

REVIEW ARTICLE

MECHANISMS OF DISEASE

Genetics of Type 1A Diabetes

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IN 1976, THE NOTED HUMAN GENETICIST JAMES NEEL TITLED A BOOK CHAPTER “Diabetes Mellitus: A Geneticist’s Nightmare.”¹ Over the past 30 years, however, the phenotypic and genetic heterogeneity of diabetes has been painstakingly teased apart to reveal a family of disorders that are all characterized by the disruption of glucose homeostasis but that have fundamentally different causes. Recently, the availability of detailed information on the structure and variation of the human genome and of new high-throughput techniques for exploiting these data has geneticists dreaming of unraveling the genetic complexity that underlies these disorders. This review focuses on type 1 diabetes mellitus and includes an update on recent progress in understanding genetic factors that contribute to the disease and how this information may contribute to new approaches for prediction and therapeutic intervention.

Type 1 diabetes becomes clinically apparent after a preclinical period of varying length, during which autoimmune destruction reduces the mass of beta cells in the pancreatic islets to a level at which blood glucose levels can no longer be maintained in a physiologic range. The disease has two subtypes: 1A, which includes the common, immune-mediated forms of the disease; and 1B, which includes nonimmune forms. In this review, we focus on subtype 1A, which for simplicity will be referred to as type 1 diabetes.

Although there are rare monogenic, immune-mediated forms of type 1 diabetes,^{2,3} the common form is thought to be determined by the actions, and possible interactions, of multiple genetic and environmental factors. The concordance for type 1 diabetes in monozygotic twins is less than 100%, and although type 1 diabetes aggregates in some families, it does not segregate with any clear mode of inheritance.⁴⁻⁷ Despite these complexities, knowledge of genetic factors that modify the risk of type 1 diabetes offers the potential for improved prediction, stratification of patients according to risk, and selection of possible therapeutic targets. As germ-line factors, genetic risk variants are present and amenable to study at all times — before, during, and after the development of diabetes. Thus, genetic information can serve as a potential predictive tool and provide insights into pathogenetic factors occurring during the preclinical phase of the disease, when preventive measures might be applied.

GENETIC STUDIES

Because of the uncertainty regarding the number and action of genes involved in type 1 diabetes, genetic studies have tended to focus on approaches that require few assumptions about the underlying model of disease risk. The two primary approaches have been linkage studies (using pairs of affected relatives, typically siblings) and association studies (using either case-control or family-based designs). Linkage studies using affected sibling pairs seek to identify regions of the genome that are shared

more frequently than by chance alone among siblings who share the phenotype of type 1 diabetes. Nuclear families, or even just the affected sibling pairs themselves, are genotyped with panels of markers spanning the genome at a modest density. Linkage between a marker and a susceptibility locus for type 1 diabetes is determined by accumulating evidence across families. Since affected sibling pairs are relatively rare in type 1 diabetes, data from linkage studies are collected from a rather unique subgroup of families with type 1 diabetes. In general, linkage studies are the method of choice when the risk factors being sought have large effect sizes but are relatively rare. As risk factors become more common and have smaller effect sizes, association methods emerge as a potentially more powerful approach (Fig. 1). Since the genetic basis of type 1 diabetes is probably a complex mixture of small, moderate, and large genetic effects, multiple strategies are needed and vary according to the population being studied and their exposure to unknown environmental factors.

Until recently, association studies in type 1 diabetes have focused on candidate genes, pathways, or chromosomal regions. Specifically selected markers in genes of interest and the regions surrounding those genes are genotyped in case subjects and unaffected control subjects or, in some studies, in case subjects and their parents, and the frequencies of marker alleles are compared between affected and unaffected chromosomes. However, association studies have recently been revolutionized by genomewide association studies,⁸ as have linkage studies (to a lesser extent) for a number of years.

