CHAPTER 14

GENETICS OF TYPE 2 DIABETES

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SUMMARY

Type 2 diabetes is thought to result from a combination of environmental, behavioral, and genetic factors, with the heritability of type 2 diabetes estimated to be in the range of 25% to 72% based on family and twin studies. Since early 2007, genome-wide association studies (GWAS) have led to an explosion of data for the genetics of type 2 diabetes and related traits. These GWAS have occurred on the background of genotyping arrays populated by common single nucleotide polymorphisms (SNPs), deployed in various cohorts that have coalesced to form large international consortia. As a result, a list of genetic loci that influence type 2 diabetes and quantitative glycemic traits has begun to accumulate. Over 100 type 2 diabetes-associated loci have been identified, in addition to others involved in determining quantitative glycemic traits, such as insulin resistance. However, no variant that is widely shared across populations has been found to have a stronger effect than the rs7903146 SNP in *TCF7L2*, which itself has only a modest effect (odds ratio ~1.4). Nonetheless, GWAS findings have illustrated novel pathways, pointed toward fundamental biology, drawn attention to the role of beta cell dysfunction in type 2 diabetes, confirmed prior epidemiologic observations, and provided possible targets for pharmacotherapy and pharmacogenetic clinical trials.

On the other hand, the causal variants have only been identified for a handful of these loci, a substantial proportion of the heritability of these phenotypes remains unexplained, and this has tempered expectations with regard to their use in clinical prediction. Together, the approximately 100 loci associated with type 2 diabetes thus far explain ~10%–15% of the genetic predisposition to the disease. Limitations of early GWAS included insufficient sample sizes to detect small effects, a nearly exclusive focus on populations of European descent, an imperfect capture of uncommon genetic variants, an incomplete ascertainment of alternate (non-SNP) forms of genetic variation, and the lack of exploration of additional genetic models.

As the community embraces complementary approaches that include systematic fine-mapping, custom-made replication, denser genotyping arrays, platforms that focus on functional variation, next-generation sequencing techniques, systems biology approaches, and expansion to non-European populations, the coming years will witness exponential growth in the understanding of the genetic architecture of metabolic phenotypes. Whether these findings prove useful in disease prediction or therapeutic decision-making must be tested in rigorously designed clinical trials.

TYPE 2 DIABETES AS A GENETIC DISEASE

The explosive parallel growth in the prevalence of the related metabolic disorders of obesity and type 2 diabetes in much of the developed and developing worlds over the past few decades is almost certainly driven by environmental and behavioral factors, since genetic components do not change in an appreciable manner over such a short time period. However, several lines of evidence suggest that variation in DNA sequence does contribute to type 2 diabetes risk. First, twin studies have shown that concordance for type 2 diabetes is greater for monozygotic twins (who share 100% of their DNA sequence) than for dizygotic twins (who, like siblings, share approximately 50% of their DNA sequence) (1,2,3,4,5). Second, the incidence of diabetes is much higher in certain racial/ethnic groups, despite an environment that is relatively comparable to that of neighboring populations (6,7,8). Third, family history is an independent risk factor for the development of diabetes in population studies (9,10). And fourth, rare familial forms of diabetes, caused by mutations in single genes (hence, termed monogenic or Mendelian), prove that single base pair changes in the coding regions of key genes, which lead to alterations in protein sequence and function, are sufficient to cause hyperglycemia in the diabetic range (11,12). Consistent with this notion, the heritability of type 2 diabetes estimated in a set of Scandinavian families ranges from 25% to 69% (13), and a large international meta-analysis of twin studies has reported a heritability estimate as high as 72% (14).

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Taken together, these observations illustrate that rapid changes in the global epidemiology of type 2 diabetes are likely caused by environmental and behavioral factors overlaid on a background of genetic predisposition. This genetic predisposition may vary across populations, in some measure due to their divergent genetic history and unequal selection pressures in specific geographic regions. Thus, it is well known and described elsewhere in this volume (see Chapter 13 *Risk Factors for Type 2 Diabetes*) that the risk of type 2 diabetes differs in the various ethnic groups that compose the U.S. population, and the presumption is that some of these differences are genetic in nature (15).

Why is genetic exploration relevant? Regardless of whether genetic predictors become useful markers of disease onset or progression in clinical practice, the identification of genetic variants associated with type 2 diabetes illuminates pathogenic mechanisms from which therapeutic windows may emerge. Because germline genetic variation always predates the onset of disease, the arrow of time establishes a causal relationship that is not evident with other biologic associations. Thus, the genetic approach has a unique opportunity to shed light on the pathophysiology of diabetes in its various manifestations, helping unravel its clinical heterogeneity and potentially refine therapeutic strategies.

DISCOVERY OF TYPE 2 DIABETES GENES

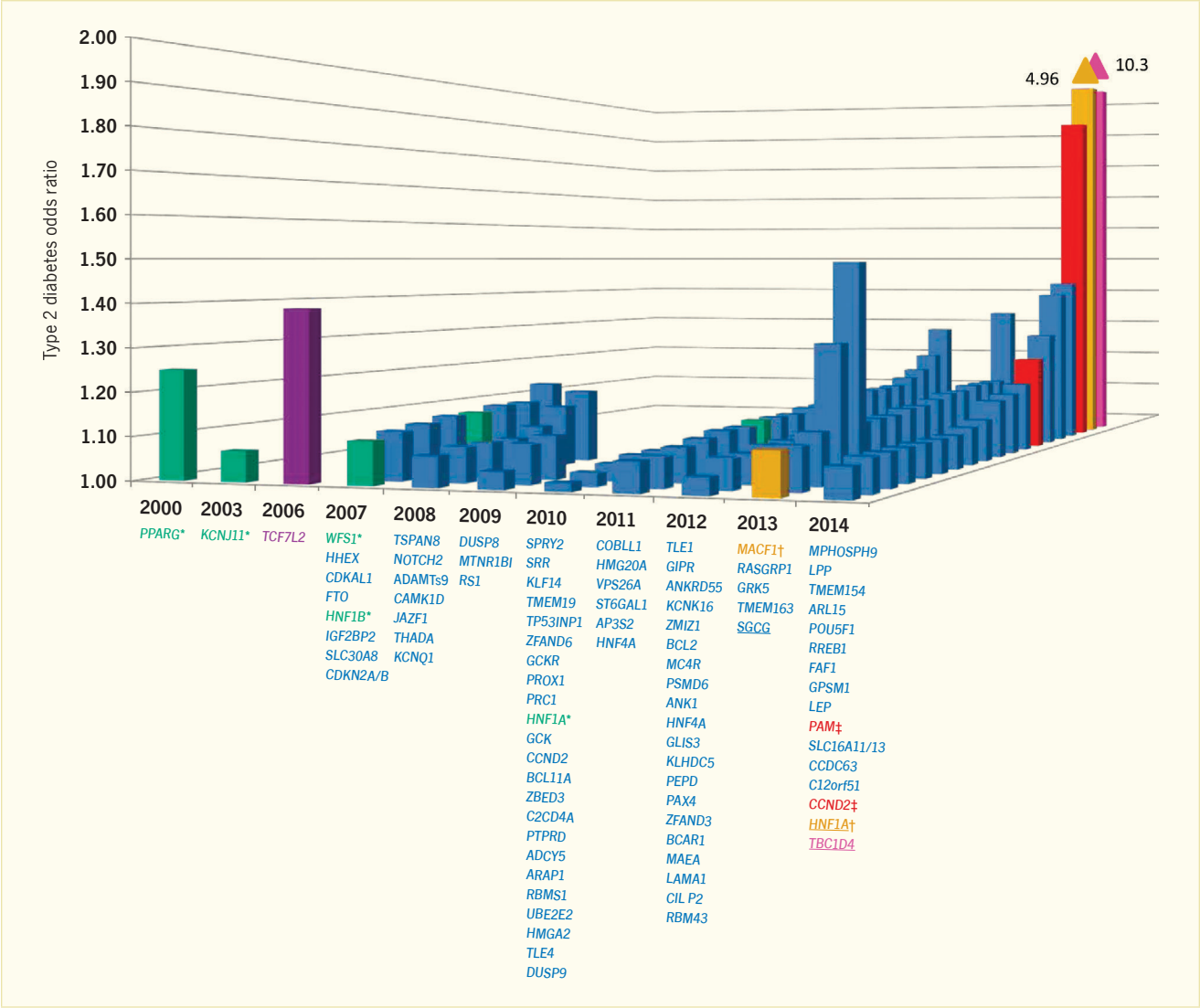
Before the sequencing of the human genome was accomplished, genetic mapping was dependent on the generation of anonymous genetic markers and their anchoring on specific locations in the genome. This task, first achieved with restriction fragment length polymorphisms and then with other markers, such as microsatellites or sequence tag sites, enabled the introduction of whole-genome linkage analysis and positional cloning, which proved extremely useful in the identification of genetic mutations that cause monogenic disease. The linkage approach, which depends on the cosegregation of a causal mutation with the anonymous marker along the lines of inheritance in pedigrees composed of affected and unaffected members, is particularly useful for traits where disease-causing alleles are highly penetrant: that is, the presence of the genetic variant virtually always co-occurs with disease, and its absence co-occurs with absence of the disease. As such, in the diabetes field, linkage analysis facilitated the discovery of the genes that underlie the various types of monogenic diabetes, such as maturity-onset diabetes of the young (MODY) (12,16) or neonatal diabetes (17,18,19); these are described in detail in Chapter 7 *Monogenic Forms of Diabetes*.

