Suggestive Evidence for Association of Human Chromosome 18q12-q21 and Its Orthologue on Rat and Mouse Chromosome 18 With Several Autoimmune Diseases

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Some immune system disorders, such as type 1 diabetes, multiple sclerosis (MS), and rheumatoid arthritis (RA), share common features: the presence of autoantibodies and self-reactive T-cells, and a genetic association with the major histocompatibility complex. We have previously published evidence, from 1,708 families, for linkage and association of a haplotype of three markers in the *D18S487* region of chromosome 18q21 with type 1 diabetes. Here, the three markers were typed in an independent set of 627 families and, although there was evidence for linkage (maximum logarithm of odds score [MLS] = 1.2; $P = 0.02$), no association was detected. Further linkage analysis revealed suggestive evidence for linkage of chromosome 18q21 to type 1 diabetes in 882 multiplex families (MLS = 2.2; λs = 1.2; $P = 0.001$), and by meta-analysis the orthologous region (also on chromosome 18) is linked to diabetes in rodents ($P = 9 \times 10^{-4}$). By meta-analysis, both human chromosome 18q12-q21 and the rodent orthologous region show positive evidence for linkage to an autoimmune phenotype ($P = 0.004$ and 2×10^{-8}, respectively, empirical $P = 0.01$ and 2×10^{-4}, respectively). In the diabetes-linked region of chromosome 18q12-q21, a candidate gene, deleted in colorectal carcinoma (DCC), was tested for association with human autoimmunity in 3,380 families with type 1 diabetes, MS, and RA. A haplotype ("2-10") of two newly characterized microsatellite markers within *DCC* showed evidence for association with autoimmunity ($P = 5 \times 10^{-6}$). Collectively, these data suggest that a locus (or loci) exists on human chromosome 18q12-q21 that influences multiple autoimmune diseases and that this association might be conserved between species. *Diabetes* 50:184–194, 2001

As much as 5% of the population suffers from autoimmune disease, a failure of the homeostatic regulation of the immune system to prevent tissue damage and maintain self-tolerance. Predisposition to autoimmune disease is universally associated with alleles of the major histocompatibility complex (MHC) genes on chromosome 6p21 (1). However, the MHC is not sufficient to explain disease occurrence, and non-MHC susceptibility genes are predicted. In type 1 diabetes in humans, the evidence for non-MHC genes is incomplete (2,3), owing to the small, statistically underpowered data sets analyzed so far. In rodent models of disease, however, the existence and location of several non-MHC loci are established (1). It has also been shown in humans and mice that autoimmunity loci, mapped in a variety of autoimmune disease models, including those for type 1 diabetes and multiple sclerosis (MS), cluster significantly (1,4,5). Furthermore, congenic strains conclusively show that *Idd3*, a mouse non-MHC type 1 diabetes susceptibility locus, also influences susceptibility to experimental allergic

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Received for publication 6 April 2000 and accepted in revised form 8 September 2000.

J.A.T. was a paid consultant of Merck Research Laboratories, which provided grants to his laboratory to conduct studies on the genetics of type 1 diabetes.

DCC, deleted in colorectal carcinoma; df, degrees of freedom; EAE, experimental allergic encephalomyelitis; GSMA, genome search meta-analysis; JDFI, Juvenile Diabetes Foundation International; MAS, maximal arthritis score; MHC, major histocompatibility complex; MLS, maximum logarithm-of-odds score; MS, multiple sclerosis; PCR, polymerase chain reaction; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TDT, transmission disequilibrium test; T_{sp}, TDT-based statistic.

