Brief Genetics Report

NOD *Idd5* Locus Controls Insulitis and Diabetes and Overlaps the Orthologous CTLA4/IDDM12 and NRAMP1 Loci in Humans

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A genome scan for B10-derived loci that reduce the frequency of diabetes and insulitis in NOD mice demonstrated a large region (34 cM) of linkage on the proximal end of chromosome 1. This locus was designated *Idd5* and encompassed candidate genes including *Il1r1, Il1r2, Stat1, Stat4, Nramp1,* and *Bcl2*. In the current study, we have confirmed the existence of *Idd5* by developing a series of congenic mouse strains that are resistant to diabetes and determined that *Idd5* is actually two genes located within a 9.4-cM interval. *Idd5.1* is in the proximal 1.5-cM portion of the interval and contains the candidates *Casp8, Cflar* (FLIP), *Cd28,* and *Cd152* (CTLA4). *Idd5.1* overlaps the orthologous CTLA4/IDDM12 locus in humans. *Idd5.2* is in the distal 5.1-cM portion of the 9.4-cM interval and contains the candidates *Nramp1,* which has a functional polymorphism between NOD and B10, and *Cmkar2* (CXCR2, interleukin [IL]-8 receptor α). Candidate genes eliminated by this analysis include *Il1r1, Ilr2, Zap70, Orch5, Stat1, Stat4, Bcl2, Cmkar4* (CXCR4), and *Il10*. On its own, the *Idd5* locus provides a significant amount of protection from diabetes (50% reduction from parental frequency) and when combined with another resistance locus (*Idd3* on chromosome 3), provides nearly complete protection from diabetes and insulitis. *Diabetes* 49:1744–1747, 2000

Idd5 is a locus linked to a 34-cM region of proximal chromosome 1 that affects the development of diabetes and insulitis in the NOD mouse (1–4). The B10 allele at *Idd5* confers resistance to diabetes and insulitis, whereas the NOD allele confers susceptibility. To confirm the existence of *Idd5*, we developed a congenic strain of mouse called *Idd5*R1. This congenic strain has a large portion (69 cM) of proximal chromosome 1 from the B10 strain introgressed onto the NOD background (Table 1). The B10 congenic interval in *Idd5*R1 mice encompasses the entire region of originally defined linkage (4). As seen in Fig. 1, *Idd5*R1 female mice had a significantly reduced frequency of diabetes compared with the NOD parental strain ($P < 0.00004$), thereby confirming the linkage data and the existence of *Idd5*.

Because significant protection was observed in the *Idd5*R1 strain, two additional congenic strains, *Idd5*R8 and *Idd5*R2, were developed by breeding selected recombinants (Table 1). *Idd5*R8 and *Idd5*R2 share the distal end of the *Idd5*R1 congenic interval but have lost the proximal 38.2 and 39.7 cM, respectively, of B10 DNA in *Idd5*R1 (Table 1). The fact that *Idd5*R8 is protected from diabetes (Fig. 1) localizes *Idd5* to a 30.6-cM interval and rules out candidates contained in the proximal 38.2-cM region of *Idd5*R1: *Il1r1*, *Ilr2*, *Zap70*, *Orch5*, *Stat1*, and *Stat4*. In contrast to *Idd5*R8, *Idd5*R2 is not protected from diabetes (Fig. 2). The small genetic difference between *Idd5*R8 and *Idd5*R2 defines a critical region for the protective effect of *Idd5*. The 1.5-cM region distinguishing *Idd5*R2 and *Idd5*R8 includes the candidate genes *Casp8*, *Cflar* (FLIP), *Cd28*, and *Cd152 (Ctla4)*.

A second series of congenic strains was selected to analyze the distal boundary of the congenic interval defined in strain *Idd5*R8. *Idd5*R394, *Idd5*R444, and *Idd5*R467 sequentially truncate the distal portion of the *Idd5*R8 congenic interval while retaining the proximal 1.5-cM region required for *Idd5*-mediated protection as defined by the *Idd5*R2 congenic strain. If only one gene (within the 1.5-cM interval) was responsible for *Idd5*-mediated protection, *Idd5*R394, *Idd5*R444, and *Idd5*R467 should be as equally protected from disease as *Idd5*R1 and *Idd5*R8. However, the *Idd5*R394 and *Idd5*R444 congenic strains have a diabetes frequency equivalent to *Idd5*R8, whereas *Idd5*R467 is significantly less protected from diabetes ($P = 0.0173$ for *Idd5*R467 vs. *Idd5*R8). These results indicate that the protection mediated by *Idd5* is caused by at least two loci: *Idd5.1* located in the proximal 1.5-cM interval of *Idd5*R8 and *Idd5.2* located in the 5.1-cM interval that differs between *Idd5*R444 and *Idd5*R467.