In complex diseases, where the phenotype presumably arises as a combination of several genetic variants and their interaction with the environment, successful linkage analysis is considerably more difficult. Though it succeeded in demonstrating the strong influence of the human leukocyte antigen (HLA) region on type 1 diabetes (20,21), by and large, linkage analysis did not yield reproducible positive results for type 2 diabetes. This is because in type 2 diabetes there is not a single genetic locus that exerts a very strong effect in the general population or even in individual family pedigrees. Thus, the effect of genetic variation is *probabilistic* rather than *deterministic*; a substantial proportion of people with some risk variants may be disease-free, whereas others who carry protective alleles may instead have type 2 diabetes, due to a constellation of other factors. In such situations, the amount of information provided by meioses within families, on which the power of linkage analysis depends, is greatly reduced, and the number of families required can be inordinately large.

To demonstrate the effect of genetic variation on human phenotypes, an alternative approach was needed: association testing, which simply asks whether a specific allele is significantly overrepresented in diabetes cases compared to controls without diabetes, and which, with large sample size, has greater statistical power to detect a common variant of weak effect. Its major limitation—prior to 2005—was that only a handful of variants could be tested at a time, which required some prior biologic knowledge on the existence of such variants and the role of a given gene in diabetes pathophysiology. Although multiple genetic associations were described before 2005, only two of these stood the test of time, both at variants that change the amino acid sequence in genes that encode antihyperglycemic drug targets: the p.Pro12Ala polymorphism in the peroxisome proliferator-activated receptor gamma 2 (encoded by *PPARG*) (22) and the p.Glu23Lys polymorphism in the islet ATP-dependent potassium channel Kir6.2 (encoded by *KCNJ11*) (22,23). A third locus, a noncoding variant in the transcription factor 7-like 2 gene (*TCF7L2*), was discovered by large-scale association testing in areas of suggestive linkage (24). The common intronic rs7903146 polymorphism had the strongest statistical association (though with a modest odds ratio ~1.4) and the most widespread effect on type 2 diabetes risk (Figure 14.1) (25,26), albeit with an interesting exception in some Native American populations (27).

The panorama changed dramatically with the advent of genome-wide association studies (GWAS) (28). Several factors coalesced to enable the conduct of GWAS: the discovery of millions of single nucleotide polymorphisms (SNPs) and their deposition in public databases; the manufacturing of genotyping arrays that could simultaneously query hundreds of thousands of SNPs with great precision; the understanding of an underlying correlation structure between SNPs, driven by the finite number of recombination events in human history, which reduced the complexity of the variation to be interrogated; the recognition that the scientific imperative of reproducibility required the acceptance of strict statistical thresholds that accounted for the universe of possible hypotheses in the human genome; and

FIGURE 14.1. Chronological Listing of Type 2 Diabetes-Associated Genes, Plotted by Year of Definitive Publication and Approximate Effect Size



Genes identified via the candidate gene approach are shown in green (*), genes identified via agnostic genome-wide association approaches are shown in blue (no symbol), genes identified by exome sequencing are shown in orange (†), and genes identified by whole-genome sequencing are shown in red (‡). *TCF7L2* (shown at 2006) was discovered by dense fine-mapping under a linkage signal. *TBC1D4* (shown last at 2014) was identified by exome sequencing of a locus found to be associated with a diabetes-related quantitative trait. Approximate allelic effect sizes were derived from the DIAGRAM (Diabetes Genetics Replication and Meta-analysis consortium) European ancestry meta-analysis (66) and the Asian ancestry meta-analysis (55) when possible. Gene names that are underlined denote identification in population isolates.

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the corollary of such awareness, that for these very small p-values to be achieved, very large sample sizes had to be assembled through international collaboration. Thus, for the first time, most of the common variants in the human genome (i.e., those with a minor allele frequency >5%) could be tested in one fell swoop.

Several independent GWAS (29,30,31,32,33) and the growing scientific exchange that led to successive meta-analyses of ever-increasing size (34,35) soon produced a plethora of robust associations, such that the landscape of type 2 diabetes-associated variants grew from three prior to the GWAS era to several dozen in just a few years (Figure 14.1, Table 14.1) (26,36,37). This list has been complemented by the implementation of similar approaches in the discovery of genetic determinants of quantitative glycemic traits (Table 14.2) (37,38,39,40,41,42,43,44,45), the extension of GWAS to non-European populations (46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64), trans-ethnic meta-analyses of many of these studies (56,65), and the deployment of custom-made arrays that allow for the rapid and efficient genotyping of top signals across thousands of additional samples (66,67).