TABLE 1
Composition of type 1 diabetes data sets

Data set (*n*)	Reference	1,708 Diabetes	627 Diabetes	2,335* Diabetes	2,359 Diabetes
U.K. multiplex (399)	12	✔		✔	✔
U.K. multiplex (24)	12		✔	✔	✔
U.K. simplex (163)	12,14	✔		✔	✔
U.K. simplex (32)	12		✔	✔	✔
U.S. multiplex (189)	12,15	✔		✔	✔
U.S. multiplex (52)	12,15		✔	✔	✔
Sardinian simplex (181)		✔		✔	✔
Sardinian simplex (60)			✔	✔	✔
Norwegian multiplex (40)	12	✔		✔	✔
Norwegian simplex (380)	12	✔		✔	✔
Danish multiplex (48)	16	✔		✔	✔
Danish multiplex (7)	16		✔	✔	✔
Danish simplex (104)	17		✔	✔	✔
Finnish simplex (104)		✔		✔	✔
Finnish simplex (135)			✔	✔	✔
Finnish multiplex (24)					✔
Romanian simplex (204)	13	✔		✔	✔
Canadian simplex (87)			✔	✔	✔
Italian multiplex (57)			✔	✔	✔
Italian simplex (69)			✔	✔	✔

*The 2,335 families were typed with 88,21-55,26 and 129,11-IO43,56-*D18S487*; the additional 24 Finnish multiplex families in the 2,359 families were typed with 88,21-55,26 only.

encephalomyelitis (EAE), a model of MS (6), and *iddm4* in rats may be a universal autoimmunity locus (7). In addition to the well-established linkage and association of the MHC region to multiple autoimmune phenotypes, the CTLA-4 gene locus on human chromosome 2 has been reported to be either linked or associated with type 1 diabetes, Graves' disease, and MS (8–10).

Previously, we reported some positive evidence of linkage ($P = 0.005$) and association ($P_c = 0.01$) of diabetes to chromosome 18q21 in the vicinity of *D18S487* (provisionally designated *IDDM6*) (11–13). In the present study, we were unable to replicate the *D18S487* association result, but we have consolidated evidence of linkage of the region to type 1 diabetes by analysis of 882 families and by meta-analyses of other linkage studies of a variety of autoimmune diseases in humans and rodents. Finally, a large family-based study suggests that the human deleted in colorectal carcinoma (DCC) gene region of chromosome 18q21 is associated with autoimmune disease.

RESEARCH DESIGN AND METHODS

Families with type 1 diabetes, MS, and rheumatoid arthritis. The families used for the association analysis were white European or European-derived with both parents and at least one affected sibling per family. The 2,359 type 1 diabetic families are summarized in Table 1. In the Sardinian, Finnish, Canadian, and Italian data sets, ages of diagnoses were <17 years, <15 years, <18 years, and <29 years, respectively. Table 1 summarizes the composition of the 1,708-family diabetes data set (13), the independent 627 families studied here, and the combined 2,335 and 2,359 families.

The 229 Sardinian MS families have been previously described (18). The 667 U.K. simplex MS families had a clinical diagnosis of disease based on the Poser criteria (19). The 125-family U.K. rheumatoid arthritis (RA) data set consisted of simplex and multiplex families, and all cases satisfied the 1987 American College of Rheumatology criteria for disease and were recruited from the Arthritis Research Campaign Epidemiology Unit in Manchester University and the Rheumatology Department at the Nuffield Orthopaedic Centre in Oxford. Healthy siblings were collected in all data sets except the U.K. MS families. In all cases, sample collection was approved by the appropriate institutional review board. The total 3,380-family autoimmune data set comprised the 2,359 type 1 diabetes families, 896 MS families, and 125 RA families.

The 882 affected sib-pair pedigrees available to us that were tested for linkage to disease consisted of 415 of the 423 U.K. families used in the association study, 284 U.S. families including the 241 used in the association study, 58 Italian families of which 57 were used in the association study, 54 of the 55 Danish multiplex families, 32 Finnish affected sib-pair families including the 24 used in the association study, and 39 Norwegian multiplex families from the previously described 420 families.

