Abstract

Except for rare subtypes of diabetes, both type 1 and type 2 diabetes are multifactorial diseases in which genetic factors consisting of multiple susceptibility genes and environmental factors contribute to the disease development. Due to complex interaction among multiple susceptibility genes and between genetic and environmental factors, genetic analysis of multifactorial diseases is difficult in humans. Inbred animal models, in which the genetic background is homogeneous and environmental factors can be controlled, are therefore valuable in genetic dissection of multifactorial diseases. We are fortunate to have excellent animal models for both type 1 and type 2 diabetes—the nonobese diabetic (NOD) mouse and the Nagoya-Shibata-Yasuda (NSY) mouse, respectively. Congenic mapping of susceptibility genes for type 1 diabetes in the NOD mouse has revealed that susceptibility initially mapped as a single locus often consists of multiple components on the same chromosome, indicating the importance of congenic mapping in defining genes responsible for polygenic diseases. The NSY mouse is an inbred animal model of type 2 diabetes established from Jcl:ICR, from which the NOD mouse was also derived. We have recently mapped three major loci contributing to type 2 diabetes in the NSY mouse. Interestingly, support intervals where type 2 diabetes susceptibility genes were mapped in the NSY mouse overlapped the regions where type 1 diabetes susceptibility genes have been mapped in the NOD mouse. Although additional evidence is needed, it may be possible that some of the genes predisposing to diabetes are derived from a common ancestor contained in the original closed colony, contributing to type 1 diabetes in the NOD mouse and type 2 diabetes in the NSY mouse. Such genes, if they exist, will provide valuable information on etiological pathways common to both forms of diabetes, for the establishment of effective methods for prediction, prevention, and intervention in both type 1 and type 2 diabetes.

Key Words: animal model; congenic strain; consomic strain; gene; Nagoya-Shibata-Yasuda (NSY) mouse; nonobese diabetic (NOD) mouse; type 1 diabetes; type 2 diabetes

Introduction

Type 1 and type 2 diabetes are two major categories of diabetes with different clinical characteristics and etiological bases. Autoimmune type 1 diabetes (type 1A) is caused by autoimmune destruction of insulin-producing beta cells of the pancreas, leading to an absolute loss of endogenous insulin, which makes patients insulin-dependent (i.e., they cannot survive without administration of exogenous insulin). In the case of type 1B diabetes, there is no evidence of autoimmune etiology. Because the etiology of type 1B diabetes is largely unknown, this review focuses on autoimmune type 1 (type 1A) diabetes.

Briefly, type 2 diabetes is caused by impaired insulin secretion and/or insulin action. Endogenous insulin secretion is impaired in a relative sense that is not enough to compensate patients’ insulin demand, thus leading to hyperglycemia. Although insulin secretion is impaired, it is not completely lost, and therefore patients are not insulin dependent, in clear contrast to patients with type 1 diabetes. Although patients with type 2 diabetes are not insulin dependent, they may require exogenous insulin to maintain better metabolic control to prevent chronic complications.

The nonobese diabetic (NOD) mouse is a well-known inbred (genetically homogeneous) animal model of autoimmune type 1 diabetes derived from a closed colony (genetically heterogeneous) of Jcl:ICR (Makino et al. 1980). The Nagoya-Shibata-Yasuda (NSY)1 mouse, in contrast, has been established as an inbred animal model of type 2 diabetes by selective breeding for glucose intolerance from Jcl:ICR mice, the same closed colony from which the NOD mouse was established (Shibata and Yasuda 1980). This review summarizes the characteristics and genetic basis of type 1 diabetes in the NOD mouse and type 2 diabetes in the NSY mouse as animal models for the corresponding human diseases. The possibility of a common genetic factor between type 1 and type 2 diabetes is also discussed.