The candidate genes *Nramp1* and *Cmkar2* (CXCR2, interleukin [IL]-8 receptor α) are located within the *Idd5.2* interval. Although no sequence polymorphism has been reported for the IL-8 receptor α-chain, there is a well-documented functional polymorphism in the NRAMP1 protein (5). The NOD strain expresses a functional NRAMP1 protein, whereas the

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IL, interleukin; PCR, polymerase chain reaction; SAP, shrimp alkaline phosphatase.

TABLE 1
Idd5 congenic strains

Marker	cM*	Gene	*Idd5*R1	*Idd5*R8	*Idd5*R2	*Idd5*R394	*Idd5*R444	*Idd5*R467
D1Mit167	6.5†		B10	NOD	NOD	NOD	NOD	NOD
		Il1r1/2	—	—	—	—	—	—
		Orch5	—	—	—	—	—	—
		Zap70	—	—	—	—	—	—
D1Mit211	17.5 (10/57)		B10	NOD	NOD	NOD	NOD	NOD
D1Mit212	7 (4/57)		B10	NOD	NOD	NOD	NOD	NOD
		Stat1/4	—	—	—	—	—	—
D1Mit478	7 (4/57)		B10	NOD	NOD	NOD	NOD	NOD
D1Mit124	0.2 (2/1,319)		B10	B10	NOD	B10	B10	B10
D1Mit414	0.2 (2/1,262)		B10	B10	NOD	B10	B10	B10
		Cflar	—	—	—	—	—	—
D1Nds27	0 (0/1,478)	*Casp8*	B10	B10	NOD	B10	B10	B10
D1Mit161	0.1 (2/1,478)		B10	B10	NOD	B10	B10	B10
D1Mit479	0.3 (5/1,478)		B10	B10	NOD	B10	B10	B10
		Cd28	—	—	—	—	—	—
D1Mit249	0.1 (2/1,478)		B10	B10	NOD	B10	B10	B10
D1Nds25	0 (0/1,478)	*Cd152*	B10	B10	NOD	B10	B10	B10
D1Mit303	0.3 (4/1,478)		B10	B10	NOD	B10	B10	B10
D1Mit300	0.3 (5/1,478)		B10	B10	B10	B10	B10	B10
D1Mit156	0.9 (2/216)		B10	B10	B10	B10	B10	B10
D1Mit178	1.9 (4/216)		B10	B10	B10	B10	B10	B10
D1Mcg5	3.2 (7/216)	*Nramp1*	B10	B10	B10	B10	B10	NOD
		Cmkar2	—	—	—	—	—	—
D1Mit46	0.5 (1/216)		B10	B10	B10	B10	B10	NOD
D1Mit132	0.5 (1/216)		B10	B10	B10	B10	B10	NOD
D1Mit134	0.9 (2/216)		B10	B10	B10	B10	NOD	NOD
D1Nds7	3.7 (8/216)	*Bcl2*	B10	B10	B10	B10	NOD	NOD
D1Mit263	6 (13/216)		B10	B10	B10	B10	NOD	NOD
		Il10	—	—	—	—	—	—
		Cmkar4	—	—	—	—	—	—
D1Mit30	1.9 (4/216)		B10	B10	B10	NOD	NOD	NOD
D1Mit498	1.9 (4/216)		B10	B10	B10	NOD	NOD	NOD
D1Mit104	5.1 (11/216)		B10	B10	B10	NOD	NOD	NOD
D1Mit267	2.6‡		NOD	NOD	NOD	NOD	NOD	NOD

* Intermarker distances in centimorgans (number of recombinants per number of meioses genotyped); †distance from the centromere according to the Mouse Genome Database; ‡distance from Mouse Genome Database. —, no variant marker available.