Microsatellite marker isolation and genotyping. With use of polymerase chain reaction (PCR) primers for *DCC* exons 19 and 29 (exon 29 is the 3′ exon of *DCC*) (20), HPAC 88_h_2 and HBAC 55_g_22, respectively, were isolated from the De Jong libraries (ResGen). HBAC 55_g_22 is telomeric to HPAC 88_h_2. Microsatellite marker 88,21 was cloned from HPAC 88_h_2 and marker 55,26 from HBAC 55_g_22 using a previously described PCR-based method (13). Primer sequences for amplifying 88,21 are CTGA CAAAACTGGGACTACCTTCC and GAATACATCTCCGTATTTGCATC and for 55,26 are GGCTAGTGGTTGCCGTATTATAC and AAATCTCAGCATGTCAGT GAA. Primer sequences for amplifying other microsatellite markers either have been published elsewhere (12,13) or are available from http://www.gdb.org. Genotyping PCRs using fluorescently labeled primers were performed and analyzed as described previously (21). Haplotypes are given with the marker genotypes in centromeric to telomeric order.

Comparative mapping. Human, mouse, and rat chromosome 18 orthology relationships were established using www3.ncbi.nlm.nih.gov/Homology, www.informatics.jax.org/searches/oxfordgrid_form.shtml, www.nih.gov/niams/scientific/ratgbase, www.otsuka.genome.ad.jp/ ratmap, and www.well.ox.ac.uk/~bihoreau. Distances along human chromosome 18 were taken from a combination of www.cedar.genetics.soton.ac.uk/pub and www.genethon.fr, along mouse chromosome 18 from www. informatics.jax.org, and along rat chromosome 18 from www.well.ox.ac.uk/~bihoreau and waldo.wi.mit.edu/rat/public/.

Meta-analysis: Fisher's method. When there is no justification for assuming a common population variance between genome scans for linkage to differing autoimmune phenotypes in differing rodent strains and differing human populations, the only common measure that can form the basis for combination is the *P* value (22). The sum of $(-2\log_e P)$ probability values from m independent tests of linkage is a χ^2 statistic with $2m$ degrees of freedom (df) (23). Under the null hypothesis of no linkage of a region to disease, observed *P* values from separate studies have a uniform distribution regardless of the test statistic used or the distribution from which they arise (24). Thus, Fisher's method is appropriate even when considering studies that exhibit heterogeneity in the phenotype measured and test statistics used. Chromosome 18