A particularly illustrative example of a combination of these approaches has been furnished by Moltke *et al.* (68). On studying the population isolate of Greenland, they selected a custom-made array, the Metabochip (69), and focused on quantitative glycemic traits. They followed-up an original signal in *TBC1D4* by sequencing the exons of this gene and

TABLE 14.1. Genetic Loci Associated With Type 2 Diabetes at Genome-Wide Levels of Statistical Significance ($p<5x10^{-8}$)

MARKER	CHR.	NEAREST GENE(S)	DISCOVERY COHORT(S) (REF.)
rs17106184	1	*FAF1*	65
rs2296172	1	*MACF1*	75
rs10923931	1	*NOTCH2*	34
rs340874	1	*PROX1**	39
rs243021	2	*BCL11A*	35
rs3923113	2	*COBLL1/GRB14*	51
rs780094	2	*GCKR**	39
rs2943641	2	*IRS1*	128
rs7560163	2	*RBM43/RND3*	54
rs7593730	2	*RBMS1*	129
rs7578597	2	*THADA*	34
rs6723108	2	*THEM163*	58
rs4607103	3	*ADAMSTS9/ PSMD6*	34
rs11708067	3	*ADCY5**	39
rs4402960	3	*IGF2BP2*	30,31,32
rs6808574	3	*LPP*	65
rs831571	3	*PSMD6*	55
rs1801282	3	*PPARG*	22
rs16861329	3	*ST6GAL1*	51
rs7612463	3	*UBE2E2*	50
rs6815464	4	*MAEA*	55
rs6813195	4	*TMEM154*	65
rs10010131	4	*WFS1*	130
rs459193	5	*ANKRD55*	66
rs702634	5	*ARL15*	65
rs35658696	5	*PAM/PPIP5K2*	77
rs4457053	5	*ZBED3*	35
rs7754840	6	*CDKAL1*	30,31,32,33
rs1535500	6	*KCNK16*	55
rs3132524	6	*POU5F1/TCF19*	65
rs9502570	6	*SSR1/RREB1*	65
rs9470794	6	*ZFAND3*	55
rs2191349	7	*DGKB/TMEM195**	39
rs6467136	7	*GCC1/PAX4*	55
rs4607517	7	*GCK**	39
rs864745	7	*JAZF1*	34
rs972283	7	*KLF14*	35
rs791595	7	*LEP*	62
rs516946	8	*ANK1*	66
rs13266634	8	*SLC30A8*	29
rs896854	8	*TP53INP1*	35
rs1081161	9	*CDKN2A/B*	30,31,32
rs7041847	9	*GLIS3*	55
rs11787792	9	*GPSM1*	62
rs17584499	9	*PTPRD*	48
rs2796441	9	*TLE1*	66
rs13292136	9	*TLE4* (formerly *CHCHD9*)	35
rs12779790	10	*CDC123/CAMK1D*	34
rs10886471	10	*GRK5*	57
rs1111875	10	*HHEX*	29
rs7903146	10	*TCF7L2*	24
rs1802295	10	*VPS26A*	51
rs12571751	10	*ZMIZ1*	66
rs1552224	11	*ARAP1* (formerly *CENTD2*)	35
rs2334499	11	*DUSP8*	116
rs5219/rs757110	11	*KCNJ11/ABCC8*	23
rs2237892	11	*KCNQ1*	46,47
rs10830963	11	*MTNR1B**	38
rs2074356	12	*C12orf51*	60
rs11065756	12	*CCDC63*	60
rs11063069	12	*CCND2*	66
rs1531343	12	*HMGA2*	35
rs7957197	12	*HNF1A*	35
rs10842994	12	*KLHDC5*	66
rs1727313	12	*MPHOSPH9*	65
rs7961581	12	*TSPAN8/LGR5*	34
rs9552911	13	*SGCG*	59
rs1359790	13	*SPRY2*	49
rs61736969	13	*TBC1D4**	68
rs2007084	15	*AP3S2*	51
rs4502156	15	*VPS13C/C2CD4A/B*	50
rs7178572	15	*HMG20A*	51
rs8042680	15	*PRC1*	35
rs7403531	15	*RASGRP1*	57
rs11634397	15	*ZFAND6*	35
rs7202877	16	*BCAR1*	66
rs9939609	16	*FTO*	131
rs4430796	17	*HNF1B*	132,133
rs312457	17	*SLC16A11/13*	61,62
rs391300	17	*SRR*	48
rs12454712	18	*BCL2*	56
rs8090011	18	*LAMA1*	134
rs12970134	18	*MC4R*	66
rs10401969	19	*CILP2*	66
rs8108269	19	*GIPR*	66
rs3786897	19	*PEPD*	55
rs4812829	20	*HNF4A*	51,55
rs5945326	X	*DUSP9*	35

Loci are arranged alphabetically by chromosome number. One representative variant and one or two genes are provided for each locus. Loci are defined as association signals located within 500 kb of each other regardless of linkage disequilibrium. Chr, chromosome.

* Discovery of type 2 diabetes association followed detection in genome-wide association studies for quantitative glycemic traits (see Table 14.2).

SOURCE: Modified from Reference 37. References for individual discovery cohorts are listed within the table.

TABLE 14.2. Genetic Variants Associated With Quantitative Glycemic Traits at Genome-Wide Levels of Statistical Significance ($p<5x10^{-8}$)

