predicting complex disease phenotypes.

A recent report by Qi et al. (1) addressed 2 questions in this regard: (a) Are single-nucleotide polymorphisms (SNPs) identified by GWASs of CHD associated with the risk of CHD in T2D, and (b) can these variants be combined in a score that will aid prediction of CHD risk in T2D? In investigating these questions, Qi and coworkers genotyped 12 CHD susceptibility loci in 3 nested case–control studies of CHD in T2D: the Nurses' Health Study, the Health Professional Follow-Up Study, and the Joslin Heart Study.

As expected, the chromosome 9p21 CHD risk locus showed a strong association with CHD risk, whereas 4 other loci [PHACTR1[4] (phosphatase and ac-

tin regulator 1), HNF1A (HNF1 homeobox A), PCSK9 (proprotein convertase subtilisin/kexin type 9), and SORT1 (sortilin 1)] demonstrated associations consistent with those seen in previous GWAS reports, with P values <0.05. Interestingly, haplotypes associated with increased CHD risk and defined by SNPs in the gene cluster containing the SLC22A3 [solute carrier family 22 (extraneuronal monoamine transporter), member 3], LPAL2 [lipoprotein, Lp(a)-like 2, pseudogene], and LPA [lipoprotein, Lp(a)] genes did not appear significantly associated with CHD risk, possibly because of the variants' low frequencies and the inadequate statistical power of the studies. None of the other variants tested showed associations with CHD below the significance threshold (P = 0.05), although the authors noted that 2 of the loci examined [MRAS (muscle RAS oncogene homolog) and KCNE2 (potassium voltage-gated channel, Isk-related family, member 2)] had summary effect sizes in the direction opposite to that described in previous reports. Although it may be tempting to speculate on the reasons for this result, the 95% CI for the summary odds ratios crosses the line of null effect, and the study had limited power to detect overall effects. Therefore, these results should be interpreted with caution.

The authors then constructed a simple unweighted genetic risk score (GRS) based on the number of risk alleles carried (each individual will carry 0, 1, or 2 risk alleles at each locus) and assessed the performance of the GRS in predicting CHD. In common with other reports of studies that used a similar methodology, the discriminative performance of the GRS was modest (area under the ROC curve, 0.5782). Addition of the GRS to a panel of clinical risk factors did lead to a modest improvement in both the area under the ROC curve and the net reclassification index. Two important features that could have aided in discrimination but were not included in the clinical parameters are the duration of diabetes in patients who developed CHD and the age of diabetes diagnosis.

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[3] Nonstandard abbreviations: T2D, type II diabetes; CHD, coronary heart disease; GWAS, genomewide association study; SNP, single-nucleotide polymorphism; GRS, genetic risk score.

[4] Human genes: PHACTR1, phosphatase and actin regulator 1; HNF1A, HNF1

homeobox A; PCSK9, proprotein convertase subtilisin/kexin type 9; SORT1, sortilin 1; SLC22A3, solute carrier family 22 (extraneuronal monoamine transporter), member 3; LPAL2, lipoprotein, Lp(a)-like 2, pseudogene; LPA, lipoprotein, Lp(a); MRAS, muscle RAS oncogene homolog; KCNE2, potassium voltage-gated channel, Isk-related family, member 2.

Some aspects of the study design may limit the overall interpretation of the results, particularly in relation to the potential for translation to clinical care.

First, the clinical predictors included in the regression model (age, sex, hemoglobin A_{1c}, HDL cholesterol, and a history of smoking, hypertension, and hypercholesterolemia) were not based on a score that is in common clinical use, such as the Framingham Risk Score algorithm, so comparison with standard practices was not possible.

Second, 2 of the SNPs included in the risk score (in the *SORT1* and *PCSK9* genes) are associated with circulating lipid concentrations, which were included among the clinical predictors. That may have led to overfitting of the model.

Third, the authors point to the fact that participants with ≥ 8 risk alleles have an almost doubling of the risk for CHD events. Although this effect may seem relatively large, there are some caveats to consider. This odds ratio compared the highest risk group with the lowest risk group, not with the mean risk group. When the score was considered as a continuous predictor, the effect was considerably smaller (odds ratio, 1.19). Although identifying those at the extremes of genetic risk may seem an attractive strategy, doing so by definition will have an impact on the number needed to screen to prevent 1 event, because the number of people at the extremes is small *(2)*. Furthermore, with regard to primary prevention of CHD, it is likely that measures that target the entire diabetic population will be of the greatest benefit, because the largest absolute number of events will occur in people with intermediate risk, as proposed by Rose's prevention paradox *(3)*.

Finally, the selection of SNPs included in the model warrants consideration. If genetic variants are to be used in clinical practice to predict the development of disease phenotypes, a robust method will be needed to identify the specific variants to be included in such risk profiles. Although all 12 loci examined in this study have previously shown a reproducible association with CHD risk in the general population, only SNPs that were associated with CHD in the cohorts tested were included in the score. To objectively answer the question, do GWAS CHD SNPs predict CHD in T2D? requires that all of the variants be tested in combination, because the current study does not have power to rule out an effect in patients with diabetes. Furthermore, calculating the P value used as a threshold for inclusion of SNPs in the score should have accounted for multiple testing; doing so would have led to only 2 SNPs showing "significant" associations.

What makes this study noteworthy is the fact that the authors used a meaningful genetic risk-prediction study, because it was conducted in a high-risk population group that might benefit from targeting novel preventive interventions. Indeed, the GRS has the potential to benefit younger individuals with T2D who have not yet developed cardiovascular risk factors, which would identify susceptibility for the disease or its severity. Although that may be a theoretical benefit when discussing personalized-medicine models, there are many factors to consider. We have previously shown that the use of T2D risk alleles in a GRS to predict T2D did not add anything to validated T2D risk algorithms *(4)*. Interestingly, many of the interventions that are currently used in primary prevention are directed at these same risk factors, some of which may not have yet become apparent, such as increased blood pressure and dyslipidemia. Therefore, other than aiding in advising on a healthy lifestyle, it is hard to see exactly how the test will guide physicians.

This study can be added to those that have shown moderately disappointing results with respect to using genetic tests to predict complex disease, but it can help guide future efforts in this regard. Understanding the genetic architecture of CHD in T2D is necessary, however, and although this study does make some progress in that regard, much larger studies are required to begin to address many of the unanswered questions. An additional caveat needs consideration. The Women's Health Initiative study, which has reported on >1 004 466 person-years of follow-up, found a concerning increase in new cases of T2D in postmenopausal women on statins, even after adjustment for confounders *(5)*. Although the relationship between statins and T2D has been examined previously in metaanalyses (with variable outcomes), this relationship needs careful consideration. The pandemic of obesity will lead to increasing numbers of children and adolescents diagnosed with T2D. Given the well-established link between T2D and premature cardiovascular deaths, the need for efficient early predictive tools and aggressive preventive interventions becomes more urgent.

References

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