GENETIC LINKAGE STUDIES

The results of several genomewide searches for linkage between genetic markers and type 1 diabetes have been reported previously.⁹⁻¹⁵ The studies have consistently reported significant evidence of linkage between the HLA region on chromosome 6p21 and type 1 diabetes. Although many studies have shown suggestive evidence of linkage at additional, non-HLA loci, findings at these loci have been inconsistent. The most likely explanation is the limited size of these studies that individually provide power to adequately detect only loci with large effects on the risk to siblings (such as HLA). A meta-analysis of data combined from most of the genomewide studies of linkage to type 1 diabetes has been carried out under the auspices of the Type 1 Diabetes Genetics Consor-

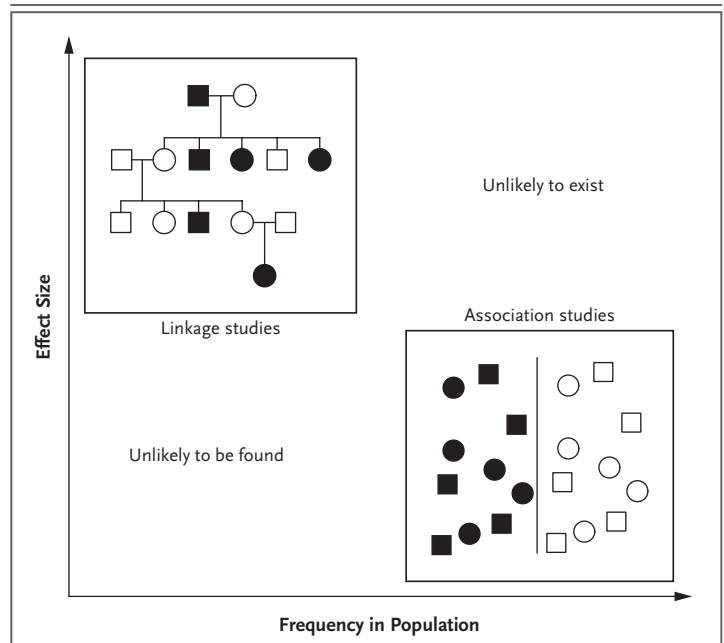


Figure 1. Relative Strengths of Linkage and Association Approaches for Mapping Genes in Complex Disorders.

The chart shows the effect of a disease allele's frequency in the population and its effect size on the optimal choice of study design. A disease allele that occurs frequently in the population and that has a large effect on disease risk is unlikely to exist. At the opposite end of the spectrum, a disease allele that is rare and has a small effect size is likely to exist but is unlikely to be found — and such alleles would be of limited public health interest. In general, linkage studies are most effective in disorders in which disease alleles are anticipated to have a large effect size but occur infrequently. Association studies are most effective for the detection of alleles that occur frequently but have a small effect size. These are general trends, and there are no specific boundaries in efficacy between the two approaches.

tium (T1DGC)¹⁵ (Table 1). This meta-analysis demonstrated overwhelming evidence supporting linkage to type 1 diabetes in the HLA region and suggestive evidence at a small number of other regions in the genome. In general, the emerging picture from linkage studies is that the class II genes encoding HLA-DR and HLA-DQ, as well as one or more additional genes within the HLA region, confer most of the genetic risk for type 1 diabetes. Genes outside the HLA region also contribute to the risk of type 1 diabetes, but their individual contributions are much smaller than that of HLA.

CANDIDATE-GENE ASSOCIATION STUDIES

Although linkage studies have pointed to a number of regions of the genome that contain novel genes that may contribute to the risk of type 1 diabetes, most identifications of actual risk loci have

Table 1. Current Status of Linkage Data for Type 1 Diabetes.*

Chromosomal Region	Position (cM)	Closest Marker	Lod Score	Sibling Risk Ratio	Lod-1 Interval†	Nominal P Value
2q31-33	192	D2S2167	3.34	1.19	177–204	9.0×10^{-5}
3p13-p14	98	D3S1261	1.52	1.15	78–112	8.2×10^{-3}
6p21	47	TNFA	116.3	3.35	46–48	4.9×10^{-52}
6q21	80	D6S283	22.39	1.56	ND	ND
9q33-q34	150	D9S260	2.20	1.13	138–161	1.5×10^{-3}
10p14-q11	61	D10S1426	3.21	1.12	52–66	1.2×10^{-4}
11p15	2	D11S922	1.87	1.16	0–14	3.4×10^{-3}
12q14-q12	81	D12S375	1.66	1.10	77–83	5.8×10^{-3}
16p12-q11.1	56	D16S3131	1.88	1.17	26–71	3.3×10^{-3}
16q22-q24	108	D16S504	2.64	1.19	100–121	4.9×10^{-4}
19p13.3-p13.2	25	INSR	1.92	1.15	0–43	3.0×10^{-3}

* Data are from the Type 1 Diabetes Genetics Consortium.¹⁵ The abbreviation cM denotes centimorgan, lod logarithmic odds, and ND not done.