MARKER	CHR.	NEAREST GENE(S)	TRAIT	DISCOVERY COHORT(S) (REF.)
rs2820436	1	*LYPLAL1*	I	43,67
rs340874	1	*PROX1**	B	39
rs9727115	1	*SNX7*	FP	42
rs2779116	1	*SPTA1*	H	41
rs6684514	1	*TMEM79*	H	135
rs10195252	2	*COBLL1/GRB14**	I	43,67
rs1371614	2	*DPYSL5*	B	43
rs560887 rs1402837	2	*G6PC2*	B H	39,41
rs780094 rs1260326	2	*GCKR**	B I	39,40
rs2972143	2	*IRS1**	I	43,67
rs733331	2	*PDK1/RAPGEF4*	B	136
rs895636	2	*SIX2/SIX3*	B	137
rs1530559	2	*YSK4*	I	67
rs11708067 rs2877716	3	*ADCY5**	B I	39,40
rs11715915	3	*AMT*	B	67
rs7651090	3	*IGF2BP2**	B, I	67
rs17036328	3	*PPARG**	I	67
rs11920090	3	*SLC2A2*	B	39
rs3822072	4	*FAM13A*	I	67
rs4691380	4	*PDGFC*	I	43,67
rs17046216	4	*SC4MOL*	I	135
rs9884482	4	*TET2*	I	67
rs459193	5	*ANKRD55**	I	67
rs4865796	5	*ARL15**	I	67
rs1019503	5	*ERAP2*	I	67
rs35658696	5	*PAM/PPIP5K2**	I	72
rs4869272 rs6235	5	*PCSK1*	B FP	43,67
rs7708285	5	*ZBED3**	B	67
rs9368222 rs7747752	6	*CDKAL1**	B, H, I	44,67,138
rs10305492	6	*GLP1R*	G	74
rs9399137	6	*HBS1L/MYB*	H	135
rs1800562	6	*HFE*	H	41
rs2745353	6	*RSPO3*	I	67
rs17762454	6	*SSR1/RREB1**	B	67
rs6912327	6	*UHRF1BP1*	I	43,67
rs2191349	7	*DGKB/TMEM195**	B	39
rs6947345	7	*EMID2*	B	139
rs4607517, rs730497	7	*GCK**	B, H, I	39,41,44,67
rs6943153	7	*GRB10*	B	44,67
rs1167800	7	*HIP1*	I	67
rs6474359	8	*ANK1**	B, H	41,44
rs983309 rs11782386	8	*PPP1R3B*	B I	43,67
rs11558471 rs13266634	8	*SLC30A8**	B FP	39,42
rs651007	9	*ABO*	B	72,73
rs10811661	9	*CDKN2A/B**	B	67
rs306549	9	*DDX31*	FP	42
rs3829109	9	*DNLZ/GPSM1**	B	67
rs7034200	9	*GLIS3**	B	39
rs16913693	9	*IKBKAP*	B	67
rs3824420	9	*KANK1*	FP	72,136
rs10885122	10	*ADRA2A*	B	39
rs7923866	10	*HHEX**	B	44
rs7072268	10	*HKI*	H	41
rs10829854	10	*TCERG1L*	I	140
rs7903146	10	*TCF7L2**	B, FP, I	39,40,42,67
rs11603334	11	*ARAP1**	B, FP	42,43,67
rs11605924	11	*CRY2*	B	39
rs174550	11	*FADS1*	B	39
rs174570	11	*FADS2*	H	135
rs7944584	11	*MADD*	B, FP	39,42
rs10830963	11	*MTNR1B**	B, H	38,41,44,141,142
rs1483121	11	*OR4S1*	B	43
rs2074356	12	*C12orf51**	B	143
rs2657879	12	*GLS2*	B	67
rs2650000	12	*HNF1A**	B	72
rs35767	12	*IGF1*	I	39
rs122229654	12	*MYL2*	I	143
rs11066453	12	*OAS1*	I	143
rs10747083	12	*P2RX2*	B	67
rs17331697	12	*RMST*	B	139
rs150781447	12	*TBCD130*	FP	72
rs7998202	13	*ATP11A*	H	41
rs576674	13	*KL*	B	67
rs11619319	13	*PDX1*	B	43,67,77
rs61736969	13	*TBC1D4**	B, I	68
rs3783347	14	*WARS*	B	67
rs11071657	15	*VPS13C/C2CD4A/B**	B, FP, I	39,40,42,44
rs2018860	15	*IGF1R*	B	136
rs1549318	15	*LARP6*	FP	42
rs9933309	16	*CYBA*	H	135
rs1421085	16	*FTO**	I	67
rs1046896	17	*FN3K*	H	41
rs4790333	17	*SGSM2*	FP	42
rs10423928	19	*GIPR**	B, I	40,44,67
rs11667918	19	*MYO9B*	H	135
rs731839	19	*PEPD**	I	67
rs6113722	20	*FOXA2*	B	43,67
rs6072275	20	*TOP1*	B	67
rs855791	22	*TMPRSS6*	H	41

Loci are arranged alphabetically by chromosome number. One representative variant and one or two genes are provided for each locus for each glycemic trait. Loci are defined as association signals located within 500 kb of each other regardless of linkage disequilibrium. B, beta cell (fasting glucose, HOMA-B, corrected insulin response, disposition index, insulinogenic index, or these traits adjusted for BMI); BMI, body mass index; Chr, chromosome; FP, fasting proinsulin; H, hemoglobin A1c; HOMA-B and HOMA-IR, beta cell function and insulin resistance by homeostasis model assessment, respectively; I, insulin resistance (fasting insulin, 1-hour glucose, 2-hour glucose, HOMA-IR, or these traits adjusted for BMI).
* Locus is also associated with type 2 diabetes.

SOURCE: Modified from Reference 37. References for individual discovery cohorts are listed within the table.

identified a nonsense p.Arg684Ter variant of Inuit ancestry that is common in the Greenlandic population (frequency 17%) and is associated with 2-hour glucose and insulin levels. Stop codon homozygotes harbor a tenfold increased risk of type 2 diabetes compared to wildtype allele carriers. Definitive identification of the implicated protein allowed for functional studies: the stop codon induces lower protein levels of TBC1D4 in human skeletal muscle, causing reduced numbers of the glucose transporter GLUT4 and decreased insulin-stimulated glucose uptake, leading to postprandial hyperglycemia and impaired glucose tolerance.

However, many of these GWAS only captured common variants, because imputation of ungenotyped variants depended on available reference panels from resources such as the HapMap (70). The introduction of massive parallel sequencing techniques and the concomitant dramatic drop in cost allowed for efficient, high-fidelity sequencing of thousands of samples. This enabled three major developments: first, denser reference panels could be developed for more accurate imputation of less common variants (71); second, targeted genotyping arrays that included less common but likely functional variation (e.g., coding variants) could be designed; and third, the allelic spectrum captured in case-control or quantitative trait studies could be expanded into less common frequencies, so that population genetics by which a rare variant may rise to prominence in a specific ethnic group could be exploited.

Arrays containing exome content deployed in large populations have identified coding variants in established or novel genes associated with type 2 diabetes or related quantitative traits (72,73,74). By detecting a robust association signal in the coding region of a specific gene (e.g., *SGSM2* and proinsulin levels) (72), these studies serve to advance the candidacy of said gene as the causal locus, from within the various possibilities under a noncoding GWAS association peak (42). Beyond genotyping, sequencing of whole exomes in Europeans (75) and Mexicans (76) has also yielded novel associations, and the extensive genetic and pedigree data available in the Icelandic population have allowed whole-genome sequences in 2,630 Icelanders to be extrapolated to a sample size of 11,114 type 2 diabetes cases and 267,140 controls for additional discovery (77). Finally, whole-genome sequencing in 2,657 European individuals with and without diabetes and whole-exome sequencing in 12,940 individuals from five ancestry groups have begun to shed light on the genetic architecture of type 2 diabetes in a more systematic fashion, in terms of plausible effect sizes, observed allelic frequencies, and the potential number of causal variants (78). All in all, these studies support a model in which type 2 diabetes is caused by hundreds or thousands of loci of modest effects, with no major role for low-frequency variants of strong effects in disease predisposition.

INSIGHTS GAINED

The tremendous success of GWAS and their follow-up for type 2 diabetes and other human phenotypes have resulted in a number of insights into the genetic architecture of type 2 diabetes.

Although the functional variants at most type 2 diabetes-associated loci are not yet known, most associated loci are located near genes that were previously unsuspected to play a role in type 2 diabetes pathophysiology. This observation highlights the complexity of the disease phenotype and the power of agnostic approaches in unearthing new knowledge. Conversely, it brings to the forefront the constraints imposed by prior knowledge on scientific inquiry and points to the inadequacy of prior candidate gene selection efforts, as most "logical" candidate genes did not yield significant associations. This observation does not necessarily minimize the role of such biologic candidates on glucose homeostasis; rather, it may indicate natural selection's little tolerance for functional variation in those key genes.

Noncoding variation can affect human phenotypes. The SNPs with the strongest associations are often found in introns, regulatory regions, or intergenic segments, i.e., they do not change the amino acid sequence of the encoded proteins. Furthermore, for the most part, no obvious missense SNP has been identified in coding regions for which the associated SNP was a proxy and, thus, might have explained the association signal. The human genome is rife with regulatory sequences that influence the timing, location, and level of expression of genes (79), and these are thought to have a substantial impact on human biology.

