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SYMPOSIUM

Genetic Susceptibility to Type 2 Diabetes and Implications for Therapy

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Abstract

Since 2000, we have witnessed an explosion of known genetic determinants of type 2 diabetes risk. These findings have seeded the expectation that our ability to make personalized, predictive, therapeutic clinical decisions is imminent. However, the loci discovered to date explain only a small fraction of overall inheritable risk for this disease. In many cases, the reported associations merely signal regions of the genome that are overrepresented in disease versus health but do not identify the causal variants. Well-powered cohort studies have shown that the set of markers detected thus far does not significantly improve individual risk prediction or stratification over common clinical variables, with the possible exception of younger subjects. On the other hand, risk genotypes may help target subgroups for more intensive surveillance or prevention efforts, although whether such a strategy improves patient outcomes and/or is cost-effective should be examined. Similarly, whether genetic information will help guide therapeutic decisions must be tested in adequately designed and rigorously conducted clinical trials.

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Introduction

Since 2000, multiple common genetic variants that underlie risk of type 2 diabetes have been identified.[1] Candidate gene approaches (*PPARG*, *KCNJ11*, *WFS1*, and *TCF2*), regional exploration (*TCF7L2*), genome-wide association scans (*SLC30A8*, *HHEX*, *CDKAL1*, *CKN2A/B*, *IGF2BP2*, *FTO*, and *KCNQ1*), their meta-analysis (*JAZF1*, *CDC123-CAMK1D*, *TSPAN8-LGR5*, *THADA*, *ADAMTS9*, and *NOTCH2-ADAM3*), and examination of glycemic quantitative traits (*MTNR1B*) have produced nearly twenty loci with incontrovertible levels of statistical evidence favoring their contribution to type 2 diabetes risk. The list is expected to grow as sample sizes continue to increase through collaboration and as these techniques are applied to non-European populations. Although this achievement represents a major quantitative leap over our prior knowledge, the small effects conferred by these variants (odds ratios 1.1–1.4) reveal why only approximately 5–10% of the inherited component of type 2 diabetes has been explained.[2]

Given these significant advances, the clinician rightly asks whether this new body of knowledge will help him or her diagnose, predict, prevent, or treat type 2 diabetes any better. This overview is meant address all four questions.

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Abbreviations: (A1C) glycated hemoglobin A1c, (DPP) Diabetes Prevention Program, (SNP) single nucleotide polymorphismt

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Diagnosis

It has become abundantly clear that type 2 diabetes is not just one disease, but a conglomerate of heterogeneous pathological processes that result in the common outcome of hyperglycemia. Data from monogenic human disease or animal models suggest that defects in both insulin secretion and action can cause elevations in fasting or stimulated glucose. In a manner analogous to that observed for Mendelian forms of diabetes, genetic approaches are helping to classify type 2 diabetes according to the molecular pathway involved. Evidence from tissue expression, subcellular localization, molecular function, and *in vivo* physiology point to the pancreatic β cell as a nodal point of action for most genetic discoveries, with only a handful of novel loci (*PPARG* and *FTO*) implicated in insulin resistance.[3] Whether this pattern will continue to hold as the genetic architecture of type 2 diabetes becomes fully unravelled awaits to be seen, although environmental factors do seem to play a larger role in the modulation of insulin sensitivity.

Besides the stated benefits for disease taxonomy, many of these findings have highlighted molecular pathways (known and unknown) that can be intervened upon in hopes of modifying the disease process. Indeed, the effect size produced by allele frequency differences between cases and controls is not at all correlated with the potential for a given molecule to be perturbed in a clinically significant manner. As a case in point, while the E23K single nucleotide polymorphism (SNP) in the islet ATP-sensitive potassium channel targeted by sulfonylureas only increases the risk of diabetes by 15%, sulfonylurea drugs can bring about a substantial decrease in hemoglobin A1c (~1.5%).[4,5] Thus it appears that genetic information may help classify different forms of type 2 diabetes in the not too distant future, each of which may be targeted differently according to the molecular defect(s) involved.