† The lod-1 interval is the size of the interval (in centimorgans) in which the lod score is greater than or equal to the maximum minus 1.0.

come from studies of candidate genes. This, in part, reflects differences in the approaches. Association depends on linkage disequilibrium between specific alleles at an unknown causative variant and testing with known polymorphic markers. Linkage disequilibrium extends over relatively short genomic distances in human populations (typically, tens to hundreds of kilobases) and is dependent on ethnic background, ancestral history, admixture, and local recombination frequencies. Thus, although a significant result in a genome-wide linkage scan may implicate a region spanning many megabases of DNA and subsequently require substantial fine-mapping studies, a significant result from an association study may implicate a region of only a few hundred kilobases or less. The associated region may contain either a single gene or a few genes or be located in an apparent “gene desert.”

A major exception to this pattern of few candidates in a disease-associated genomic region is chromosome 6p21 (the HLA region), where significant linkage disequilibrium spreads over several megabases encoding hundreds of genes, many of which are reasonable candidates for involvement in type 1 diabetes. Specific genes in this region were originally investigated as candidate genes for type 1 diabetes because of the roles of their prod-

ucts in the presentation of antigens to the cellular immune system.¹⁶ Subsequent candidate-gene studies have identified and confirmed other risk loci for type 1 diabetes, including the gene for insulin (*INS*), a major autoantigen in type 1 diabetes, and *CTLA4*, which plays a role in T-cell development and antigen recognition¹⁷⁻²⁰ (Fig. 2). Since the status of these genes as risk loci is well established and they have been reviewed elsewhere, they will not be discussed in detail here.

An examination of the loci in Figure 2 might raise the question as to whether such loci, many of which are predicted to have only modest individual effects on risk, could have a clinically relevant effect on phenotype or disease progression. A relatively recent addition to the list of replicated candidate-gene associations to type 1 diabetes, *PTPN22*, is an excellent example of the insights that can be gained through the identification of such loci, the phenotypic effects that might be associated with such a gene, and its potential use as a target for intervention. *PTPN22* encodes the lymphoid protein tyrosine phosphatase (LYP).²¹ In T cells, LYP acts in a complex with C-terminal Src kinase (CSK) to negatively regulate signaling from the T-cell receptor. Specifically, LYP dephosphorylates positive regulatory tyrosines on LCK, VAV, ZAP-70, and CD3 zeta chains, thereby caus-

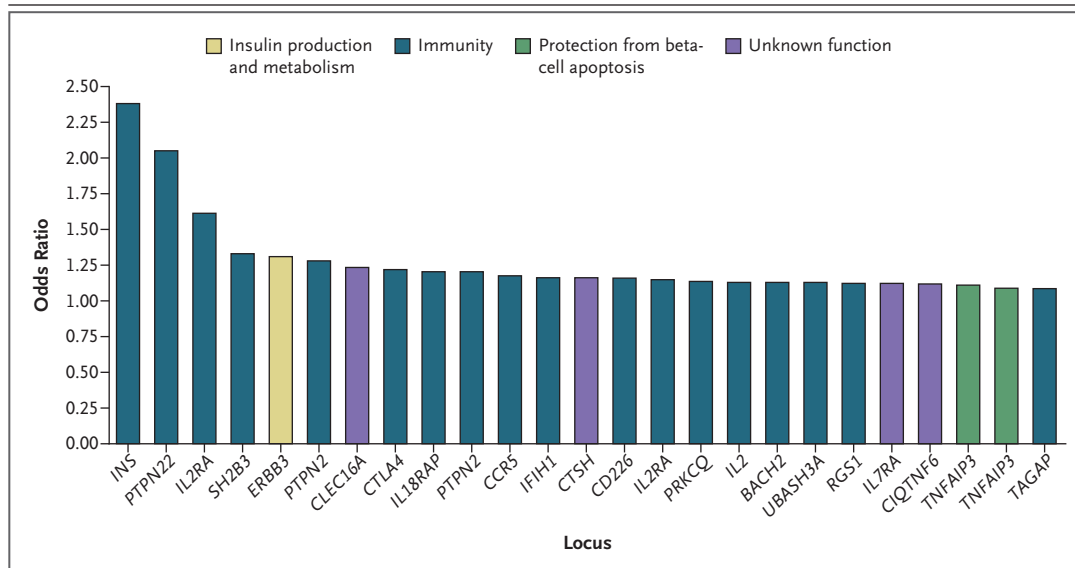


Figure 2. Putative Functions of Non-HLA-Associated Loci in Type 1 Diabetes.