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1Abbreviations used in this article: B6, C57BL/6; B10, C57BL/10; CTS, cataract Shionogi; HNF, hepatocyte nuclear factor; IIS, inbred ICR Shionogi; LETL, Long-Evans Tokushima lean; MHC, major histocompatibility complex; NOD, nonobese diabetic; NON, nonobese nondiabetic; NSY, Nagoya-Shibata-Yasuda; OLETF, Otsuka Long-Evans Tokushima fatty; type 1A, autoimmune type 1 diabetes.
Relatedness of Mouse Strains

NOD Mouse: Animal Model of Type 1 Diabetes with an Unexpected History of Discovery

The NOD mouse was established in 1980 as an animal model of autoimmune type 1 diabetes by Dr. Makino and coworkers (Makino et al. 1980). As mentioned above, NOD mice are derived from a closed colony, Jcl:ICR. Initially, a mouse with cataracts and small eyes was found in a closed colony of Jcl:ICR maintained in animal facilities at Aburahi Laboratories, Shionogi Pharmaceutical Company, and an inbred strain of mice with cataracts and small eyes, termed the CTS mouse, was established (Figure 1) (Ohtori et al. 1968). CTS initially denoted cataract and small eyes, but was later changed to cataract Shionogi, to include the name of the pharmaceutical company where the strain was established. Because cataract is a common complication of diabetes, two lines, one with slight hyperglycemia and the other with normoglycemia, were separated at the F6 generation with the aim of obtaining diabetic and control strains, respectively (Figure 1) (Ikegami and Makino 2001; Makino et al. 1980). Contrary to the initial expectation, a diabetic mouse was found in the normoglycemic line, but not in the hyperglycemic line, and an inbred NOD strain was established (Makino et al. 1980). Despite the selective breeding for hyperglycemia, none of the mice in the slightly hyperglycemic line developed overt diabetes, and selective breeding for hyperglycemia was therefore discontinued after discovery of a diabetic mouse in the other line (Ikegami and Makino 2001). Inbreeding of this line, however, was continued without selection for glycemia to obtain a control strain for the NOD mouse, and the nonobese nondiabetic (NON1) strain was established (Figure 1). As expected from this history, glucose tolerance of NON mice is not completely normal, but slightly impaired (Ikegami and Makino 2001). Due to the discontinuation of selective breeding, however, glucose intolerance in the NON mouse is not a fixed phenotype. Its variation from mouse to mouse makes it difficult to use this strain as an animal model of glucose intolerance (Ikegami and Makino 2001; Makino et al. 1992).

NSY Mouse: Animal Model of Type 2 Diabetes Derived from the Same Closed Colony as NOD Mouse

Investigators first identified a diabetic mouse in 1974, and the NOD mouse was subsequently established (Makino et al. 1980). Also in the mid- to late 1970s, Jcl:ICR mice that were maintained in the same closed colony at Shionogi Aburahi Laboratories from which the NOD mouse was derived were shipped to animal facilities at the Branch Hospital of Nagoya University Medical School. Professor Shibata initiated selective breeding for glucose intolerance, and an inbred NSY strain of mice with markedly impaired glucose tolerance was established (Figure 1) (Shibata and Yasuda 1980). The common (same closed colony) origin of the NSY and the NOD mice mouse is indeed noteworthy. 

In the NSY mouse, the following characteristics of diabetes closely mimic human type 2 diabetes: (1) the development of diabetes is age dependent; (2) both impaired insulin secretion and action contribute to the disease; (3) mild obesity with visceral fat accumulation is associated with the disease; (4) it is characterized by polygenic inheritance; and (5) environmental factors such as a high fat diet and sucrose administration accelerate the development of the disease (Hamada et al. 2001; Ueda et al. 1995, 2000). Lymphocytic infiltration of pancreatic islets (insulitis) was not observed (Ueda et al. 1995), suggesting that glucose intolerance in NSY mice is not due to incomplete destruction of pancreatic beta cells by an autoimmune pathological mechanism.

![Figure 1](image-url) Genealogy of the nonobese diabetic (NOD) mouse and related strains. CTS, cataract Shionogi; NON, nonobese nondiabetic; NSY, Nagoya-Shibata-Yasuda.
Genetics of Type 1 Diabetes in the NOD Mouse

