Perspectives in Diabetes

Comparative Genetics of Type 1 Diabetes and Autoimmune Disease

Common Loci, Common Pathways?

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Genome-scale analysis in type 1 diabetes has resulted in a number of non–major histocompatibility complex loci of varying levels of statistical significance. In no case has a specific gene been proven to be the source of genetic linkage at any candidate locus. Comparative analysis of the position of loci for type 1 diabetes with candidate loci from other autoimmune/inflammatory diseases shows considerable overlap. This supports a hypothesis that the underlying genetic susceptibility to type 1 diabetes may be shared with other clinically distinct autoimmune diseases such as systemic lupus erythemastosus, multiple sclerosis, and Crohn's Disease. *Diabetes* 48:1353–1358, 1999

Type 1 diabetes is an autoimmune disease thought to arise through a complex interaction of genetic and environmental factors. Like many autoimmune diseases, type 1 diabetes is characterized by immune disregulation that precedes overt clinical onset of the disease. These abnormalities include antibody disturbances as well as disregulation in cellular immune responses (1–4).

Type 1 diabetes in humans and corresponding animal models have long been associated with specific alleles of the major histocompatibility complex (MHC) (2). This genetic region found at human chromosome 6p21.3 covers ~8.5 cM (5) and has been linked or associated with both disease susceptibility and resistance in many, if not most, autoimmune diseases. The MHC codes for a cluster of at least 30 (5) related class I and class II HLA genes. The MHC also contains many genes that are not related to HLA surface antigens. Specific alleles of genes found within the MHC have also been associated with susceptibility and resistance to infectious diseases in humans and in animal models (6).

The relationship of the MHC with immune/inflammatory diseases is thought to be due to the essential requirement of HLA molecules in normal antigen recognition, processing, and presentation, ultimately leading to activation and progression of the immune system. This process is somehow perturbed in the disease state and has a combinatorial effect with other genetic modifiers and environmental triggers, leading to disease in some individuals. The genes, protein products, and biological pathways of the MHC associated with type 1 diabetes are central to normal immune function, are found in normal and affected individuals, and are not uniquely disease specific. Recently, a number of non-MHC loci have been linked to type 1 diabetes using a genome-wide scanning strategy. These loci have been given disease-specific provisional designations: *IDDM1* through *-15* (7). As described here, the genetic location of many of those provisional loci co-localize or overlap with loci from other autoimmune/inflammatory diseases, suggesting shared pathways in the etiology of clinically distinct autoimmune diseases.

APPROACHES IN THE STUDY OF TYPE 1 DIABETES

Molecular approaches in the study of type 1 diabetes can be categorized in two general ways: a traditional candidate gene approach and the more recent reverse-genetic approach. The candidate gene strategy is highly focused and logical. This is the classical hypothesis-driven approach and is usually focused on a small number of genes, proteins, and biological pathways of high information content and current critical importance. In the case of type 1 diabetes, this has often involved either immune specific regulatory proteins (4,8) or autoantigens specifically expressed on or related to the pancreas, such as insulin itself, islet cell autoantibody-69 (ICA69), GAD65, and IA-2 (2,9). This straightforward approach is well suited for the analysis of later-stage active disease processes. However, this strategy is based somewhat on prior knowledge and suffers from a significant lack of information (>95%) concerning the human genome sequence and complex regulatory pathways. It is inherently limited and subjective because of the critical need to focus on specific proteins or genes.

The more recent reverse-genetic approach in the study of type 1 diabetes typically involves genome-wide scans using affected sib pairs or multiplex families studied with a large set of polymorphic markers covering the entire human genome. This approach is objective, broadly focused, and statistically rigorous. Genome scanning methods have been used in the analysis of common complex multigenic diseases, including many autoimmune and infectious diseases, psychiatric dis-

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LOD, logarithm of odds; MHC, major histocompatibility complex; SLE, systemic lupus erythemastosus.

orders such as schizophrenia and bipolar illness, and hypertension, as well as animal models of complex human diseases. Limitations of genome-wide scans when applied to complex autoimmune diseases include: heterogeneity in disease phenotypes, population and ethnic differences, imperfect statistical and analytical models, and the use of different polymorphic marker panels and genetic maps. This has resulted, in some cases, in a lack of replication and confirmation at different loci among different groups studying the same disease. The typical result of a successful first-stage genome-wide scan ends with linkage to one or more genetic intervals of ~10–30 cM genetic distance. This is a huge distance at a molecular level, quite often with few biological clues as to the exact molecular basis of the linkage. This makes the next task of identifying and cloning the linked gene in that interval quite difficult.