B10 strain does not (6). A functional NRAMP1 protein confers resistance to infection by intracellular pathogens such as *Salmonella typhimurium*, *Leishmania donovani*, and *Mycobaterium bovis* bacillus Calmette-Guérin. NRAMP1 is found in macrophages and is thought to be a H^+/divalent cation antiporter that facilitates the killing of bacteria within lysozomes. Recently, it has been suggested that NRAMP1 allotypes contribute to the mouse immune response by differentially affecting class II expression on macrophages and altering the profile of cytokines secreted by these cells (7,8). In addition, a promoter polymorphism in human NRAMP that increases expression of the NRAMP1 protein in macrophages has been associated with protection from infectious disease (9,10) and susceptibility to rheumatoid arthritis (11,12). Thus, *Nramp1* is a prime candidate gene for *Idd5.2*.

A number of interesting candidate genes map to the *Idd5.1* interval (Table 1). Of these, *Cd28* and *Cd152* have been sequenced previously, and no coding variants were identified between NOD and B10 (13). In this study, we sequenced cDNAs encoding *Casp8* and *Cflar*. Six variants were found in *Casp8*, one in the 5′ untranslated region, and five in the coding region (Table 2). Of the variants in the coding region, four are synonymous and one is nonsynonymous, resulting in a conservative Ala-to-Val substitution at position 96 (Table 2). No variants were identified in *Cflar*. Although no obvious functional variants have been observed in any of these candidate genes, it is possible that expression-altering variants may be located in their promoter regions. *Idd5.1* overlaps the orthologous CTLA4/IDDM12 locus in humans, where polymorphisms in CTLA4 have been associated with Graves' disease and type 1 diabetes (14,15). If CTLA4 polymorphisms are responsible for this association, it is likely that promoter differences are causative rather than alterations in the structural gene.

In the initial genome scan for diabetes susceptibility genes, protection from diabetes was linked to regions on chromosomes 1, 3, 4, 6, and 11; however, insulitis was linked only to chromosomes 1 (*Idd5*) and 3 (*Idd3* and *Idd10/18*) (3,4). We have previously observed that *Idd3* and *Idd10/18* together provide potent protection from insulitis (16) but that the individual regions only affect the time of onset of insulitis (*Idd3*) or have no detectable effect (*Idd10/18*) (16). To address the issue of insulitis protection conferred by *Idd5*, we developed

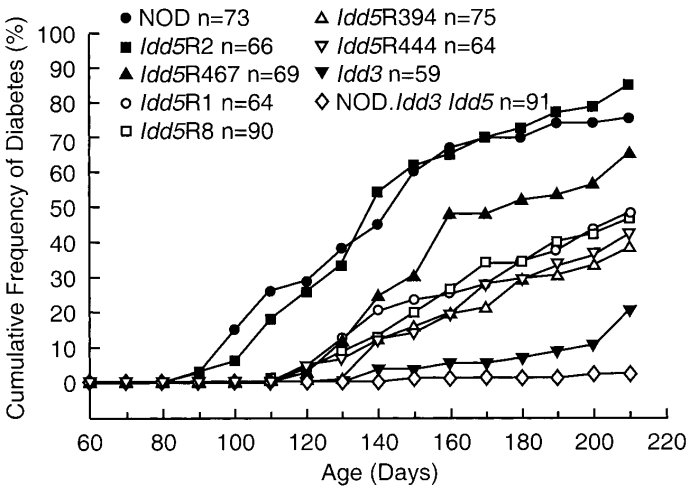

FIG. 1. Cumulative frequency of diabetes in congenic strains.

a double congenic strain in which the *Idd3* resistance locus has been transferred to the *Idd5*R8 strain. Data indicate that the NOD.*Idd3 Idd5* congenic strain is highly protected from disease because <3% of females develop diabetes by 7 months of age (Fig. 1, $P = 0.0002$ for *Idd3* vs. NOD.*Idd3 Idd5*). In addition, only a small proportion of double congenic NOD.*Idd3 Idd5* mice have insulitis (Fig. 2) compared with the *Idd5*R8 or *Idd3* single congenic strains. These results suggest that the substantial protection from insulitis linked to chromosomes 1 and 3 in the genome scan (4) was due to an interaction between multiple loci contributing to a reduction in the accumulation of inflammatory cells in the islets. None of the single genes identified so far that reduce insulitis in conjunction with other loci (*Idd5*, *Idd3*, *Idd10*, and *Idd18*) are sufficient on their own to substantially reduce the frequency of insulitis.

