Diabetes mellitus hoy

Novel genetic findings applied to the clinic in type 2 diabetes

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Genome-wide association studies (GWAS) have both validated known loci and introduced several novel type 2 diabetes genes (table 1; fig. 1). Interestingly, many of the newly discovered variants appear to influence insulin secretion rather than insulin resistance[1]. This rapid pace of novel discoveries can elicit a variety of different reactions. By addressing the various questions that arise. I will attempt to place these findings in the appropriate context.

The skeptic may argue that *"we have not learned anything new"*. Nothing is further from the truth: most of the loci uncovered by GWAS were not in any investigator's short list of candidate genes, and thus these results have opened new pathways of physiological investigation. Furthermore, areas of the genome of unknown function (e.g. so-called "gene deserts") have been unquestionably associated with a higher risk of disease, challenging molecular biologists to determine how such genomic regions can have functional effects at the level of the organism. An intriguing link between diabetes and cancer has emerged, where an allele that increases risk of prostate cancer protects from diabetes and vice versa[2], possibly implicating cellular proliferation in the pathogenesis of both diseases[3]. Finally, genetic associations have also provided a potential molecular basis for epidemiological observations, as illustrated by the putative involvement of circadian genes in glycemic regulation[4-6].

The absolutist may conclude that *"all of the genetic contribution to type 2 diabetes leads to* β*-cell dysfunction"*. While it is true that the heritability of insulin resistance measures is generally lower than that of insulin secretion measures, the former still display a sizeable heritable component[7]. Loci discovered via GWAS of type 2 diabetes as a categorical trait are sensitive to study design: when such scans deliberately focus on enrolling leaner cases so as to find genes that cause type 2 diabetes without the mediation of obesity[8,9], their ability to detect genes that increase insulin resistance via adiposity is impaired. Thus, GWAS that intend to discover insulin resistance genes must be designed with that goal in mind, either accounting for the effect of obesity or searching for insulin resistance as a quantitative trait in population cohorts that display enough of a variance in this phenotype[1]. It is also possible that the genetic architecture of insulin resistance may differ from that of β-cell function, that our current genotyping arrays do not cover the rele-

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TABLE 1. Genetic variants associated with type 2 diabetes at genome-wide levels of statistical signicance, ordered by chromosome (Chr)

Marker	Chr	Description	Gene region	Function	Risk allele	Odds ratio	P value	Reference
rs10923931	1	Intronic	*NOTCH2*	Transmembrane receptor implicated in pancreatic organogenesis	T	1.13	4.1×10^{-8}	11
rs7578597	2	Missense: *T1187A*	*THADA*	Thyroid adenoma; associates with PPAR	T	1.15	1.1×10^{-9}	11
rs4607103	3	38 kb upstream	*ADAMTS9*	Secreted metalloprotease expressed in musle and pancreas	C	1.09	1.2×10^{-8}	11
rs4402960	3	Intronic	*IGF2BP2*	Growth factor binding protein; pancreatic development	T	1.14	8.9×10^{-16}	28
rs1801282	3	Missense: *P12A*	*PPARG*	Transcription factor involved in adipocyte development	C	1.19	1.5×10^{-7}	29
rs10010131	4	Intron-exon junction	*WFS1*	Endoplasmic reti culum transmembrane protein	G	1.15	4.5×10^{-5}	28
rs7754840	6	Intronic	*CDKAL1*	Homologous to CDK5RAP1, CDK5 inhibitor; islet glucotoxicity sensor	C	1.12	4.1×10^{-11}	28
rs864745	7	Intronic	*JAZF1*	Transcriptional repressor; associated with prostate cancer	T	1.10	5.0×10^{-14}	11
rs13266634	8	Missense: *R325W*	*SLC30A8*	β-cell zinc transporter ZnT8; insulin storage and secretion	C	1.12	5.3×10^{-8}	28
rs10811661	9	125 kb upstream	*CDKN2A/B*	Cyclin-dependent kinase inhibitor and p15 tumor suppressor; islet development	T	1.20	7.8×10^{-15}	28
rs12779790	10	Intergenic region	*CDC123-CAMK1D*	Cell cycle/protein kinase	G	1.11	1.2×10^{-10}	11
rs7903146	10	Intronic	*TCF7L2*	Transcription factor; transactivates proglucagon and insulin genes	T	1.37	1.0×10^{-48}	30
rs1111875	10	7.7 kb downstream	*HHEX*	Transcription factor involved in pancreatic development	C	1.13	5.7×10^{-10}	28
rs5219	11	Missense: *E23K*	*KCNJ11*	Kir6.2 potassium channel; risk allele impairs insulin secretion	T	1.14	6.7×10^{-11}	31
rs2237892	11	Intronic	*KCNQ1*	Encodes the pore-forming α subunit of $I_{Ks}K^+$ channel	C	1.42	2.5×10^{-40}	32
rs7961581	12	Intronic	*TSPAN8-LGR5*	Cell surface glycoprotein implicated in GI cancers	C	1.09	1.1×10^{-9}	11
rs8050136	16	Intronic	*FTO*	Alters BMI in general population	A	1.17	1×10^{-12}	28
rs757210	17	Intronic	*HNF1B*	Transcription factor involved in pancreatic development	A	1.12	5×10^{-6}	28