Using the genome-wide scan approach, many groups have identified a number of candidate susceptibility loci for type 1 diabetes having varying levels of statistical significance: from suggestive to highly significant (10). These loci generally include the MHC, as well as numerous non-MHC candidate loci. Many of the candidate loci have suggestive significance values less than the traditional values (logarithm of odds [LOD] ≥ 3.0) observed in monogenic diseases displaying Mendelian inheritance. Many of these candidate loci have been given a disease-specific designation (i.e., *IDDM1* through *-15*) as a temporary operational designation. While some of these loci have been confirmed, a number of loci have not been replicated (11).

Similar studies have been performed on other complex autoimmune/inflammatory diseases including multiple sclerosis (12–15), Crohn's disease (16,17), rheumatoid arthritis (18,19), psoriasis (20,21), systemic lupus erythematosis (22–25), and asthma (26), among others. Similar results have been found in these disease studies as well: multiple loci (5–10), most with suggestive levels of statistical significance (LOD 1–3), disease-specific designations (*IBD1*, *-2*, *-3*; *SLE1*, *-2*, *-3*, etc.), and a lack of replication of some loci in subsequent studies. In no case for the candidate loci identified using the genome-wide scan approach in the study of common autoimmune diseases, including type 1 diabetes, has a specific non-MHC gene been shown to be the source of the genetic linkage.

CO-LOCALIZATION OF AUTOIMMUNE DISEASE LOCI: A PATTERN IS EMERGING

Recently, it has been noted that the position of provisional loci found in type 1 diabetes co-localize or overlap with loci found in different autoimmune/inflammatory diseases (27–30). This is consistent with a hypothesis that, like the MHC, some of these provisional loci may involve common susceptibility genes or biochemical pathways that are central to normal immune function. These genes or pathways may contribute to immune disregulation shown to be present in different autoimmune diseases, possibly before the onset of overt clinical symptoms (2). Table 1 shows the names and chromosomal locations of the candidate loci identified for type 1 diabetes. This includes loci given provisional disease-specific designations (*IDDM1*, *-2*, *-3*, *-4*, etc.), as well as other loci linked to type 1 diabetes. Also shown are loci from other human autoimmune/inflammatory disease genome-wide scans that co-localize, overlap, or are within at least 10 cM of a type 1 diabetes locus. Ten centimorgans is the approximate limit of resolution of a typical first-stage genome-wide scan. For example, *IDDM2* found at 11p15.5 (31) is found at the exact same position as loci for systemic lupus erythematosus (SLE) (23), ankylosing spondylitis (32), asthma (26), and multiple sclerosis (14). All four disease loci have been defined by the same polymorphic marker, D11S922, at 0.323 cM position on human chromosome 11 (5). A candidate gene at 11p15.5 is the insulin gene itself. Variable number of tandem repeat (VNTR) polymorphisms at the 5′ end of the insulin gene have been linked to type 1 diabetes (32,33). One interpretation of this genetic linkage to insulin as a candidate gene is that insulin acts as an autoantigen (34). Another interpretation is that insulin or the tightly linked IGF-2 acts as a growth factor expressed in the thymus, promoting the immune response (35). Co-localization of multiple autoimmune diseases at this location suggests that whatever the exact gene is that is ultimately found at the locus *IDDM2*, it may play a broader role in autoimmune development.

As shown in Table 1, most (15 of 17, or 88%) of the provisional loci for type 1 diabetes identified to date have co-localized or overlapping loci found in other autoimmune or inflammatory diseases. In some cases, different autoimmune diseases are defined by the same genetic marker, including the loci *IDDM1*, *IDDM2*, *IDDM8*, *IDDM12*, *Xp11.4*, and *Xp11.1*. There has been no specific effort to study different autoimmune/inflammatory diseases using a standard panel of polymorphic markers to allow direct comparisons. This general pattern of locus co-localization is not found in human nonautoimmune disease (28). Three loci for type 1 diabetes (*IDDM5*, *-10*, *-15*) do not appear to have overlapping loci from other autoimmune studies. Data for *IDDM14* are not publicly available (7). This pattern of co-localization of loci from related immune diseases has been found in both human and animal studies and has been shown to be statistically significant (27,28). It has been proposed that co-localization of autoimmune loci may be due to common biological pathways shared among related autoimmune/inflammatory diseases in both human disease (28,36) and animal models (27,29,30,37).