Prediction

Our ability to query the entire genome with a high degree of precision has led many to announce the imminent arrival of personalized medicine. The hope is that unique genetic information can yield an individual signature that will predict a person's risk of specific pathologies, disease course, medication response, or susceptibility to side effects. Such expectations have led to the proliferation of genetic tests that claim to provide accurate risk estimates and are marketed directly to consumers.

The availability of nearly two dozen genetic variants that increase type 2 diabetes risk has allowed investigators to determine to what extent this genetic information improves individual risk prediction over existing clinical markers. Meigs and colleagues[6] selected 18 SNPs associated with type 2 diabetes at high levels of statistical confidence and constructed a genotype score ranging from 0 to 36 based on the number of risk alleles. This score was applied to 2377 Framingham Heart Study participants, and it was found that the mean genotype score was 17.7 ± 2.7 among the 255 subjects who developed diabetes and 17.1 ± 2.6 among those who did not; while the mean scores of each group were distinguishable statistically, the overall distributions essentially overlapped. We then used the area under the receiver operator characteristic curve or C-statistic, a quantitative measure of a test's ability to discriminate true from false positives (ranging from 0.5/no discrimination to 1.0/perfect discrimination), to compare three different clinical regression models: a model using only sex as predictor, a model using sex and family history as predictors, and one that included clinical risk factors (age, sex, body mass index, fasting glucose, systolic blood pressure, high-density lipoprotein cholesterol, and triglycerides) that together generate a previously validated "simple clinical model."[7] The genotype score was superimposed on each one of these models. There was no substantial improvement in the C-statistic with the addition of genotypic information for each model; the only significant difference was found for the sex-only model (designed to include information available at birth), in which the C-statistic rose from 0.534 to 0.581 when genotypic information was included (p = .01) and the score appropriately reclassified 4.1% of the participants (p = .004). For the simple clinical model, the C-statistic only increased from 0.900 without the genotype score to 0.901 with it (p = .49), with only 2.1% net reclassification improvement. Interestingly, a parental history of diabetes was an independent predictor of risk even when the genotype score was added to the model, suggesting that the number of variants evaluated thus far only captures a small fraction of the information contained in family history or that family history likely reaches beyond purely genetic information to capture shared environment and behaviors. In subgroup analyses, the genotype score performed better in participants younger than 50 years of age, with an increase in the C-statistic from 0.532 to 0.609 (p = .009) and a net reclassification improvement of 11.9%.

A much larger prospective study was conducted by Lyssenko and associates[8] in two Scandinavian populations and published concurrently with Meigs and colleagues.

It should be noted that the simple clinical prediction model originally derived from the Framingham population did not perform as well in this sample, allowing for greater improvement after the addition of genotypic information. Nevertheless, their findings were comparable to those from Framingham; after genotyping 16 type 2 diabetes-associated SNPs, the inclusion of genetic risk factors to clinical determinants had a marginal increase in the area under the receiver operating characteristic curve (from 0.74 to 0.75) rendered statistically significant because of the much larger sample size. This study also showed that the ability of genetic risk factors to predict future type 2 diabetes improves with an increasing duration of follow-up, while clinical risk factors measured at baseline conversely decrease in their discriminative ability, demonstrating that assessment of genetic risk factors may be more useful when assessed earlier.

The general lack of clinically meaningful improvement in risk prediction from addition of currently available genetic information has also been shown in British[9] and Dutch[10] cohorts. These results may be unimpressive, because existing phenotypic information already incorporates the genotypic information from the available risk alleles, the number of evaluated variants is too low to account for the overall genetic predisposition to type 2 diabetes, or environmental factors such as obesity and diet have a much a stronger influence of the development of type 2 diabetes, such that modest genotypic effects are overwhelmed by this environmental contribution. On the other hand, both the Framingham and the Scandinavian studies suggest a potential role for genetic testing in younger patients when genetic factors may be useful in early detection of at-risk groups before clinical determinants such as body mass index or fasting glucose manifest themselves.