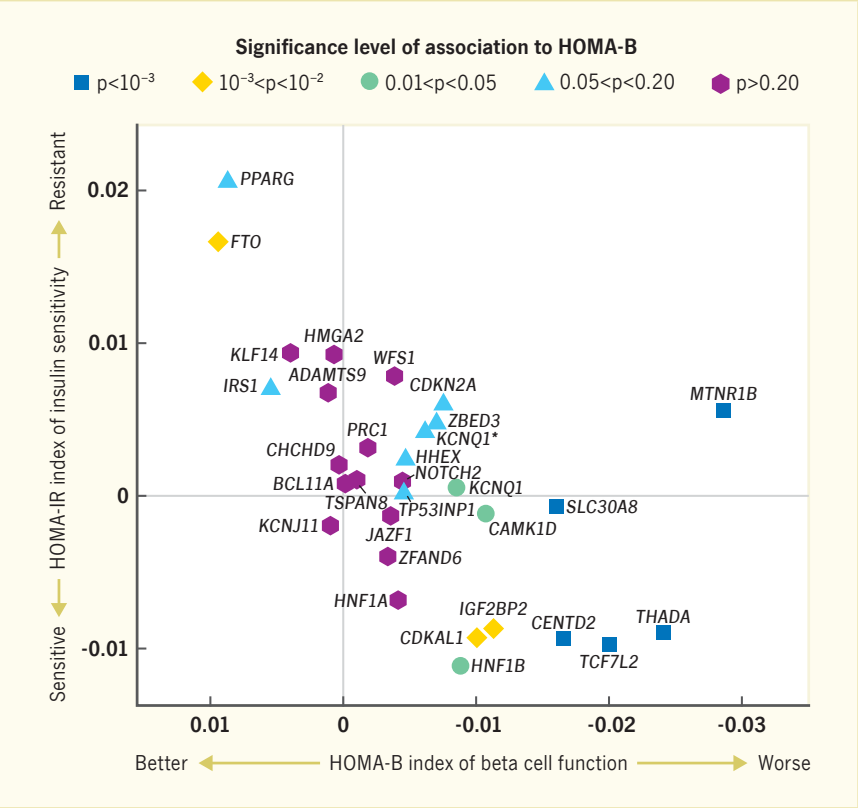
Most genetic determinants of type 2 diabetes have modest effects. No common variant that is widely shared across populations has been found to have a stronger effect than the rs7903146 SNP in *TCF7L2*. The handful of variants with stronger effects (e.g., *TBC1D4* p.Arg684Ter in Greenland, odds ratio ~10 (68), or *HNF1A* p.Glu508Lys in Mexico, odds ratio ~5 (76)) are either rare or unique to specific populations. Moreover, pioneering whole-exome and whole-genome sequencing experiments in thousands of samples across multiple ethnic groups have failed to unveil a plethora of rare variant associations, and they have not provided support for the hypothesis that common variant association signals are undergirded by rare variants of strong effects (78,80). Thus, the genetic architecture of type 2 diabetes appears to involve hundreds of variants with modest effects (66,78,81). While rare variants might be found that have stronger effects in specific families or population groups, they are most likely to be private, as shared rare variants of strong effects should have been found by linkage. A corollary of this observation is that any single variant is unlikely to have significant predictive power in the individual, and even when many variants are combined into a genotype risk score (GRS), predictive power is poor. Together, the approximately 100 loci associated with type 2 diabetes thus far explain ~10%–15%

of the familial aggregation of the disease, or 5.7% of the variance in type 2 diabetes susceptibility (66).

The majority of genetic variants that influence type 2 diabetes risk affect beta cell function (Figure 14.2) (35,82,83). Human studies have shown that most of the identified variants (whether causal or tagging a causal variant) are associated with impaired beta cell function, directly or indirectly (83). Insulin secretion appears to be more heritable than insulin resistance (39,84), confirming the pathogenic hypothesis put forth by early geneticists, by which a mostly environmental insult causing insulin resistance is overlaid on a mostly genetic predisposition to beta cell dysfunction.

The genetic architecture of beta cell function and insulin action seem to differ (Figure 14.3) (39). As mentioned, measures of estimating beta cell function in humans are more amenable to genetic approaches (i.e., they have a higher likelihood of yielding significant findings) than measures of insulin sensitivity (39,84). Incorporating adiposity as a modulator of insulin resistance (43) or focusing genetic investigation on more sophisticated and

FIGURE 14.2. Two-Dimensional Plot of Type 2 Diabetes-Associated Loci Placed in Relationship to Beta Cell Function and Insulin Resistance



Fasting measures of beta cell function (HOMA-B, X axis) and insulin resistance (HOMA-IR, Y axis) were obtained by homeostasis model assessment. The majority of loci are associated with impaired beta cell function, though some do clearly impact insulin resistance. Colors and shapes denote the significance level of the association to HOMA-B. The two *KCNQ1* associations are distinguished by the notation *KCNQ1* for rs163184 and *KCNQ1** for rs231362.

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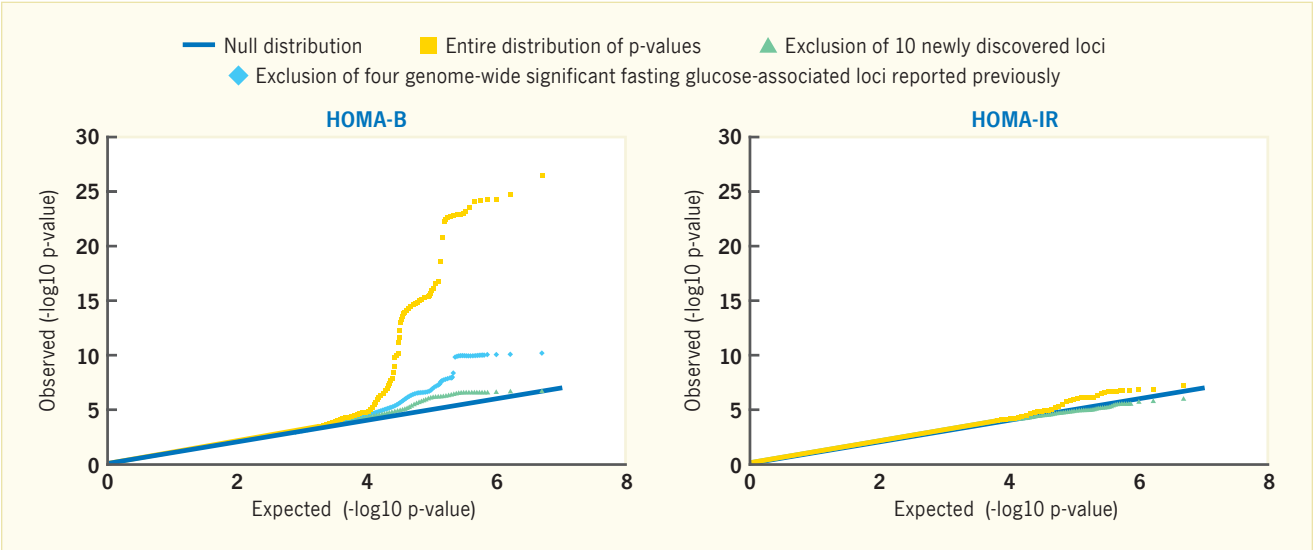
FIGURE 14.3. Quantile-Quantile Plots for Genome-Wide Association Studies of Beta Cell Function and Insulin Resistance



Homeostasis model assessments of beta cell function (HOMA-B) and insulin resistance (HOMA-IR) were generated for the Meta-analyses of Glucose and Insulin-related Traits Consortium (MAGIC) meta-analysis of fasting glycemic traits. The quantile-quantile plot illustrates the observed p-values in the full distribution versus those that would be expected under the null hypothesis of no association. The HOMA-B p-values have a larger deviation from expected compared to HOMA-IR, indicating that genetic associations with HOMA-B are more likely to be detected than those with HOMA-IR. The fasting insulin distribution (not shown) parallels that of HOMA-IR, suggesting that the plot illustrates the true genetic architecture of the trait and is not affected by the use of a mathematical formula to calculate HOMA-IR. Because the same number of samples and types of insulin assays were used to estimate HOMA-B and HOMA-IR, sample size and assay heterogeneity cannot be invoked to explain the observed difference.