The y axis indicates the best estimate of the odds ratio for risk alleles at each of the indicated loci on the basis of currently published data. Although not shown, the HLA region has a predicted odds ratio of approximately 6.8. On the x axis are indicated possible candidate genes within genomic regions in which convincing associations with type 1 diabetes have been reported. On the basis of the known functions of these candidate genes, the corresponding bars in the graph depicting odds ratios have been color-coded to suggest possible roles of these loci in susceptibility to type 1 diabetes. At *IL2RA* and *TNFAIP3*, there is evidence of two independent effects on risk with different odds ratios, so these loci both appear twice in the figure. An excellent resource for current information on all aspects of genes implicated in type 1 diabetes is T1DBase (www.t1dbase.org).

ing down-regulation of signals emanating from the T-cell receptor.²² The minor allele of a single-nucleotide polymorphism (SNP) in the coding region of *PTPN22*, rs2476601 (1858C→T), results in an arginine-to-tryptophan substitution at residue 620 in LYP (R620W), disrupting its ability to interact with CSK.

In the case of *PTPN22*, it might be anticipated that autoimmunity would arise when a genetic variant resulted in reduced LYP activity and consequent T-cell hyperactivity. This hypothesis is consistent with the expansion of T-cell populations in mice in which the orthologue of LYP is knocked out.²³ However, the *PTPN22* 1858T allele is associated with reduced T-cell activation. T cells from heterozygous carriers of this allele have reduced phosphorylation of LYP targets and decreased T-cell signaling as assayed by antigen-stimulated calcium flux or cytokine secretion.^{24,25} There is also a suggestion of a dose effect of *PTPN22* 1858T in some studies.²⁶⁻²⁸ These results are consistent with studies using mice engineered with different genetic defects in T-cell signaling.

Severe, inactivating mutations tend to result in immunodeficiency, whereas more subtle missense mutations result in dysregulation and, in some cases, autoimmunity.²⁹ Thus, T-cell signaling may be similar to a quantitative trait with thresholds for different phenotypes that might be amenable to pharmacologic manipulation. The apparent “gain of function” associated with the *PTPN22* R620W variant and the putative effect of gene dose raise the possibility that selective inhibitors could target *PTPN22* as a possible therapeutic approach. Such an approach is further encouraged by numerous reports that the same allelic variant (R620W) modifies risk in several other common autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, and Graves’ disease.^{26,30,31}

GENOMEWIDE ASSOCIATION STUDIES

Genomewide association studies take advantage of newly developed, high-throughput SNP genotyping platforms and the development of dense maps of SNPs from the human genome. The re-

sults of three association scans of type 1 diabetes have been reported, including an initial study that genotyped only nonsynonymous coding SNPs and two later studies that used much denser panels of SNPs ($\geq 300,000$ per subject) distributed across the genome.³²⁻³⁵ The results of these studies replicate findings for confirmed loci cited earlier in this review but, more important, provide evidence for a number of novel loci. A subsequent meta-analysis of genomewide association studies³⁶ and follow-up studies³⁷ has further added to the list of new loci.

Among the genes implicated in the scan of nonsynonymous coding SNPs and replicated in a separate population were the previously identified 1858C→T SNP in *PTPN22* and a SNP in *IFIH1*.^{32,38,39} *IFIH1* is a gene that encodes an interferon-induced helicase, also known as Mda-5, which plays a role in innate immunity through the recognition of the RNA genomes of picornaviruses.⁴⁰ Numerous attempts have been made to link various infectious agents to the risk of type 1 diabetes, making the identification of a gene specifically involved in viral defenses as a risk factor for type 1 diabetes particularly intriguing. Prominent among the viruses that have been proposed as potential environmental triggers for type 1 diabetes is coxsackievirus B4, an enterovirus belonging to the picornavirus family.⁴¹ The coding SNP in *IFIH1* at which association with type 1 diabetes is detected predicts an alanine-to-threonine substitution. Whether it is this specific substitution in the helicase protein that confers a risk for type 1 diabetes has yet to be determined.