Multiple Susceptibility Genes

Inheritance of type 1 diabetes in the NOD mouse is polygenic with at least 20 susceptibility loci, termed Idd for insulin-dependent diabetes. The loci have been mapped in the mouse genome by breeding studies in crosses of NOD mice with several control strains (Ghosh et al. 1993; Grattan et al. 2002; Hattori et al. 1986; Ikegami and Makino 2001; Ikegami et al. 1988; McAleer et al. 1995; Prochazka et al. 1987; Rogner et al. 2001; Todd et al. 1991; Wicker et al. 1987, 1995; Yang and Santamaria 2003). Some, but not all, of these loci have been confirmed by means of congenic strains in which the Idd region from control strains was introgressed onto the genetic background of the NOD mouse. Protection from diabetes in such congenic strains indicates that the control strain-derived Idd region is protective against diabetes and the NOD-derived Idd region is necessary for type 1 diabetes susceptibility. Among Idd loci mapped by the initial segregation and linkage analyses, at least seven loci have been confirmed to be involved in disease susceptibility: Idd1, -3, -4, -5, -6, -9, and -13 (Grattan et al. 2002; Hill et al. 2000; Ikegami and Makino 1993; Ikegami et al. 1996, 2003; Lyons et al. 2000; Serreze et al. 1994, 1998; Todd and Wicker 2001; Wicker et al. 1995). For other loci, additional studies such as either breeding studies with other strains or congenic mapping are necessary to confirm whether the loci truly contribute to disease susceptibility.

Possibility That Each Locus Consists of Multiple Components

Linkage of a locus with type 1 diabetes in segregation and linkage analyses does not necessarily mean that the effect of the locus is due to only one gene. Rather, it is becoming evident that susceptibility conferred by a locus mapped to a chromosomal interval is often the cumulative effect of multiple linked genes. This evidence is clear in a series of chromosomal interval studies with at least four distinct loci—lloca-00R 117, 10, 17, and 18—on the same chromosome. In fact, no susceptibility gene existed in the central region where peak linkage was observed in initial mapping studies. Black boxes indicate C57BL/6 (B6)-derived resistance chromosomes. A multiple susceptibility loci on chromosome 3. (A) Idd3 was initially mapped to a central region of chromosome 3 as a single locus. White box: support intervals of at least 1:100 (the chromosome region within which there is at least 1:100 likelihood of finding the gene by maximum likelihood estimate). Bars: support intervals of at least 1:1000. (B) Subsequent studies with congenic strains revealed that susceptibility is due to a combined effect of at least four distinct loci—Idd3, 10, 17, and 18—on the same chromosome. In fact, no susceptibility gene existed in the central region where peak linkage was observed in initial mapping studies. Black boxes indicate C57BL/6 (B6)-derived resistance chromosomes. A combined effect of at least four loci on the same chromosome. In fact, no susceptibility gene existed in the central region where peak linkage was observed in initial mapping studies. Black boxes indicate C57BL/6 (B6)-derived resistance chromosomes.
ease prediction, prevention, and intervention. The larger the number of susceptibility genes, the greater the possibility for disease prevention and intervention. Even if the effect of each locus on overall susceptibility is small, information on the locus provides important information for prevention and intervention, as is clearly shown by the easy protection of NOD mice from type 1 diabetes by a small modification of environmental factors as well as introgression of a chromosomal segment from control strains (Todd and Wicker 2001). Thus, studies on Idd genes are of clinical importance for disease prevention and intervention in patients with type 1 diabetes.

Evidence for Susceptibility Conferred by the Idd Gene

NOD strains congenic for Idd loci from control strains provide solid evidence that alleles of the loci from control strains provide protection against type 1 diabetes, which in turn indicates that alleles from NOD mice are necessary for disease susceptibility. Studies using a congenic strain in the opposite direction (i.e., introgression of a susceptibility allele of the NOD mouse onto the genetic background of a control strain) have shown that such congenic strains do not develop type 1 diabetes, because a combination of multiple susceptibility genes is necessary for disease development. This necessity applies even to the strongest susceptibility gene, Idd1 in the major histocompatibility complex (MHC1) region on chromosome 17. Congenic strains, in which NOD alleles of Idd1, H2\textsuperscript{K}\textsuperscript{7} were introgressed onto the genetic background of control B6 or B10 strains, did not develop type 1 diabetes or insulitis (Ikegami and Makino S 1993; Ikegami et al. 1996, 2003; Wicker et al. 1995; Yui et al. 1996). Thus, it is not possible with this straightforward congenic approach to demonstrate directly that NOD alleles of Idd genes confer susceptibility to type 1 diabetes.