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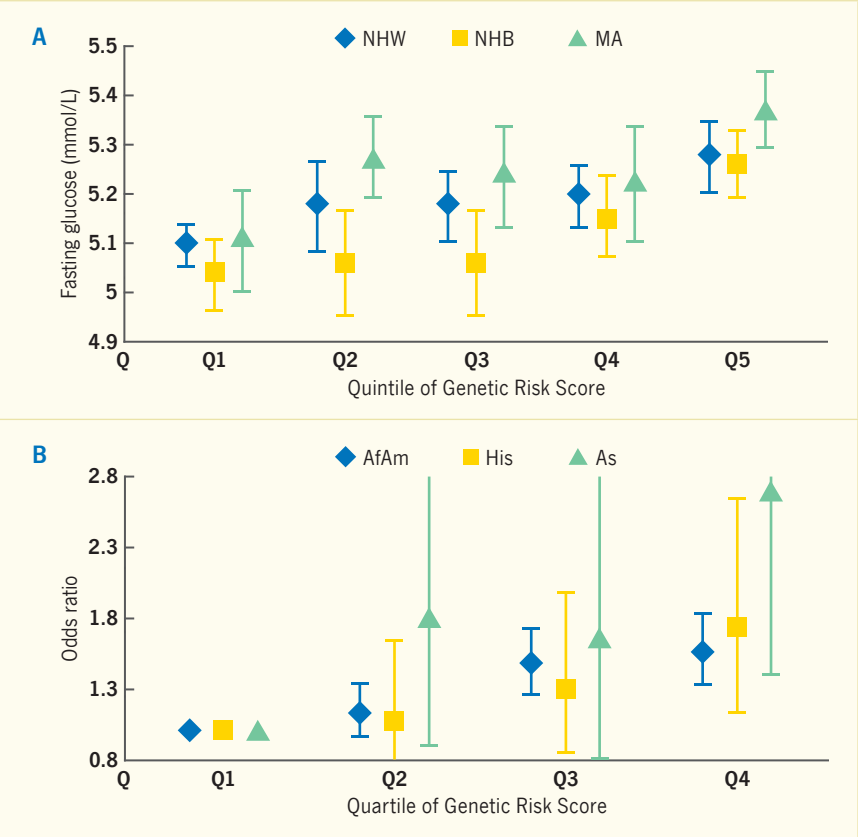
refined measures of insulin sensitivity (45) has yielded additional loci; nevertheless, the majority of type 2 diabetes-associated loci for which a physiologic mechanism has been determined seem to influence beta cell function (35,83). Insulin resistance might be influenced by fewer loci, less frequent variants or those with more modest effects, or a stronger environmental component.

The genes that elevate fasting glucose in normal individuals are not necessarily the same genes that cause type 2 diabetes. While a simple model would predict that any locus that raises fasting glucose should raise risk of type 2 diabetes, the exploration of genetic determinants of glucose homeostasis in nondiabetic individuals has yielded a number of variants that do both (i.e., raise fasting glucose and increase type 2 diabetes risk), but also a non-trivial number that raise fasting glucose without appreciably increasing risk of type 2 diabetes. This observation has led physiologists to consider not just the magnitude of the glucose increase, but the manner in which this happens, as relevant to the emergence of disease (39). A simple elevation of the glucose set point, for example, may not necessarily lead to hyperglycemia in the diabetes range, if beta cell function is otherwise intact; however, an alteration that leads to progressive beta cell deterioration would cause diabetes in the future.

Genetic studies support prior epidemiologic observations. A GWAS for fasting glucose yielded significant associations near two circadian genes (*MTNR1B* and *CRY2*) (39). A growing literature implicates circadian dysregulation, through epidemiologic reports (85), animal studies (86,87), and human perturbation experiments (88), in metabolically deleterious phenotypes. Thus, a GWAS for glycemia provides a potential genetic link between the two systems. Similarly, a SNP in *ADCY5* has been associated with fasting glucose, type 2 diabetes, and low birth weight, once again corroborating the known relationship between being born small for gestational age and future risk of obesity and diabetes (89). In addition, SNPs in *FTO* and *MC4R* contribute to obesity, insulin resistance, and type 2 diabetes, thus connecting various components of the metabolic syndrome (67,90).

FIGURE 14.4. Loci Initially Identified in Populations of European Descent Appear to Have Similar Effects in Other Racial/Ethnic Groups



Genetic risk scores constructed from variants associated with fasting glucose by the Meta-analyses of Glucose and Insulin-related Traits Consortium (MAGIC) investigators (39) or the Diabetes Genetics Replication and Meta-analysis (DIAGRAM) consortium (35) in populations of European descent also predict, in aggregate, rising glucose or type 2 diabetes in other racial/ethnic groups. (A) Data obtained for fasting glucose from the National Health and Nutrition Examination Surveys 1991–1994 (92). (B) Data obtained for type 2 diabetes using the IBC (ITMAT-Broad-CARe) chip (56). AfAm, African American; As, Asian; His, Hispanic; MA, Mexican American; NHB, non-Hispanic black; NHW, non-Hispanic white.

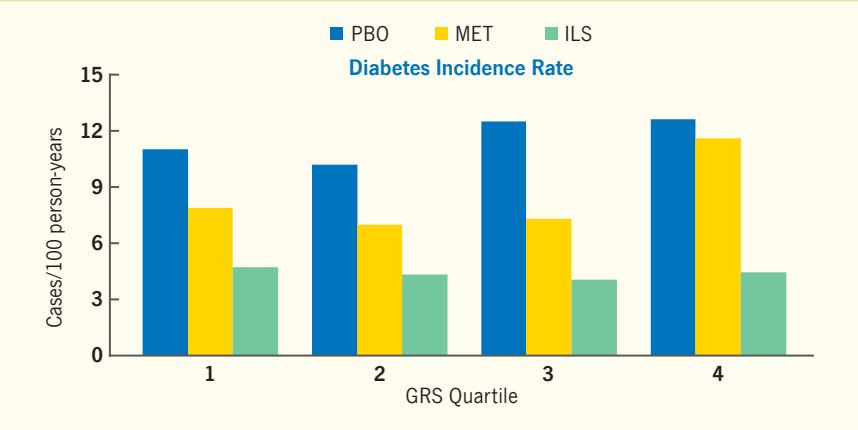
SOURCE: References are listed within the figure legend.