The high-density genomewide association studies in type 1 diabetes provide confirmatory evidence for previously identified loci such as *INS*, *PTPN22*, *CTLA4*, and *IL2RA*, as well as significant findings for a number of new regions. Although considerable fine mapping and characterization of these new regions remain to be performed, likely candidate genes within the regions suggest a prominent role for effects on immunity (Fig. 2). Notable among the genes contained within these regions are *PTPN2*, a second protein tyrosine phosphatase. *PTPN2* is expressed ubiquitously but at highest levels in hematopoietic cells, where it acts, in part, to regulate signaling by dephosphorylating multiple JAK and STAT molecules. One region that is implicated in genomewide association studies of type 1 diabetes contains a gene of unknown function, *CLEC16A*, that has been annotated as a possible C-type lectin.^{33,34,38} A SNP in this gene

had a significant association with multiple sclerosis in a separate genomewide study,⁴² which also showed evidence of association at two other loci — *IL7R* and *IL2RA* — that are implicated in type 1 diabetes. These data provide suggestive evidence, beyond that provided by the examples of HLA and *PTPN22*, of common genetic risk factors and common mechanisms that may lead to autoimmunity.

DISEASE PREDICTION

Current approaches for the prediction of type 1 diabetes take advantage of the major genetic risk factors, genotyping for HLA-DR and HLA-DQ loci (which is then combined with family history), and screening for autoantibodies directed against islet-cell antigens.^{43,44} The individual distribution of specific risk alleles correlates with gradations in disease penetrance, enabling a tiered staging strategy for the prediction of type 1 diabetes. For example, children who carry both of the highest-risk HLA haplotypes (DR3-DQ2 and DR4-DQ8) have a risk of approximately 1 in 20 for a diagnosis of type 1 diabetes by the age of 15 years.⁴⁵ If the child has a sibling who has diabetes and the same haplotypes, the risk is even higher (approximately 55%).⁴⁶ Since this haplotype combination occurs in only 2.3% of the white population, it is possible to envision universal screening strategies that pinpoint this highest-risk group. Inclusion of additional moderate HLA risk haplotypes and screening for autoantibodies would add cost and complexity to a population-screening approach but have the potential to identify the majority of all children with diabetes before the onset of the disease. If this were possible, then tests of potential preventive strategies could be performed, as outlined later in this article. The large number of new risk loci for type 1 diabetes that were recently identified from genomewide association studies could be added to these prediction schemes. These genetic factors are relatively easy, inexpensive, and noninvasive to measure and can be detected well before other features, such as autoantibodies, would typically develop.

As true risk variants for type 1 diabetes are fine mapped, identified, and characterized, their functional use for prediction and prevention should become clearer. Even based on the current collection of implicated risk loci, it is obvious that multiple distinct biochemical pathways are involved. Not all pathways are likely to influence the risk