However, recombinant chromosomes, in which NOD alleles in candidate genes for Idd loci are flanked with non-NOD alleles of adjacent markers, make it possible to demonstrate the contribution of NOD alleles of Idd genes to disease susceptibility directly. Such chromosomes can be introgressed onto NOD background genes by using flanking variants as selection markers, and the resulting NOD strains congenic for recombinant chromosomes can be used to test whether a candidate variant can cause type 1 diabetes in the presence of NOD background genes. Such a recombinant chromosome, however, is difficult to obtain by usual breeding due to strong linkage disequilibrium in a small interval. To overcome this difficulty, we searched for the same candidate variants as those in the NOD mouse in NOD-related strains derived from the same common ancestor, Jcl:ICR. The same candidate variant for Idd1, H2\textsuperscript{K}\textsuperscript{7}, was found in a sister strain of the NOD mouse, the CTS mouse, with different flanking markers (Ikegami et al. 1996, 2003; Wicker et al. 1995; Yui et al. 1996). Thus, it is not possible with this straightforward congenic approach to demonstrate directly that NOD alleles of Idd genes confer susceptibility to type 1 diabetes.

Table 1 Susceptibility loci for type 1 diabetes consisting of multiple components

<table>
<thead>
<tr>
<th>Initial locus</th>
<th>Chromosome</th>
<th>Component</th>
<th>Interval</th>
<th>Candidate genes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idd1</td>
<td>17</td>
<td>Idd1</td>
<td>&lt;0.1 cM</td>
<td>H2-A and H2-E</td>
<td>Hattori et al. 1986</td>
</tr>
<tr>
<td>Idd16</td>
<td>10.5 cM</td>
<td></td>
<td></td>
<td>H2-K, Tnf</td>
<td>Ikegami et al. 1995</td>
</tr>
<tr>
<td>Idd3</td>
<td>3</td>
<td>Idd3</td>
<td>0.15 cM</td>
<td>I2, I21</td>
<td>Lyons et al. 2000</td>
</tr>
<tr>
<td>Idd10</td>
<td>1.6 cM</td>
<td></td>
<td></td>
<td>Cd101</td>
<td>Penha-Goncalves 2003</td>
</tr>
<tr>
<td>Idd17</td>
<td>1.1 cM</td>
<td></td>
<td></td>
<td></td>
<td>Podolin et al. 1997</td>
</tr>
<tr>
<td>Idd18</td>
<td>2.4 cM</td>
<td></td>
<td></td>
<td></td>
<td>Podolin et al. 1998</td>
</tr>
<tr>
<td>Idd4</td>
<td>11</td>
<td>Idd4.1</td>
<td>proximal part of Idd4 interval (5.2 cM)</td>
<td>PAF-AH1b1</td>
<td>Gratten et al. 2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Idd4.2</td>
<td>distal part of Idd4 interval (5.2 cM)</td>
<td>CC chemokine</td>
<td></td>
</tr>
<tr>
<td>Idd5</td>
<td>1</td>
<td>Idd5.1</td>
<td>1.5 cM</td>
<td>Cita4</td>
<td>Hill et al. 2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Idd5.2</td>
<td>5.1 cM</td>
<td>Nramp1</td>
<td></td>
</tr>
<tr>
<td>Idd6</td>
<td>6</td>
<td>Idd6</td>
<td>4.5 cM</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Idd19</td>
<td>7 cM</td>
<td>Cd27, Ltb, Tnfr1</td>
<td>Rogner et al. 2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Idd20</td>
<td>4 cM</td>
<td></td>
<td>Lyons et al. 2000</td>
</tr>
<tr>
<td>Idd9</td>
<td>4</td>
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<td>35.7 cM</td>
<td>Tnfr2, Cd30</td>
<td></td>
</tr>
<tr>
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<td></td>
<td>Idd9.2</td>
<td>5.6 cM</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Idd9.3</td>
<td>2.0 cM</td>
<td>Cd137</td>
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<tr>
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<td>2</td>
<td>Idd13a</td>
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<td>B2m</td>
<td>Serreze et al. 1998</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Idd13b</td>
<td>1.2 cM</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
was obtained, whereas evidence against the Fcgr1 Idd10 was obtained for Idd3, have been established (Ikegami et al. 2002, 2003). As for strain, and NOD mice congenic for IIS at each of these loci (1999). They also obtain significant evidence of linkage with dependent diabetes locus 1 in the NSY mouse (Ueda et al. 1999, 2000). The strongest linkage was for Idd3, evidence for the I2 variant as a susceptibility gene was obtained, whereas evidence against the Fcgr1 variant was obtained for Idd10.