Most common risk variants are shared across ethnic groups. Although GWAS of comparable size and power have not yet been performed in non-European populations, when investigators have tried to ascertain whether common variants that influence these traits in people of European descent also do so in individuals of other continental ancestries, by and large, they have found similar effects; though, some loci do show heterogeneity. Once allele frequency differences and altered haplotype structures are taken into account, analogous patterns of association emerge in African American, Hispanic, Asian, or Native American populations (Figure 14.4) (56,91,92,93).

Genetic information does not add much beyond clinical variables for type 2 diabetes prediction. Commonly ascertained clinical variables are fairly precise at capturing future risk of type 2 diabetes (10); thus, adding the set of common variants known to date (which only explains a minor fraction of the genetic predisposition to type 2 diabetes) does not seem to improve predictive accuracy at the individual level or the ability to discriminate between risk strata in a clinically meaningful way (94,95,96). Prediction is slightly improved in younger individuals, in whom clinical risk factors are not yet fully manifest.

An intensive lifestyle intervention is effective in people with the highest burden of known risk alleles. The Diabetes Prevention Program showed that an intensive lifestyle intervention, consisting of dietary and physical activity components, is effective even in the quartile of participants who carry the highest load of known risk variants (Figure 14.5) (97).

FIGURE 14.5. An Intensive Lifestyle Intervention, as Deployed in the Diabetes Prevention Program, is Effective Regardless of Genetic Risk Score for Type 2 Diabetes



Diabetes Prevention Program participants were stratified by quartile of genetic risk constructed by adding risk alleles from 34 known type 2 diabetes-associated variants. Whereas the GRS predicts diabetes incidence in the placebo arm, it does not do so in the lifestyle arm; indeed, the intervention is highly effective in reducing diabetes incidence even in the quartile with the highest genetic risk. GRS, genetic risk score; ILS, intensive lifestyle; MET, metformin; PBO, placebo.

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Genetic variation may affect drug response. Genetic information may eventually be used to guide medication choices in type 2 diabetes. Though this is the standard of care for monogenic diabetes with examples in both MODY and neonatal diabetes (98,99), the potential of genetically guided therapy is yet to be realized in common type 2 diabetes. A polymorphism in a metformin transporter may affect glycemic response to metformin (100,101,102), and a GWAS for metformin response in people with type 2 diabetes has identified a polymorphism near the *ATM* gene that influences metformin response in several independent cohorts (103,104), although it does not seem to exert the same effect for diabetes prevention in people with prediabetes (105). Some sulfonylureas are metabolized by the cytochrome P450 enzyme CYP2C9, and patients with loss-of-function variants in this gene are at increased risk of sulfonylurea-related hypoglycemia (106). These early pharmacogenomic lessons suggest that genes relevant to drug response may be the same as those that increase risk for type 2 diabetes, or they may be different.

LIMITATIONS OF CURRENT APPROACHES (AND THEIR SOLUTIONS)

Despite the overwhelming success of GWAS strategies in advancing knowledge of the genetic determinants of type 2 diabetes, a number of limitations must be recognized. These limitations have been identified by the research community and are being addressed to complement gaps in understanding.

GWAS were initially undertaken only in populations of European descent. A large swath of genetic variation is unique to other populations, especially those of African descent, due to the bottleneck introduced when a limited subset of human ancestors migrated out of Africa. In addition, genetic variants have been identified that, though present in Europeans, are much more common in other populations, thereby acquiring greater statistical power to detect modest effects. As described above, GWAS efforts in East Asian (46,47,48,49,50,55,57,60,62), South Asian (51,58,59), African American (54,63), Hispanic (52,53,61), and Native American (64) cohorts have already yielded novel genome-wide significant findings, many of which are also seen in Europeans. As larger consortia and trans-ethnic meta-analyses are undertaken, more novel findings are expected to come to light.

GWAS of large cohorts suffer from relatively crude phenotyping. Because sample size is paramount to achieve adequate statistical power, GWAS are typically carried out in very large population cohorts where only limited phenotyping is feasible. The estimates of beta cell function or insulin sensitivity derived from simple measures, such as fasting glucose or insulin (107) (as opposed to those obtained from more labor-intensive and costly dynamic testing), are relatively imprecise. However, some of the participating cohorts do have more sophisticated phenotyping: while the participants have contributed their simple traits to the meta-analytic efforts, the investigators are also able to form subconsortia where additional physiologic inquiry can be carried out. This type of analysis has been performed for proinsulin levels adjusted for fasting insulin (42), various dynamic measures of insulin secretion (44), and insulin sensitivity derived from clamp studies (45), and it is underway for insulin sensitivity derived from oral glucose tolerance tests (108) and insulin clearance (109,110).

GWAS only capture common variants. Due to the composition of genotyping arrays and statistical issues around rare observations, most GWAS to date have concentrated solely on common variation (i.e., minor allele frequency >5%). The introduction of next-generation DNA sequencing technologies has allowed for a downward expansion in the characterization of shared uncommon variation, as sequencing >1,000 individuals from multiple ethnic groups in the 1000

Genomes Project (71) has produced a catalog of uncommon variants that can be captured by their correlation to previously known common variants. Imputation to these 1000 Genomes panels is expanding the subset of testable variants in extant meta-analyses. The pioneering whole-exome (75,76) and whole-genome (77) sequencing studies described above are beginning to yield fruit, particularly when expanded to larger multi-ethnic samples (78). Nevertheless, under a model that the genetic architecture of type 2 diabetes is composed of several thousand variants of modest effects (66,81), even sequencing experiments require sample sizes of upwards of 25,000 cases to detect true associations, as either effect size or allele frequency is limiting (111).

Most analyses have not taken into account interactions with the environment. Type 2 diabetes results from complex interactions among multiple genetic and environmental factors, and the rapid rise of its prevalence cannot be attributed to genetics. Because most GWAS are designed to detect loci that have main effects on type 2 diabetes risk, regardless of the environmental context, many variants whose impact varies according to an environmental parameter might be missed. This is due in part to the imprecision inherent to environmental measures and the noise introduced by a single cross-sectional environmental exposure; in contrast, genotyping methods are extremely accurate, and the genetic exposure is uniform across an individual's lifetime. Nevertheless, analytical methods are being developed that allow for the joint inquiry of main gene effects and gene × environment interactions (112), and these methods have already been deployed to identify loci for insulin sensitivity (43) and for the regulation of body mass index (113).

Analyses of predictive properties have only included the SNPs meeting genome-wide significance. Analytical methods have been developed that utilize information from the entire genome (114,115), and these methods may provide better predictive properties than models that use only the established SNPs that have met genome-wide significance. The clinical utility of such approaches remains to be determined.