Prevention

The ability to identify groups or individuals at high risk of developing type 2 diabetes is particularly meaningful when effective preventive strategies can be implemented. Several clinical trials have shown that lifestyle[11–14] or pharmacological[13–16] interventions can prevent or delay the onset of type 2 diabetes in populations at risk. In the Diabetes Prevention Program (DPP), the prevention study whose multiethnic composition was most representative of the U.S. population (in contrast to other prevention trials conducted in a single ethnic group), a lifestyle intervention aimed at ~7% weight loss and ~150 min of physical activity per week achieved a 58% risk reduction in diabetes incidence, while metformin 850 mg twice daily reached 31% risk reduction.[13] In this context, it would be informative to determine whether genetic markers modify the effects of preventive interventions on the development of diabetes.

Therefore, we tested whether the established risk variants at *TCF7L2*,[17] the strongest genetic predictor of type 2 diabetes identified to date,[18] predict the onset of diabetes and influence the effectiveness of the preventive strategies implemented in the DPP. Indeed, homozygous carriers of the risk T allele at rs7903146 showed an 80% increase in their likelihood of developing diabetes over their wild type counterparts.[19] More significantly, however, the lifestyle intervention was just as effective, or perhaps more, in risk allele carriers, showing that a behavioral approach can overcome the genetic risk conferred by this variant. This finding was confirmed in the Finnish Diabetes Prevention Study.[20]

A similar result has been obtained for risk genotype carriers at the missense polymorphism K121Q in the candidate gene *ENPP1*.[21] Though this locus has not reached levels of statistical significance comparable to those of other loci definitively associated with type 2 diabetes, a large meta-analysis of the many studies published on this variant,[22] a comprehensive association study of quantitative glycemic traits in Framingham,[23] an unrelated association study of quantitative glycemic traits in Italy,[24] a prospective study,[25] and the DPP[21] have independently provided nominal evidence of the association of this SNP with hyperglycemia. In the DPP, it was noted a significant interaction of lifestyle modification with genotype, such that this intervention was particularly effective in risk allele carriers. Together with *TCF7L2*, these results offer hopeful evidence of approaches to reduce the risk of type 2 diabetes at the population level and perhaps target groups for whom this intervention might be particularly cost-effective.

Treatment

Pharmacogenetics refers to the use of genetic information to select, from various treatment options, those most likely to benefit a particular patient. Within diabetes, monogenic forms of the disease have already afforded tantalizing proofs of concept; for instance, patients with maturity onset diabetes of the young type 3 (due to mutations in *HNF1A*) seem to respond better to sulfonylureas than to metformin,[26] and children with permanent neonatal diabetes due to functional mutations in the genes that encode the islet ATP-sensitive potassium channel Kir6.2 (*KCNJ11*) or its associated sulfonylurea receptor

SUR1 (*ABCC8*) can be safely transitioned from insulin to sulfonylureas.[27,28] Early pharmacogenetic studies in common type 2 diabetes focused on the two associated SNPs that emerged from candidate gene explorations; as it turns out, both the P12A variant in *PPARG*[29] and the E23K variant in *KCNJ11*[30] are located in genes that encode drug targets (for thiazolidinediones and sulfonylureas, respectively). Most studies that have examined the effect of *PPARG* P12A on thiazolidinedione response (defined in various ways) have shown no evidence of a genetic effect on drug efficacy;[31–33] the sole exception is a small Korean study that included 15 risk allele carriers.[34] A more comprehensive evaluation of common variation at this locus provided nominal evidence of association for several SNPs in *PPARG* with response to troglitazone,[35] but this result could not be replicated in a larger sample.[33] Thus knowledge of allelic variation at this locus does not yet offer a rationale for therapeutic choices.