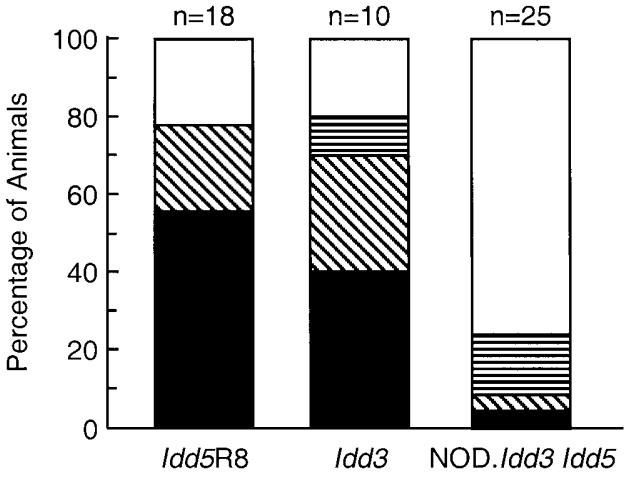

FIG. 2. The frequency and severity of insulitis are reduced in NOD.*Idd3 Idd5* mice. Females of the indicated strains were monitored for diabetes. Insulitis was assessed at the onset of diabetes or at 7 months of age in mice not developing disease. The number of diabetic mice in the *Idd5*R8, *Idd3*, and NOD.*Idd3 Idd5* strains was seven, one, and one, respectively. Each animal received one of the following scores: none (□; all islets observed are free of insulitis), mild (▤; <10% of the islets are infiltrated), moderate (▧; 10–50% of the islets are affected), or extensive (■; >50% of the islets have insulitis).

TABLE 2
Variants within *Casp8*

Position*	B10	NOD	Codon	Amino acid
–23	A	G	—	—
+144	G	T	48	Leu > Leu
+276	T	C	92	Asp > Asp
+287	C	T	96	Ala > Val
+564	C	T	188	Ser > Ser
+949	C	T	317	Leu > Leu

*Position in cDNA sequence relative to the A residue of the initiation methionine.

The results of our initial dissection of the *Idd5* region reported here are reminiscent of results obtained on chromosome 3. There, an initial broad linkage was shown by congenic strain dissection to be due to four loci: *Idd3*, *Idd17*, *Idd10*, and *Idd18*. Like the single-gene congenic strains NOD.B6 *Idd10* and NOD.B6 *Idd18* (17), the NOD.B10 *Idd5.1* (*Idd5*R467) and NOD.B10 *Idd5.2* (*Idd5*R2) congenic strains have a modest (*Idd5*R467, $P = 0.0093$ for NOD vs. *Idd5*R467) or undetectable (*Idd5*R2) protection from diabetes. There is one locus, *Idd3*, localized to a 0.15-cM region (and therefore likely to represent a single gene), which causes substantial protection from diabetes on its own, but this locus appears to be more the exception than the rule (18). Thus, it is likely that the fine-mapping of many of the *Idd* loci will require the constant presence of an additional resistance gene. This additional resistance gene would have the attribute that it interacts with the gene of interest to produce increased disease protection compared with the activity of the individual resistance alleles. For example, development of additional congenic strains that recombine within the 1.5-cM *Idd5.1* DNA segment defined by the *Idd5*R2 and *Idd5*R8 strains (Table 1) will enable the positional cloning of *Idd5.1* because a gene within the interval defined by the *Idd5*R2 strain is essential for the disease protection caused by *Idd5.1*. The identification of individual *Idd* loci will lead to the identification of pathways that must combine to reduce the genetic predisposition to diabetes. Effective therapeutic intervention of inflammation-based diseases such as type 1 diabetes will most likely require the attenuation of more than one of the pathogenic pathways.