TABLE 2
Meta-analysis of linkage of rodent chromosome 18 to autoimmunity

Cross (n)*	Sp	5 cM Marker	5 cM P	15 cM Marker	15 cM P	25 cM Marker	25 cM P	35 cM Marker	35 cM P	45 cM Marker	45 cM P	50 - tel Marker	50 - tel P	Ref.
Diabetes														
(B10×NOD)F1 × NOD (296)	M	Mit21	0.63	Mit12	0.36	Csfmr	0.65	Nds3	0.29	Mit8	0.09	—	—	35
(NOD × Spretus)F1 × NOD (175)	M	—	1.0	—	1.0	—	1.0	—	1.0	—	1.0	—	1.0	36
(BB × WF)F1 × BB (140)	R	Mit1	0.31	—	—	—	—	Arb3	0.005	Mgh3	0.001	—	—	34
(TM × KDP)F1 × KDP (168)	R	Mit1	0.20	Mit4	0.18	Tilp	0.15	Mgh11	0.34	Gja1	0.021	Mit9	0.15	37
			0.59		0.48		0.60		0.05		9×10^{-4}		0.44	
EAE														
(B10.S × SJL/J)F1 × B10.S (68)	M	Mit19	0.32	—	—	—	—	Mit123	0.62	—	—	Mit44	0.024	38
(SJL/J × B10.S)F2 (681)	M	Mit67	0.22	Mit62	0.24	Mit24	0.24	—	—	Mit81	0.56	Mit3	0.47	32
(ABH × NOD)F1 × NOD (155)	M	Mit19	0.65	—	—	Mit37	0.042	Mit124	0.019	Mit9	0.003	Mbp	0.022	39
(ABH × BALBc)F1 × BALBc (59)	M	Mit19	0.69	Mit12	0.59	—	—	—	—	Mit184	0.24	Mbp	0.43	40
(B10.RIII × RIIIS/J)F2 (92)	M	—	—	Mit36	0.055	Mit50	0.24	Mit6	0.24	—	—	—	—	41
(DA × BN)F2 (45)	R	Mit2	0.40	—	—	Mgh1	0.32	Adrb2	0.49	Mit8	0.40	Mgh4	0.52	30
(LEW × BN)F2 (146)	R	Mit1	0.26	—	—	Mgh1	0.89	—	—	Mgh3	0.91	—	—	42
			0.49		0.14		0.15		0.11		0.06		0.03	
SLE														
(NZB × NZW)F1 × NZW (60)	M	—	—	Mit14	0.79	—	—	—	—	Mit8	0.12	Mit16	0.26	43
(NZB × NZW)F1 × NZB (148)	M	—	—	Mit14	0.58	Mit74	0.65	—	—	Mit8	1.0	Mit16	0.75	44
(NZB × NZW)F2 (144)	M	—	—	Mit34	0.94	Mit39	0.14	—	—	Mit8	0.0005	Nds1	0.0066	45
(MRL.lpr × B6lpr)F2 (254)	M	Mit20	0.54	—	—	—	—	—	—	Mit9	0.092	Mit36	0.78	46
			0.54		0.95		0.31		—		0.002		0.08	
Arthritis														
(DA × F344) × (F344 × DA) (111)	R	Mit1	0.05	Mit3	0.10	—	—	Arb3	0.22	Mgh2	0.21	Mit6	0.41	47
(DA × ACI) × (ACI × DA) (47)	R	Wox7	0.13	Mgh7	0.16	—	—	Mgh11	0.04	—	—	Mgh4	0.004	26
(DA × F344) × (F344 × DA) (40)	R	Mit12	0.37	Mit3	1.0	—	—	Mgh11	0.74	—	—	Mit6	0.11	27
(E3 × DA)F2 (92)	R	Wox7	0.032	Mit3	0.15	Mgh1	0.097	—	—	Wox12	0.055	Mgh4	0.28	48
(B10RIII × RIIISJL/J)F2 (174)	M	Mit117	0.63	Mit105	0.50	Mit50	0.08	Mit16	0.042	—	—	—	—	49
(BB[DR] × BN/SsN)F2 (152)	R	Mit1	0.22	Rat145	0.27	Mit5	0.63	—	—	Mit8	0.07	Rat82	0.54	28,29
(BALBc × DBA/2)F2 (423)	M	Mit110	0.0022	—	—	—	—	Mit51	0.0015	Mit80	0.0034	—	—	50
(B10.Q × DBA/1)F2 (86)	M	Mit31	0.097	—	—	Mit36	0.085	—	—	Mit50	0.023	Mit4	0.075	33
			9×10^{-4}		0.19		0.05		0.0001		3×10^{-4}		0.01	
Others†														
(BALBc × DBA) × BALBc (44)	M	—	—	Mit34	0.89	—	—	Mit40	0.65	Mit80	0.55	—	—	51
(C3H × B6) × (B6 × C3H) (86)	M	—	—	Mit119	0.052	—	—	Mit124	0.052	—	—	Mit7	0.89	31
(LEW × F344) × (F344 × LEW) (40)	R	Mit1	0.50	Tilp	0.37	—	—	—	—	Mit8	0.83	—	—	52
(MRL/lpr × C3H/lpr) × MRL/lpr (175)	M	Mit117	0.0084	Mit14	0.00044	Mit22	0.00012	Mit124	0.0084	Mit142	0.012	—	—	53
Total			0.005		0.03		0.002		3×10^{-5}		2×10^{-8}		0.003	