Genetics of Type 2 Diabetes in the NSY Mouse

Genome Scan Mapping of Three Major Loci

Ueda and colleagues (1999, 2000b) performed a genome scan with a F2 progeny in crosses of NSY mice, an animal model of type 2 diabetes, with control C3H/He mice. They obtained significant evidence for linkage with hyperglycemia and related phenotypes for chromosomes 11, 14, and 6 (Ueda et al. 1999, 2000). The strongest linkage was for chromosome 11, with maximal LOD score of more than 8; and the locus was designated Nidd1n, for non-insulin-dependent diabetes locus 1 in the NSY mouse (Ueda et al. 1999). They also obtain significant evidence of linkage with hyperglycemia for chromosome 14, designated Nidd2n. The chromosome 6 region was significantly linked to abdominal fat accumulation and also possibly linked to hyperglycemia, and the locus was designated Nidd3n. Collectively, these three loci explain 54% of the genetic variance under a three locus model (Ueda et al. 1999).

Consomic Strains

Based on increasing evidence that strong linkage with a chromosomal region is often due to the cumulative effect of multiple loci on the same chromosome, as is clearly shown by the studies of Idd3 in the NOD mouse mentioned above, we decided to make consomic, rather than congenic, strains to prove that each of the Nidd loci contributes to the disease phenotype, for subsequent identification of responsible genes. In a consomic strain, a whole chromosome of interest from one strain was introgressed onto the genetic background of another strain. In a congenic strain, in contrast, a gene or a chromosomal segment harboring a gene, from one strain was introgressed. It is relatively easy to make congenic strains possessing different segments of the chromosome from a consomic strain, but it is impossible to reconstitute the multiple loci on the same chromosome from congenic strains, once they are separated by recombination. We therefore decided to make consomic strains when multiple loci on the same chromosome appear to contribute to the disease phenotype. Once a significant effect of a chromosome on the disease phenotype is confirmed in a consomic strain, then the chromosome can be dissected into multiple components by making congenic and subcongenic strains.

There are two possible ways to make consomic or congenic strains. One method is to introgress a disease chromosome onto the background genes of a control strain (Figure 3, Consomic A), and the other method is to introgress a control chromosome onto the background genes of a disease model (Figure 3, Consomic B). In the case of the NOD mouse, the former congenic strain (Figure 3A) did not show any detectable changes in diabetic phenotypes, and we therefore used the latter congenic strain (Figure 3B). We used suppression of the disease was used as evidence that the introgressed chromosome from the control strain possessed a resistant allele, which in turn indicated that the NOD allele on the same chromosome was necessary for disease susceptibility. For studies on susceptibility genes for type 2 diabetes in the NSY mouse, we introgressed a chromosome from a disease model, the NSY mouse in this case, onto the genetic background of the control mouse, C3H/He (Consomic A) (Babaya et al. 2001). This direction is opposite from the congenic strategy used in the NOD mouse mentioned above.