vant variants, or that our measures of insulin resistance in population samples are too crude to reflect insulin action at the tissue level.

The impatient may declare that *"most of the genetic basis of type 2 diabetes has been explained"*, and urge policy makers to devote resources to alternative research directions. However, the current working list of convincing type 2 diabetes loci may explain as little as 5-10% of the genetic basis of type 2 diabetes. Furthermore, the variants found to date merely flag areas of the genome—which can be very far away from known genes—that appear overrepresented in disease versus health: while they may be statistically correlated with the true causal SNP (single nucleotide polymorphism) they do not necessarily play a functional role themselves. Thus, fine-mapping and molecular studies are needed before the true contribution of these loci to type 2 diabetes can be assessed accurately. Moreover, the genotyping arrays utilized thus far do a poor job of assaying structural variants (e.g. copy number polymorphisms such as deletions and duplications), do not capture rare variants, and in the best case scenario only cover 80% of common SNPs in the European genome (with a lower percentage of covered regions in the more diverse African population)[10]. In sum, the genetic basis of type 2 diabetes remains largely unexplored, and significant gaps must yet be filled.

The cynic may state that *"larger and larger sample sizes are just going to uncover smaller and smaller effects"*. Indeed, higher numbers do raise statistical power; but the power to detect the genetic associations discovered so far was also quite low in the studies published to this point. That is to say, if a study only has 10% power to detect an effect size of 20% for a given allele frequency, then larger samples will typically discover many more polymorphisms that increase diabetes risk by the very same odds ratio. As an illustration of this phenomenon, the DIAGRAM Consortium, comprising approximately 10,000 samples of European descent, constitutes the largest discovery panel in type 2 diabetes published to date[11]. That sample size had nearly 100% power to identify genetic variants that increase type 2 diabetes risk by 40%, but much lower power for effect sizes of the modest magnitude (odds ratio: 1.1-1.2) that seem to underlie type 2 diabetes.

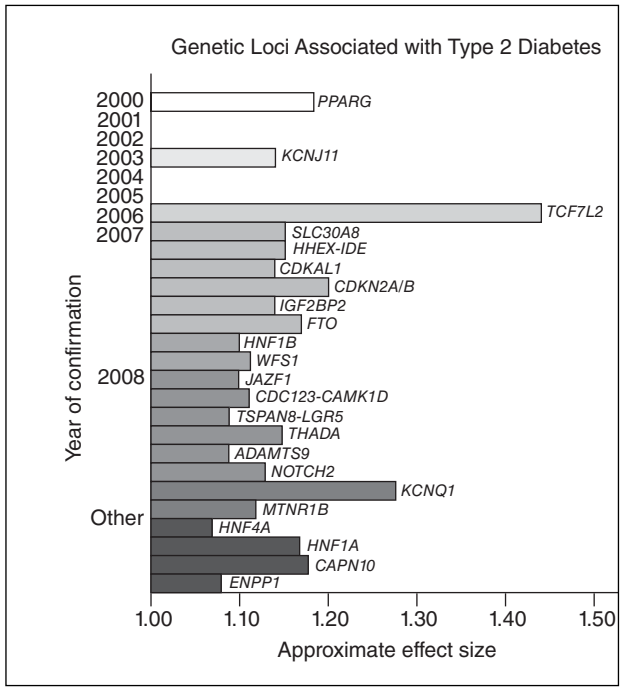

Fig. 1. Type 2 diabetes-associated loci, plotted by year of definitive publication and approximate effect size. Genes implicated in type 2 diabetes by functional and genetic evidence but short of genome-wide significance are shown at the bottom.