*Number of animals analyzed; †phenotypes were orchitis, colitis, uveoretinitis, and sialadenitis, respectively. M, mouse; R, rat.

data used here for the meta-analyses were derived from whole genome-wide scans and were obtained either directly from publications or from the corresponding author. P values were either published values or, when not presented, were determined as follows. For rodents, P values were calculated by a χ^2 test of heterogeneity between affected and unaffected animals or, if unaffected animals were not genotyped, were calculated by a χ^2 test of heterogeneity against the hypothesis of no linkage. For humans, P values were calculated for maximum logarithm-of-odds scores (MLS) and Z scores. If necessary, logarithm of odds scores were converted into χ^2 (1df) statistics by multiplication by a factor of 4.6 (25) and the resulting P value included in the analysis. Autoimmune phenotypes that were characterized by both inflammation and association and/or linkage to the HLA region were analyzed. Where more than one scan was reported for a rodent autoimmune disease model, to reduce heterogeneity we chose the most consistently used end-point phenotype for each model. For type 1 diabetes, this end point was elevated urinary glucose levels, paralysis for EAE, swelling and erythema in joints for arthritis, and nephritis (which causes death) for systemic lupus erythematosus (SLE). Genome scans examining associated phenotypes (insulitis in diabetes and factors influencing autoantibody production, for example) were excluded. For two rat arthritis scans (26,27), which assessed linkage to severity of disease, data from severely affected animals were used and P values calculated by a χ^2 test of heterogeneity against the null hypothesis of no linkage to arthritis. For the (BB × BN)F2 data (28,29), animals with a maximal arthritis score (MAS) >33 were compared, using a χ^2 test for linkage, to animals with MAS <3. In two reports (30,31), a two-stage genotyping strategy was used requiring markers showing suggestive linkage to disease in an initial panel of animals to be genotyped over a second panel of animals; in the analysis presented here, data from the first panel of animals only were used. Data from the scans of Butterfield et al. (32) and Yang et al. (33) were analyzed using a χ^2 test for linkage to disease susceptibility. In the (BB × WF)F1 × BB rat backcross, linkage of diabetes to chromosome 18 was not reported owing to the relative paucity of available polymorphic markers but tested here by a χ^2 test of heterogeneity between affected and unaffected animals using data obtained from the corresponding author (34).

To meta-analyze linkage of the entire length of chromosome 18 to autoimmunity, the rodent and human chromosomes were divided into 10-cM intervals and P values combined as described above to yield a total P value for each of human and rodent (Tables 2 and 3). The $-(\log_{10})$ of these values were plotted at intervals of 10 cM (Fig. 2). Only scans with at least three markers, each in separate intervals of 10 cM, along the chromosome length were included. Six genome-wide scans (77–82) were excluded on this criterion. Scans in which partial data only were available for chromosome 18 (83–85) were excluded from