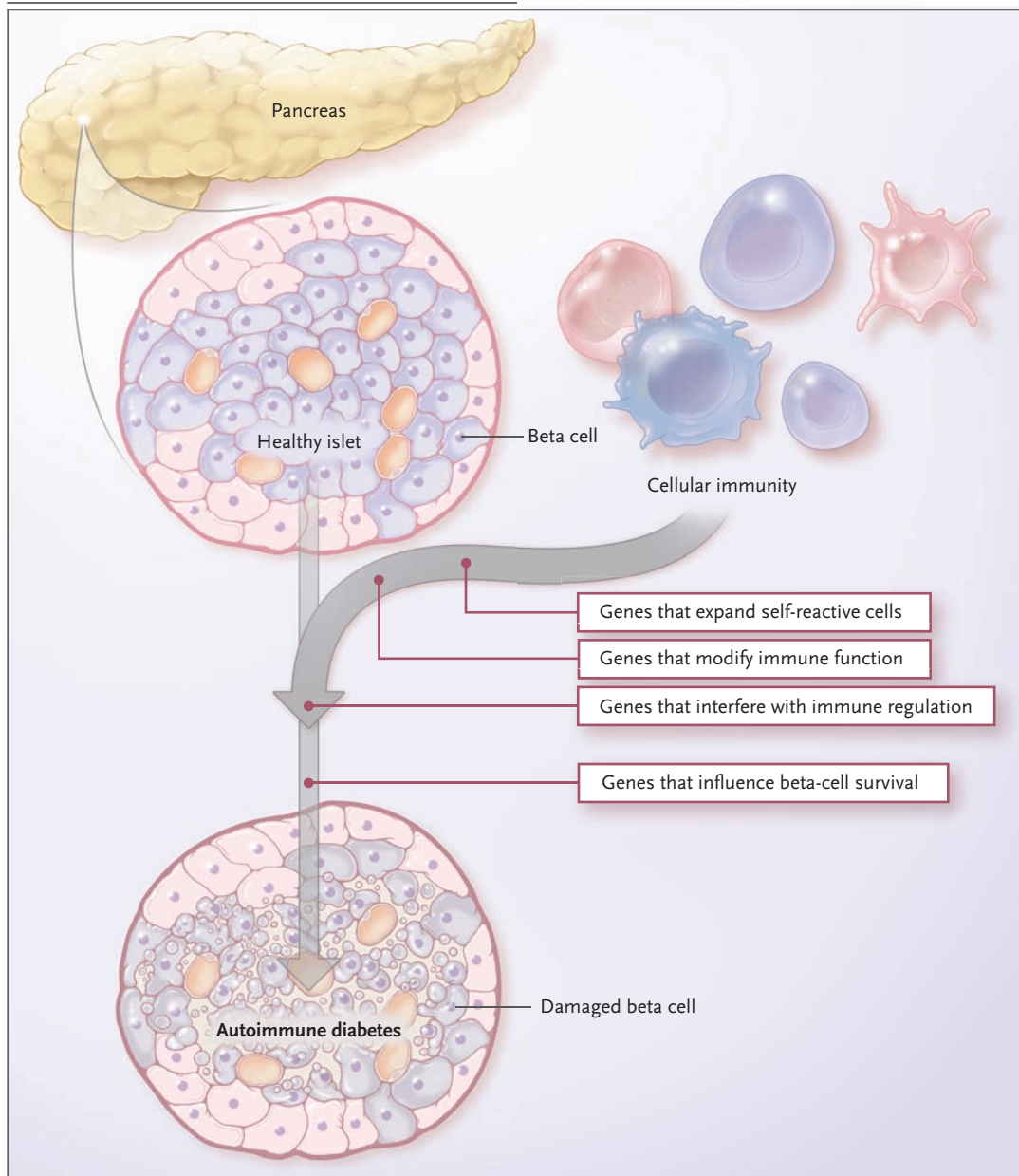


Figure 3. Differential Roles of Risk Loci in the Pathogenesis of Type 1 Diabetes.

Current data suggest that many risk loci for type 1 diabetes may exert their effects through the immune system. Within the immune response, these genes can act at multiple levels, affecting the establishment of the immune repertoire, the function of cell types in the immune system, or the regulation of cellular responses that can lead to autoimmunity.

of type 1 diabetes in the same way (Fig. 3). Some may be associated with an earlier (or a later) age of onset, a slower or faster rate of loss of beta cells, or a different pattern of epitope spreading in the autoimmune destruction of islets. Although some variants make small individual contributions to risk, they may cluster in pathways so that func-

tional assays targeting these processes may have useful predictive value.

FUTURE GENETIC STUDIES

Despite the increasing number of potential target genes, considerable work remains to develop these

findings into a better understanding of the cause of type 1 diabetes and to translate these findings into clinical applications. A first step in following up on association results is detailed fine mapping of the region. This step is necessary to determine whether the primary association is confined to a gene of interest in the region and whether the association can be attributed to an allele of the original SNP, to a group of alleles that are commonly co-inherited on a single haplotype, or to alleles at multiple SNPs in the region that independently contribute to disease risk. Additional genotyping may also provide evidence that the association is stronger in a flanking gene or an intergenic region.

Once a credible risk variant has been identified, a second step is required to determine the proximal effect of the SNP — that is, the immediate effect of genetic variation at this position on gene expression or on the function of a specified protein. Possible effects might include moderation of transcription levels, differential splicing, direct effects of nonsynonymous substitutions on protein function, or indirect effects mediated through microRNAs.

The third step is to determine whether the presence of the risk variant is associated with a discernible phenotype in patients with type 1 diabetes. Identifying such endophenotypes may require a substantial number of subjects genotyped at all known risk loci in order to dissect the effects of individual loci as well as carefully planned clinical research (perhaps based on genotype). An advantage in doing this type of study with type 1 diabetes is that many of the implicated loci appear to function primarily in cells of the immune system, which allows for access to the involved cell populations in subjects with known genotypes.