THE IMPORTANCE OF SUBPHENOTYPING

In some cases, using genome-wide scans in animal models of autoimmune disease, the general disease phenotype has been broken down into individual loci having discrete subphenotypes. This has generally not been possible in human studies, and emphasizes the importance of animal models in autoimmune studies. This subphenotyping at specific loci can potentially provide clues to the functional significance of candidate genes at each locus (37). For example, in murine experimental allergic encephalomyelitis, Butterfield et al. (38) define independent quantitative trait loci with linkages to susceptibility, onset, severity, and duration of disease. In murine SLE, Morel et al. (39) identified independent loci for glomerulonephritis and anti-dsDNA antibody production. This subphenotyping in animal models allows greater functional characterization of contributing loci in complex autoimmune phenotypes and may provide useful biological information in the search for candidate genes at specific human type 1 diabetes loci.

Recently, Concannon et al. (7) identified a novel locus for type 1 diabetes (maximum LOD score = 3.31) at human chro-

TABLE 1
Names and chromosomal locations of candidate loci identified for type 1 diabetes

Loci	Chromosomal location	Marker	Reference	Overlapping autoimmune loci	Marker	Reference
IDDM1	6p21	**D6S426**	7	MS	D6S273	14
				MS	D6S273	13
				Asthma	D6S276	26
				CD	D6S276	17
				Ankylosing spondylitis	D6S276	32
				SLE	**D6S426**	23
				Coeliac disease	HLA-DQ	63
IDDM2	11p15.5	**D11S922**	31	SLE	**D11S922**	23
				Ankylosing spondylitis	**D11S922**	32
				Asthma	D11S96	26
				Multiple sclerosis	**D11S922**	14
IDDM3	15q26	D15S107	57	SLE	D15S127	23
				Ankylosing spondylitis	D15S127	32
				Coeliac disease	D15S642	64
				Coeliac disease	D15S207	63
IDDM4	11q13	FGF3	31	Asthma	FCER1B	26
		FGF3	57	EAE	(D7Mit37)	65
		FGF3	58			
		D11S1296	11			
IDDM5	6q25	D6S290	11	None		
IDDM6	18q21	D18S39	59	Rheumatoid arthritis	D18S57, D18S474	18
		D18S64	31			
IDDM7	2q31–33	D2S152	60	SLE	D2S1391	22
IDDM8	6q27	D6S264	31	SLE	D6S1027	22
		D6S281	11	Ankylosing spondylitis	**D6S281**	32
IDDM9	3q21	D3S1303	31	Rheumatoid arthritis	D3S1267	18
		(kdp1)	61	Multiple sclerosis	D3S1309	12
IDDM10	10p11–q11	D10S193	62	None		
IDDM11	14q24.3	D14S67	57	SLE	D14S74	23
				Graves' disease	D14S81	66
				Antibody response	(D12Mit27)	67
IDDM12	2q33	D2S152	60	SLE	D2S1391	22
		CTLA4	7	Thyroiditis	**CTLA4**	68
IDDM13	2q36	D2S301	7	Rheumatoid arthritis	D2S377, D2S2354	18
				Ankylosing spondylitis	D2S126	32
IDDM14	NA	NA		NA		
IDDM15	6q21	D6S283	7	none		
1q42	1q42	AGT	7	SLE	D1S103	40
		D1S1644		SLE	D1S3462	22
				SLE	D1S235	23
				Ankylosing spondylitis	D1S229	32
Xp11.4	Xp11.4	**DXS1068**	69	Rheumatoid arthritis	**DXS1068**	18
				Multiple sclerosis	**DXS1068**	12
Xp11.1	Xp11.1	**DXS991**	31	Multiple sclerosis	**DXS991**	13