Most analyses are simple additive tests for association and do not explore more complex modes of inheritance. There are good statistical reasons to primarily base GWAS experiments on the additive genetic model, in which the presence of two copies of the risk allele in an individual essentially doubles the risk associated with a single allele. This may not always be the case: in the two extreme examples, under a dominant model, two copies of the risk allele will not add any further risk to that conferred by a single copy, and under a recessive model, the risk will not be made manifest unless both copies are present. While the majority of type 2 diabetes-associated SNPs have been found to exert their action via an additive model, this is expected as their discovery took place precisely under such a model. A comprehensive examination of alternative modes of inheritance is needed in the existing GWAS datasets, which now are reaching adequate sizes to compensate for the smaller number of homozygous minor allele carriers and for the penalty incurred by additional statistical testing. Similarly, tests of gene × gene interactions (epistasis) and accounting for divergent effects depending on parental line of inheritance, where that information is available (116), are likely to yield additional loci.

GWAS only identify correlated SNPs but do not yield the causal variant. Because GWAS leverage the correlative structure of the human genome to identify associations, they simply point to regions of the genome in which certain alleles are overrepresented in cases versus controls. Identifying which of the SNPs present in that segment is the actual molecular cause of the disease phenotype requires fine-mapping and functional studies. Fine-mapping can be performed by sequencing and saturation genotyping of all variants in the associated segment, retesting them and their haplotypes (linear arrangements of SNPs in a chromosome) for association with the phenotype. While custom-made arrays have been designed to achieve this task in type 2 diabetes and related metabolic traits (69), the conditional statistical testing that is required to distinguish the strength of the association of one variant from another's is laborious and requires inordinate sample sizes. Oftentimes, functional experiments are needed to establish which of the equally associated variants is pathogenic; these efforts have succeeded in some cases, for instance, in identifying the p.Ser1369Ala polymorphism in the sulfonylurea receptor gene *ABCC8* as the likely culprit for gliclazide response, rather than its tightly linked nearby polymorphism p.Glu23Lys in *KCNJ11* (117).

The road from association to function is arduous. As intimated in the previous point, a genetic association does not necessarily yield insights into molecular function. While this may be relatively easier to establish for coding missense variants that change amino acid sequence (because appropriate protein-based experiments can be designed), only a handful of type 2 diabetes associations fulfill this description (*KCNJ11* p.Glu23Lys/*ABCC8* p.Ser1369Ala, *SLC30A8* p.Arg235Trp, and *GCKR* p.Pro446Leu). For many other variants that fall in regulatory regions, a different sort of investigation must be designed (118). The publication of a comprehensive catalog of functional regulatory elements in the human genome and availability of public tissue expression data linked to genotype data should facilitate this task enormously (79,119). The ability to perform genome editing (e.g., with CRISPR/CAS9) in informative experimental systems, such as induced pluripotent stem cells, should also greatly expand the ability to investigate function.

A pioneering illustration of how such an effort can yield fruits was achieved for *TCF7L2*: fine-mapping had established rs7903146 as the likely culprit SNP, and physiologic studies had placed its pathogenic activity squarely in the beta cell (120,121); an intelligent integration of these data with areas of open chromatin in beta cells, combined with expression experiments, led to the determination that

rs7903146 affects an enhancer element that regulates *TCF7L2* expression (122). In another example, *KLF14* had been associated with type 2 diabetes, but the risk allele appeared to cause insulin resistance (35); by combining the GWAS finding with expression datasets in adipose tissue, the associated SNP was discovered to influence expression of *KLF14*, which itself is a master regulator of adipose gene expression and thereby responsible for multiple metabolic phenotypes (123). Analogous experiments have clarified the role of SNPs around the glucose-6-phosphatase catalytic subunit 2 gene (*G6PC2*) (124). A fuller description of successful association-to-function efforts in type 2 diabetes is available elsewhere (125).

THE FUTURE OF RESEARCH ON THE GENETICS OF TYPE 2 DIABETES

Given the rapid progress achieved in genetic discovery in type 2 diabetes and the multipronged approach deployed to overcome experimental limitations, there is great hope that the pace will be maintained and a substantial part of the genetic architecture of type 2 diabetes will be elucidated in the coming years. If this vision is realized, a number of conceptual advances can be expected.

The nosology of disease will be refined. Type 2 diabetes, diagnosed solely on the basis of the final common pathway of hyperglycemia, is likely a heterogeneous syndrome that can be caused by a variety of processes (126). Genetic etiologies have already helped classify the various forms of MODY and neonatal diabetes, and an analogous exercise could take place in type 2 diabetes. The categorization of the disease into subtypes based on genetic determinants of physiology, prognosis, or predisposition to complications should help stratify the patient population into groups for which therapeutic or surveillance decisions might be better tailored.

Novel pathways will be identified. Unsuspected biology is already being uncovered via genetic discovery. With a greater number of genetic loci at hand, pathways or systems (e.g., cell proliferation) can be identified, some of which may be amenable to the development of new therapeutics.

Genetic discovery may identify drug targets. As mentioned above, among the initial type 2 diabetes genetic associations were coding variants for *PPARG*, the gene that encodes the target of thiazolidinediones (22), and *KCNJ11/ABCC8*, the genes that encode the targets for sulfonylureas (23,127). More recent studies have identified the target for glucagon-like peptide 1 receptor agonists as another type 2 diabetes-associated gene (73,74). This proof of principle for established type 2 diabetes drug targets indicates that among the many type 2 diabetes-associated loci, there might be other genes for which a suitable drug might be found or developed. Aggregating all of the genetic data in humans and model systems, as well as ancillary associations that might point to off-target effects, will be essential if the genomic revolution is to catalyze new drug discovery.

Stratification of patients may allow for better targeting of public health or clinical trial interventions. Some preventive or therapeutic measures may be too expensive to deploy in the population at large, or they may be futile in specific subgroups. Genetic characterization may help identify the groups of people more likely to benefit from particular public health strategies. Similarly, the efficiency of clinical trials may be enhanced by enrolling participants who are more likely to reach the desired endpoints or benefit from the agents being tested.

Genetics may facilitate the implementation of precision or personalized medicine. Though it is not yet clear that genetic information will be powerful enough to apply therapeutic decisions at the individual level, it may help do so for specific subgroups. For example, genetic approaches may unveil who is more likely to develop a particular diabetic complication. For such an approach to be feasible, researchers envision that in the not too distant future, any individual who joins a public or private health care system would be genotyped or sequenced for the full list of actionable genetic variants (e.g., those that modify risk of common diseases or response to available medications), such that his/her information is available in the electronic medical record. When the time comes to make specific screening or therapeutic decisions, genetic information filtered through appropriate decision support tools would automatically guide the practitioner into the course of action most appropriate to the person and situation at hand.

CONCLUSION

In sum, the genetics of type 2 diabetes is in a steep discovery curve. Progress has been uneven, however, with most efforts focused on common variants and populations of European descent. The rapid and continuing progress in genotyping and sequencing technologies, with a concomitant improvement in affordability, the growing understanding of the human genome, and the ongoing development of analytical tools and methods present an optimistic perspective on the future. Whether this newfound knowledge will translate into improved patient care depends on the ability to design and execute genetically based and outcomes-driven clinical trials.

LIST OF ABBREVIATIONS

GWAS . . . . . genome-wide association study
MODY . . . . . maturity-onset diabetes of the young
PPARG. . . . . peroxisome proliferator-activated receptor gamma
SNP . . . . . single nucleotide polymorphism
TCF7L2 . . . . transcription factor 7-like 2

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DUALITY OF INTEREST

Drs. Florez, Udler, and Hanson reported no conflicts of interest.

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