RESEARCH DESIGN AND METHODS

Mice. NOD.B10 *Idd5* chromosome 1 mice were developed by backcrossing C57BL/10 mice purchased from The Jackson Laboratory (Bar Harbor, ME) to NOD/MrkTacfBR mice obtained from Taconic Farms (Germantown, NY) with selection for the described regions on chromosome 1 (Table 1). The strategy used to generate congenic strains has been described in detail previously (19). The strain NOD.B10*Idd5*R1 (N8F2–4), referred to as *Idd5*R1, was the founding congenic strain and contains the greatest amount of introgressive B10 DNA. Founders of the *Idd5*R1 strain were tested for the presence of B10 chromosomal segments throughout the genome using a panel of microsatellite markers that differentiate NOD and B10 genomic segments (20). All non–chromosome 1 markers examined were of NOD origin in the *Idd5*R1 strain. The NOD.B10*Idd5*R2 (N11F2-4) and NOD.B10*Idd5*R8 (N11F2-4) strains, referred to as *Idd5*R2 and *Idd5*R8, respectively, were derived from *Idd5*R1. All other strains were subsequently derived from *Idd5*R8: NOD.B10*Idd5*R467 (N13F2-4), NOD.B10*Idd5*R444 (N13F2-4), and NOD.B10*Idd5*R394 (N13F2-4), referred to as *Idd5*R467, *Idd5*R444, and *Idd5*R394, respectively. The double congenic strain, NOD.B6 *Idd3* B10 *Idd5*R8 (N12F2), referred to as NOD.*Idd3 Idd5*, was developed by intercrossing *Idd5*R8 with a NOD.B6 *Idd3* diabetes-resistant strain NOD.B6^7 (21), herein called *Idd3*.

Assessment of diabetes and insulitis. Elevated urinary glucose was detected using Diastix (Miles, Elkhart, IN). Animals were classified as diabetic

when urinary glucose was at least 500 mg/dl. Diabetic mice also exhibited polydipsia, polyuria, and weight loss. Frequency of diabetes in different strains was compared using the Kaplan-Meier log-rank test. Pancreases were fixed in 10% buffered formalin and processed for paraffin embedding. Tissue sections (5 µmol/l) were stained with hematoxylin and eosin and microscopically evaluated for the presence of mononuclear cell infiltrates. Two noncontiguous sections of each pancreas were examined.

Determination of marker order. The marker order shown in Table 1 was determined by genotyping progeny from crosses between NOD and the NOD.B10 *Idd5* congenic strains *Idd5*R1 and *Idd5*R8 and minimizing recombinants. Markers that could not be resolved genetically were ordered by typing the T31 mouse-hamster radiation hybrid panel (22).

Mapping of candidate genes. Previously published microsatellite markers variant between B10 and NOD were used to map *Bcl2* (*D1Nds7*) and *Nramp1* (*D1Mcg5*). The microsatellite marker *D1Nds27* was developed by designing primers that amplify a variant dinucleotide repeat within an intron of *Casp8* (GenBank accession number AF067835, *D1Nds27 For* 5′-CAT ACA GGG CAG GTG ATG TG-3′ and *D1Nds27 Rev* 5′-CAT CTC TGC AAG CAA CCA AA-3′). The microsatellite marker *D1Nds25* was isolated from a mouse BAC clone (Research Genetics) positive for *Ctla4* (*D1Nds25 For* 5′-CCT GTC AGT CTG GCA TTC ATA-3′ and *D1Nds25 Rev* 5′-ATC TTC CCT TTA TTA AAT CTT TGT T-3′). Variant microsatellite markers were not available for the following candidate genes: *Stat1*, *Cflar*, *Cd28*, and *Il10*. These genes were placed on the framework map by typing the T31 mouse hamster radiation hybrid panel (22).

Sequencing *Cflar* and *Casp8*. cDNA for *Cflar* and *Casp8* was generated by reverse transcriptase–polymerase chain reaction (PCR) using total RNA extracted from splenocytes from *Idd5*R8 and NOD mice. Briefly, RNA was extracted using the Trizol reagent (Life Technologies), and 1 µg was used as template for cDNA synthesis using Superscript RT (Life Technologies). *Cflar* and *Casp8* were amplified by PCR, and PCR products were cleaned up using shrimp alkaline phosphatase (SAP) and ExoI (Amersham) and then sequenced directly using the BigDye Terminator Cycle Sequencing Kit (PE Biosystems). Before gel electrophoresis, excess dye terminators were removed by SAP treatment. DNA sequences were assembled using the GAP4 program and aligned using the clustalx program.

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