It is also important to recognize that although linkage studies are perhaps not currently as fashionable as genomewide association approaches, the regions that are identified through a family-based linkage approach still merit follow-up. In addition, family studies are useful in establishing effects of any variant identified as a risk factor for type 1 diabetes. Mendelian transmission of the causal variant cosegregating with an endophenotype that clusters family members who are at risk from those who are protected against the disease would have important biologic, clinical, and therapeutic implications.

DIABETES AND PERSONALIZED
MEDICINE

In type 1 diabetes, there is an extended preclinical period during which escalating autoimmune destruction depletes beta cells and thereby reduces insulin secretion and the ability to maintain glucose homeostasis. This period provides a window for interventions that could prevent overt diabetes by slowing or halting the progression of beta-cell loss. Early attempts at prevention using broadly immunosuppressive treatments have progressed to targeted approaches that seek to induce immune tolerance.⁴⁷⁻⁵⁰ The design of such trials requires a very careful risk–benefit analysis that puts a premium on prediction of disease risk and potential outcome. Ideally, therapies with a higher risk of adverse effects would be matched to patients with a higher predicted risk of type 1 diabetes. As therapies become more targeted, the likelihood of differential responsiveness to therapy among patients will increase. Biomarkers that could more accurately predict response to specific types of therapies would increase the efficiency of trials. There is also suggestive evidence that for at least some therapies, earlier intervention, at a stage at which an increased beta-cell mass remains, may improve outcomes.⁵⁰

Similarly, there may be biochemical pathways that are affected by particular risk variants that play a role in response to certain preventive therapies. As one example, a short course of treatment with humanized non–Fc-receptor–binding monoclonal antibodies to the T-cell receptor component CD3 has been shown to have long-term effects by slowing the loss of insulin secretion in patients with newly diagnosed diabetes.⁴⁹ This effect does not appear to result from T-cell depletion, since treated patients attain normal levels of circulating lymphocytes within 2 weeks after cessation of treatment, but may result from tolerization through the induction of regulatory T cells.⁵¹ Since this therapy targets T-cell activation through the T-cell receptor, the recruitment of intracellular signaling proteins, such as LCK, FYN, and SYK, is required. These signaling pathways are potentially affected by the products of several of the currently identified risk loci, including LYP, which normally acts to dephosphorylate LCK and down-regulates signaling from the T-cell receptor; SH2B3, an adapter protein that is a phosphorylation target of

LCK, which binds to the CD3 zeta chain⁵²; and UBASH3A (also called TULA and Sts2), which together with the related UBASH3B protein suppresses T-cell signaling, in part, through the dephosphorylation of ZAP70, FYN, and SYK.⁵³ Risk loci such as these, whose products act within T-cell signaling pathways, could be candidate biomarkers for predicting responsiveness to therapies with agents such as anti-CD3 monoclonal antibody that are directed at T-cell activation.

CONCLUSIONS

What general conclusions can be drawn from our current state of understanding of the genetics of type 1 diabetes? Genes within the HLA region, predominantly those that encode antigen-presenting molecules, confer the greatest part of the genetic risk of type 1 diabetes. The existence of other loci with individual effects on risk of a similar magnitude is very unlikely. The remaining non-HLA loci will make only modest individual contributions to risk; most will probably have odds ratios of 1.3 or less. A majority of these other loci appear to exert their effects in the immune system, particularly on T cells, affecting antigen-driven T-cell activation and cytokine signaling, proliferation, or maturation. Careful dissection of the biochemical pathways in which the products of these loci are known to function should allow an under-

standing of how they act to confer a risk of type 1 diabetes. Refinement of our genetic mapping of these loci may improve our ability to predict the risk of type 1 diabetes and facilitate the testing of more aggressive preventive therapies. Dissection of the phenotypic effects of variation at these loci should provide new insights into the preclinical period of type 1 diabetes and potentially suggest new, rationally designed therapies.

It has long been anticipated that loci contributing in some generalized manner to the development of autoimmunity would be identified. The apparent identification of multiple common risk loci in recent independent genomewide association studies in different autoimmune disorders appears to fulfill this prediction.⁵⁴ Although these loci are identified because of their association with specific autoimmune disorders, such as type 1 diabetes, it will be desirable to study their effect on human health prospectively by following large cohorts of genotyped subjects to understand the broader range of immune variation, including responses to infection and vaccines.

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