The impact of *KCNJ11* E23K on the effectiveness of sulfonylurea therapy is also unclear, with two early studies of small size that yielded contradictory results.[36,37] Later, Feng and coworkers published the first seemingly well-powered prospective pharmacogenetic study in type 2 diabetes.[38] They selected 25 common SNPs from 11 candidate genes, including the A1369S missense polymorphism in *ABCC8*. Because of its genomic location immediately adjacent to *KCNJ11* and the strong correlation (i.e., linkage disequilibrium) between SNPs in the region, risk allele carriers at *ABCC8* A1369S almost always carry the risk allele at *KCNJ11* E23K. Thus investigators cannot distinguish, on statistical grounds alone, whether the association signal arises from one variant versus the other.[39] The authors enrolled two independent cohorts of 661 patients from northern China and 607 patients from southern China, all of whom had type 2 diabetes of relatively recent onset (diagnosis within 5 years and no hypoglycemic therapy within the previous 2 months). They treated them with gliclazide for 8 weeks and measured percent changes in fasting glucose, fasting insulin, 2 h glucose after an oral glucose tolerance test and glycated hemoglobin A1c (A1C) according to genotype. *ABCC8* A1369S was associated with percent decrease in fasting glucose both in the first cohort and on replication, even after Bonferroni correction for the 25 SNPs tested (nominal $p = .002$). When both datasets were pooled, fasting glucose decreased by 26.1% in Ser/Ser homozygotes compared to a 31.6% decrease in Ala/Ala homozygotes (which translates into a statistically significant difference of ~12.6 mg/dl between genotypic groups; whether this separation is clinically relevant is up for discussion). The A1C difference of 0.3% between the two homozygous genotypes approached but did not reach nominal significance ($p = .06$). Although methodological issues related to SNP selection, choice of endpoints, and short duration raise questions about the study and its interpretation, significant strengths include its sample size, a simple design focused on monotherapy, its prospective nature, and the use of a replication cohort.

One notable omission from the aforementioned pioneering sulfonylurea pharmacogenetic study is *TCF7L2*, which is known to exert its effects by impairing insulin secretion.[19,40] While it is likely that the same Chinese group will soon evaluate this important locus in the samples at their disposal, a large retrospective pharmacogenetic study has already been published by Pearson and colleagues, who reported the effect of *TCF7L2* genotypes on therapeutic response in 901 diabetic patients treated with sulfonylureas and 945 patients treated with metformin.[41] Carriers of the risk *TCF7L2* variant rs7903146 were more likely to fail sulfonylureas but not metformin, as measured by a A1C > 7% within 3–12 months after initiation of therapy.

Finally, attention must also be paid to genes that encode drug metabolizing enzymes. Metformin is taken up into hepatocytes by the organic cation transporter 1, encoded by *OCT1*. Prompted by animal experiments that showed reduced adenosine monophosphate kinase phosphorylation in *Oct1*-deficient mouse hepatocytes and poor absorption of metformin in *Oct1*-deficient mice, Shu and associates also showed that the *OCT1* reduced-function allele is associated with higher glucose levels during an oral glucose tolerance test in healthy human subjects, consistent with lower metformin bioavailability.[42] These findings, obtained in a very small sample of 20 subjects, need to be replicated; a retrospective study of 1531 metformin-treated patients followed in a clinical database showed no differential effects on A1C reduction conditioned on the two index variants at this locus.[43]

An analogous result was recently published by the Rotterdam Study investigators.[44] The other side of the coin impacting metformin bioavailability concerns its excretion into bile and urine, catalyzed by the multidrug and toxin extrusion 1 protein, which is encoded by the *SLC47A1* gene. The authors evaluated a set of common variants in this gene and tested them for association with metformin response (defined as change in A1C) in 116 incident metformin users. They found that one of the 12 SNPs was modestly associated with metformin response, even after correction for the number of hypotheses tested. Once again, this preliminary finding requires

replication. Nevertheless, it is possible that, for molecules that are absorbed and/or metabolized via relatively simple pathways, variation in the relevant genes may affect treatment response in a detectable manner.

Conclusion

The deluge of new genetic results in type 2 diabetes presents a number of implications for personalized medicine:

1. Association studies, if well powered, can indeed help characterize the genetic architecture of complex diseases.
2. In type 2 diabetes, the genetic effects are modest, with a ceiling of effect hovering around *TCF7L2*; known genetic associations explain 5–10% of the inheritable basis of type 2 diabetes.
3. These discoveries point to new avenues of investigation.
4. Their application to disease prediction is premature; before the deployment of prediction rules, their cost effectiveness and utility in improving patient outcomes must be demonstrated.
5. Whether these genetic variants prove useful in disease prediction or choice of therapeutic strategies must be tested scientifically in a prospective fashion.

Thus it is hoped that the years ahead clarify the extent to which inherited variation and its interaction with the environment guides clinicians' diagnostic and therapeutic decisions.

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