All chromosomal positions are from Location Database (5). Identical markers are in bold. NA, not available.

mosome 1q at marker D1S1617. This locus co-localizes with loci for SLE (40) and ankylosing spondylitis (32). In human SLE, this locus is linked to serum levels of anti-chromatin antibody, and in mouse SLE to both anti-chromatin and anti-DNA antibody production (24,40–42). The co-localization of these three autoimmune diseases at this position suggests that this locus may be involved in a pathway that affects the quantitative regulation of antibody levels, and that this may contribute to the ultimate disease phenotype in all three diseases. Interestingly, the immune disorder Chediak-Higashi syndrome maps to 1q42 as well (43). The mouse equivalent of Chediak-Higashi is the beige locus. Mutations at the beige locus have been associated with severe immune abnormalities (44). Comparative analysis across related diseases and across species, especially in the context of subphenotyping, may help in identifying the biological basis of each locus.

AN ANALOGY TO TUMOR BIOLOGY PATHWAYS

The process of tumorigenesis is thought to arise from a complex combination of environmental and genetic events. Generally, this involves familial or somatic mutations in sets of genes essential to critical pathways related in part to cellular growth control. Mutations in ubiquitously expressed genes combine with alterations in tissue-specific pathways, resulting in the overall phenotype in a specific tumor type. This combinatorial process quite often involves

shared general factors in basic cell cycle control (CDK4, p16, Rb1, WAF1), signal transduction (MET, ras, B-catenin, src), DNA repair (p53, ATM, MSH2, MLH1), and apoptosis (BAX, BCL2) (45). Different combinations of these general factors in concert with more tissue-and tumor-specific factors, such as BRCA1 and -2, PTC, WT1, NF1, and PML, lead to tumorigenesis in a given cell type (45). Each tumor is unique. It is the interaction and sequential expression of these factors in a given tumor that help define the tumor specific characteristics of aggressiveness, drug resistance, and metastatic potential.

Complex autoimmune diseases can be thought of as similar to cancer in that they are thought to involve environmental triggers in the context of complex sets of interacting susceptibility genes. The end-stage phenotype of a specific autoimmune disease may be clinically distinct and/or organ specific, while the etiology of many autoimmune diseases may involve shared processes of immune regulation (46). It is likely that basic pathways affecting proinflammatory/anti-inflammatory cytokine ratios, apoptosis, complex antibody regulation, effector T-cell populations, and hormonal control of the immune system are involved in these related diseases (46). Overlapping of provisional loci between type 1 diabetes and other autoimmune/inflammatory diseases suggests that, in some cases, common pathways may be involved, in part, in the etiology of clinically distinct autoimmune diseases. Environmental factors, a subset of genetic loci, or epigenetic mechanisms may contribute to disease or target-tissue specification.

SUMMARY AND IMPLICATIONS FOR THE STUDY OF TYPE 1 DIABETES

Genome-scale analysis of the genetics of type 1 diabetes has identified more than 15 provisional loci of varying levels of statistical significance. The next task is to assign biological significance to each genetic interval. This quite often involves painstaking analysis of polymorphisms in large populations, quite often with conflicting results. The association of the MHC with type 1 diabetes has been known for more than 2 decades (47), and although much has been learned about the biology of the MHC, the exact biological basis for the MHC linkage to type 1 diabetes is still unknown. This suggests that establishing the exact biological nature of genetic linkage to provisional loci for type 1 diabetes will be quite difficult.

The specific basis for co-localization of loci between multiple autoimmune diseases at each locus could be due to *1*) the same allele of the same gene, *2*) different alleles of the same gene, or *3*) different members of a tightly linked complex of functionally related genes. Of course, for any given locus, co-localization of loci from different autoimmune diseases could be coincidental. Familial association of different autoimmune diseases in the same pedigree (48–50), co-incidence of different autoimmune diseases, including type 1 diabetes, in the same individual (51–55), and shared clinical parameters of different autoimmune diseases (46,56) suggest a common biological basis in autoimmune/inflammatory disease. Co-localization and overlapping of candidate loci in autoimmune diseases, including type 1 diabetes, suggests that in some cases, common biological pathways may be involved in the etiology of type 1 diabetes and other clinically distinct autoimmune diseases.

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