In contrast to type 1 diabetes, which is a qualitative trait, type 2 diabetes-related phenotypes of the NSY mouse are quantitative (e.g., blood glucose level for diabetes, quantity of abdominal fat for obesity, and basal insulin level for insulin resistance). A change in a quantitative trait is expected to be more easily detectable than one in a qualitative trait, type 1 diabetes, because the development of type 1 diabetes is the result of the cumulative effect of many steps (e.g., a break in immunological tolerance, targeting of immune cells to islets, invasion of immune cells into islets, and destruction of pancreatic beta cells) and because type 1 diabetes becomes detectable only when a significant portion (> 90%) of beta cells are destroyed. Glucose tolerance in patients with type 1 diabetes and in the NOD mouse is reported to be normal until soon before the development of overt diabetes (Kano et al. 1986; Srikanta et al. 1984). In contrast, type 2 diabetes is the result of functional abnormalities in insulin secretion and/or insulin action, and these functional changes can be easily detected by measuring blood glucose and insulin levels during glucose tolerance testing. In addition, type 2 diabetes of the NSY mouse ap-
pears to be oligogenic with three major genes contributing to the disease development, which is in clear contrast to the polygenic nature of type 1 diabetes in the NOD mouse in which as many as 20 susceptibility genes contribute to disease susceptibility. We therefore hypothesized that the effect of one gene or one chromosome harboring susceptibility genes for type 2 diabetes of the NSY mouse can be detectable when introgressed onto the control genetic background. In fact, both chromosome 11 (\textit{Nidd1n}) and chromosome 14 (\textit{Nidd2n}) consomic strains showed significant elevation of blood glucose during glucose tolerance testing (Babaya et al. 2001), indicating that both chromosomes harbor susceptibility genes for type 2 diabetes, which in themselves show a significant effect without the aid of other susceptibility genes. In addition, the data on double consomic strains, in which chromosomes 11 and 14 from the NSY mouse were introgressed onto the control genetic background, suggested an interactive effect between the two chromosomes (N. Babaya et al., Osaka University Graduate School of Medicine, Suita, Japan, unpublished observation).

Congenic Mapping and Candidate Sequencing

To localize further the \textit{Nidd} genes whose effect on diabetes-related phenotypes was confirmed in consomic strains, congenic strains are being produced by repeated backcrossing of consomic strains to control C3H mice. As for \textit{Nidd2n} on chromosome 14, investigators have produced several lines of congenic strains, which possess a different part of chromosome 14 from the consomic strain, and preliminary data suggest that \textit{Nidd2n} on chromosome 14 consists of at least two components. Thus, susceptibility loci for type 2 diabetes mapped to chromosomal segments in the NSY mouse consist of multiple components, as in the case of type 1 susceptibility genes in the NOD mouse.

Several candidate genes for type 2 diabetes are located in \textit{Nidd} intervals on chromosomes 11, 14, and 6. Among these, the gene for the glucose transporter, GLUT4, is a candidate for \textit{Nidd1n} on chromosome 11, but no difference in sequences was found between NSY and control strains (Ueda et al. 2000a). \textit{Tcf2} encoding HNF (hepatocyte nuclear factor) 1-beta is another candidate gene for \textit{Nidd1n}. Nucleotide and predicted amino acid sequences of \textit{Tcf2} of the NSY mouse are allelically variant from those of the control C3H mouse (Ueda et al. 1999, 2001), suggesting the possibility that HNF1-beta may be a candidate for \textit{Nidd1n}. The support interval for \textit{Nidd1n}, however, is still large (i.e., containing a large number of genes), and additional studies are therefore necessary to confirm this observation.

Co-localization of Genes for Type 1 and Type 2 Diabetes in the Same Chromosomal Regions

Chromosomal segments where susceptibility genes for type 2 diabetes (\textit{Nidd1n}, \textit{Nidd2n}, and \textit{Nidd3n}) were mapped in the NSY mouse (Ueda et al. 1999) overlap chromosomal segments where susceptibility genes for type 1 diabetes
Idd4, Idd8, and Idd6, respectively) were mapped in the NOD mouse (Ghosh S et al. 1993; Rogner UC et al. 2001; Wicker et al. 1995) (Figure 4). Because a number of susceptibility genes have been mapped in the NOD mouse, it is possible that the co-localization of genes for type 1 and type 2 diabetes in the same chromosomal regions may be coincidental. However, the fact that both the NOD and the NSY mouse were derived from the same closed colony maintained in the same facility (Figure 1) suggests the possibility that some of these genes may have segregated from a common ancestor to both strains, contributing to type 1 diabetes in the NOD mouse and type 2 diabetes in the NSY mouse as a common genetic factor. Initial mapping studies suggested that Idd4, Idd6, and Idd8 are linked to type 1 diabetes, but not to insulitis (Ghosh et al. 1993; Wicker et al. 1995), suggesting that these genes do not contribute to the initiation of autoimmunity but instead, to the destruction of beta cells, which leads to diabetes. Among the possible functions of such genes are impaired protection against autoimmune attack and/or impaired proliferation and regeneration in response to destruction. Genes responsible for such functions can also act as susceptibility genes for type 2 diabetes, because several lines of evidence suggest that the function of such genes is also operable in beta-cell dysfunction through chronic hyperglycemia, termed glucose toxicity, in type 2 diabetes. Such common susceptibility genes, if they exist, will contribute to susceptibility to type 1 diabetes when combined with susceptibility genes specific to type 1 diabetes (e.g., autoimmune-related genes) through vulnerability of beta cells under autoimmune attack. Such genes may also contribute to type 2 diabetes when combined with susceptibility genes specific to type 2 diabetes (e.g., genes related to insulin resistance) through vulnerability of beta cells under increased insulin demand due to insulin resistance and/or glucose toxicity due to hyperglycemia, leading to exhaustion of insulin secretary capacity of beta cells (Figure 5).