The pessimist may announce, *"these genetic effects are so small that they cannot possibly be clinically relevant"*. Here, it should be noted that effect sizes computed as allele frequency differences between cases and controls say nothing about biological or clinical relevance. The evolutionary constraints imposed by natural selection may be expected to prevent strongly deleterious mutations from rising to high frequencies in the population; but genetic variants that have modest effects on human physiology may indeed shed light on specific molecules or pathways which could be targeted for therapeutic intervention. This concept is illustrated by two polymorphisms of very modest effects (*PPARG* P12A and *KCNJ11* E23K) which lie in genes that encode targets for routine anti-diabetic medications, thiazolidinediones and sulfonylureas respectively. In another relevant example, a polymorphism in the gene that encodes HMG-CoA (3-hydroxy-3 methylglutaryl coenzyme A) reductase explains a small proportion of the variance in LDL-cholesterol[12]; but this minor effect does not imply that HMG-CoA reductase is not an adequate target for LDL-cholesterol lowering, and suggests that this validated target for statin therapy would have been identified by GWAS even if nothing had been known about its mode of action.

The optimist, in turn, may naively proclaim that *"the variants identified will be useful in individual clinical prediction",* heralding a quick and successful implementation of personalized medicine. While these discoveries may indeed illuminate biology and highlight opportunities for therapeutic intervention, their clinical use as risk factors in diabetes prediction is much less clear. Current simple clinical tools developed to predict risk of type 2 diabetes perform quite well, with an area under the receiver-operator characteristics curve as high as 85-90%[13]. Recent publications evaluating the ability of a genotype score composed of an aggregate of known risk variants to predict diabetes prospectively have shown marginal, clinically insignificant improvements over routinely tested risk factors[14,15]. The genotype score improved its predictive power when applied to subjects under 50 years of age, allowing for 12% of this group to be "correctly" reclassified into a high-risk group. This supports the notion that genetic factors may be useful in early detection of at-risk groups before clinical risk factors such as obesity or hyperglycemia manifest themselves, allowing practitioners to recommend effective long-term preventive interventions at earlier stages.

Finally, the pragmatist simply asks whether *"genetic information will help guide therapeutic decisions"*. While genetic data has proven invaluable in the treatment of monogenic forms of diabetes, such as MODY (maturity onset diabetes of the young)[16] and neonatal diabetes[17], the pharmacogenetics of complex disease is still very much in its infancy. In a retrospective study, Pearson et al showed that patients with the risk variants at *TCF7L2* were more likely to fail sulfonylurea therapy than metformin[18]. The lifestyle intervention of the Diabetes Prevention Program has been particularly effective in carriers of the risk alleles at *TCF7L2*[19] and *ENPP1*[20]. In contrast, the *PPARG* P12A variant does not seem to impact the individual response to thiazolidinediones[21-23]. In one of the few prospective studies published to date, carriers of the risk Ala allele at *ABCC8* A1369S showed a heightened response to sulfonylurea therapy, a finding that must be replicated[24]. Examination of drug metabolism genes may also prove fruitful: the OCT1 transporter responsible for metformin uptake harbors variants which influence the human response to an oral glucose tolerance test[25]. In sum, whether this emerging body of genetic knowledge will direct response to different classes of therapeutics must be empirically tested.

In conclusion, widespread clinical genetic testing for common variants associated with type 2 diabetes is premature[26]. It is not yet clear that any single variant or a set that includes all of them can predict diabetes onset at the individual level. Furthermore, the impact of this genetic knowledge on the response of patients or clinicians has not been formally tested: it is quite possible that a negative test may provide false reassurance and discourage healthy behaviors. Until such testing demonstrates a beneficial effect on outcomes and is proven to be cost effective, it should only be conducted in the setting of clinical trials.

A number of genetic variants have already been reproducibly associated with type 2 diabetes; the list is

only expected to grow. As large datasets of genome-wide data become available, distinguishing true associations from spurious findings due to statistical fluctuations will be essential to guide future work. Testing novel associations prospectively, measuring their precise effects on glycemic traits and assessing whether they affect response to therapy is a key step in their experimental validation. Thus, it is crucial to harness this novel genetic knowledge so that it can refine our understanding of the pathophysiology of diverse forms of diabetes, enhance our prognostic ability and direct our choice of appropriate therapies[27]. The discovery that some of these variants may have measureable effects on glycemic parameters opens the door to targeted pharmacogenetic studies. The information obtained from such experiments should provide the foundation needed to design and implement genome-based clinical trials, with the hope that these new genetic insights will translate into improved medical care and preventive measures for public health.

Conflict of interest

Jose C. Florez has received consulting honoraria from Merckz, Pfizer, bioStrategies, XOMA and Publicis Healthcare Communications Group, a global advertising agency engaged by Amylin Pharmaceuticals.

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