Despite the difference in clinical characteristics and etiological basis, epidemiological data have indicated clustering of type 1 and type 2 diabetes in the same families (Chern et al. 1982; Dahlquist et al. 1989; Li et al. 2001; Figure 4 Co-localization of susceptibility genes on chromosomes 11 and 14 for type 1 diabetes in the NOD mouse (Idd loci: Idd4 and Idd8, respectively) and those for type 2 diabetes in the NSY mouse (Nidd loci: Nidd1n and Nidd2n, respectively).

![Figure 4](image_url)  
**Figure 4** Co-localization of susceptibility genes on chromosomes 11 and 14 for type 1 diabetes in the NOD mouse (Idd loci: Idd4 and Idd8, respectively) and those for type 2 diabetes in the NSY mouse (Nidd loci: Nidd1n and Nidd2n, respectively).

![Figure 5](image_url)  
**Figure 5** Hypothetical scheme for shared genetic susceptibility to type 1 and type 2 diabetes.
Wagener et al. (1982), which suggests shared susceptibility loci between the two types of diabetes. The occurrence of type 1 and type 2 diabetes in sister strains derived from the same closed colony of mice and rats further supports this possibility. As in the case of the NOD mouse and the NSY mouse, animal models for both type 1 and type 2 diabetes exist in sister strains of the rat: the Long-Evans Tokushima lean (LETL) rat and the Otsuka Long-Evans Tokushima fatty (OLETF) rat (Figure 6). The LETL rat is a model for type 1 diabetes, derived from a closed colony of Long-Evans rats (Kawano et al. 1991). From the same closed colony, an animal model of type 2 diabetes, the OLETF rat, was derived (Kawano et al. 1992) (Figure 6). Thus, as in humans, type 1 and type 2 diabetes cluster in sister strains of mice and rats derived from the same closed colony. Although two major susceptibility genes in the LETL rat—MHC and Cblb—its high incidence subline, the Komeda diabetes-prone (KDP) rat are immune-related genes, and therefore unlikely to contribute to susceptibility to type 2 diabetes in the OLETF rat, other susceptibility genes with a modest effect or modifiers may be shared between the two strains of rats.

Thus, positional and functional data on susceptibility genes for type 1 and type 2 diabetes as well as the familial clustering of both type 1 and type 2 diabetes in humans, mice, and rats suggest the possibility of shared genetic susceptibility to both type 1 and type 2 diabetes. Although it is difficult to identify such genes in humans (Elbein et al. 1997; Takekawa et al. 1997), the data from a very recent study suggest that a susceptibility gene for type 2 diabetes also contributes to susceptibility to type 1 diabetes (Eftychi et al. 2004). Although it is difficult to prove functionally that such shared genes contribute to both types of diabetes, the existence of mouse models for type 1 (NOD) and type 2 (NSY) diabetes derived from the same closed colony provide an opportunity to prove this hypothesis experimentally. For example, shared susceptibility to type 1 and type 2 diabetes can be proved functionally by making congenic strains in which a chromosomal segment of interest is exchanged between type 1 and type 2 models. If the same phenotypes are retained even after chromosomal exchange, then candidate genes in the interval are sequenced and compared between type 1 and type 2 models as well as the control strains used for initial mapping of the respective genes. Such studies are under way (Yamada et al. 2001), and once identified, such genes will provide valuable information on etiological pathways common to both forms of diabetes, to establish effective methods for the prediction, prevention, and intervention in both type 1 and type 2 diabetes.

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References