TABLE 3
Meta-analysis of linkage of human chromosome 18 to autoimmunity

	n†	5 cM	15 cM	25 cM	35 cM	45 cM	55 cM	65 cM	75 cM	85 cM	95 cM	105 cM	115 cM	120 cM
Colitis														
Greco et al. (54)	39	1.0	—	1.0	—	0.40	1.0	—	0.20	0.25	0.33	0.27	0.043	—
Zhong et al. (55)	40	0.094	1.0	—	0.47	—	1.0	0.10	0.01	0.21	1.0	0.13	0.30	1.0
Satsangi et al. (56)	160	1.0	1.0	0.33	0.20	0.11	0.095	0.13	0.095	0.055	0.07	0.095	0.095	0.095
Cho et al. (57)	174	0.24	1.0	0.24	0.085	0.10	0.10	0.10	0.075	0.085	0.24	1.0	0.15	1.0
Hampe et al. (58)	353	1.0	1.0	1.0	1.0	0.34	1.0	1.0	1.0	1.0	1.0	1.0	0.41	1.0
Hugot et al. (59)	25	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Ma et al. (60)	65	0.20	0.60	1.0	1.0	0.40	0.32	0.02	0.02	0.09	0.06	0.11	0.36	0.36
Duerr et al. (61)	127	1.0	0.34	1.0	1.0	1.0	0.50	0.34	0.07	0.08	0.08	0.02	0.11	0.17
Rioux et al. (62)	158	0.01	0.01	0.01	0.03	0.02	0.04	1.0	1.0	1.0	1.0	1.0	0.23	—
SLE														
Gaffney et al. (63)	187	0.005	0.01	0.008	0.03	0.33	0.19	0.13	0.13	0.78	0.78	1.0	1.0	1.0
Moser et al. (64)	94	0.81	0.76	0.81	0.68	0.45	0.42	0.71	0.56	0.62	0.48	0.46	0.51	—
Shai et al. (65)	80	0.31	0.59	—	0.65	0.33	0.34	0.33	0.05	0.006	0.03	0.37	0.30	0.47
Multiple sclerosis														
Kuokkanen et al. (66)	16	0.47	0.16	0.39	0.47	0.45	0.39	0.45	0.64	0.56	0.70	0.33	0.50	—
The MS Genetics Group (67)	81	0.46	0.09	—	0.34	0.48	0.006	0.08	0.88	0.34	—	0.33	0.09	—
Sawcer et al. (68)	129	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.28	—
Ebers et al. (69)	100	0.11	1.0	—	—	0.036	—	0.18	1.0	—	0.11	1.0	—	1.0
Rheumatoid arthritis														
Cornelis et al. (70)	114	0.33	0.15	0.22	0.23	0.41	0.07	0.04	0.012	0.012	0.02	0.01	0.25	1.0
Jawaheer et al. (71)	184	1.0	1.0	1.0	1.0	0.35	1.0	1.0	0.11	0.56	0.4	1.0	0.79	1.0
Psoriasis														
Nair et al. (72)	224	0.64	0.62	—	0.56	0.39	0.087	—	0.096	0.53	0.54	0.39	0.6	—
Trembath et al. (73)	66	0.15	0.29	—	—	0.088	—	0.27	—	0.50	—	0.36	—	—
Samuelsson et al. (74)	134	0.49	0.23	0.06	0.06	0.13	0.26	0.12	0.09	0.12	0.16	0.32	0.39	0.40
Others*														
Hashimoto et al. (75)	61	1.0	0.20	—	1.0	0.15	1.0	0.92	—	1.0	—	1.0	—	0.65
Tomer et al. (76)	53	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Total		0.27	0.34	0.25	0.46	0.09	0.10	0.07	0.004	0.07	0.14	0.35	0.21	0.98

Data are *P* values. *Phenotypes were type 1 diabetes and autoimmune thyroid disease, respectively; †number of sib pairs (except refs. 57,59,64–66, where number of multiplex families used is given).

this analysis (the first two publications reported positive linkage of the 40- to 50-cM portion of rat chromosome 18 to type 1 diabetes [$P = 0.004$ and 0.045, respectively] and the third reported positive linkage of chromosome 18q21 to Graves' disease [$P = 3 \times 10^{-4}$], but linkage data for other chromosome 18 markers were not available). When no chromosome 18 data were available either in the published paper or by request (36,59), $P = 1.0$ was included in each 10-cM window and 2 df added to each final χ^2 statistic. Where a scan included no marker in a particular 10-cM window, no data were included for that window and no degrees of freedom added to the total χ^2 statistic.

Meta-analysis: permutation method. A simulation/permutation method was used to additionally evaluate the pointwise significance of the test statistic obtained using Fisher's method. Test statistics at a single location were constructed using data from Tables 2 and 3, in 10^4 (for human) or 10^6 (for rodent) replicates. In each replicate, the *P* value contribution from a single study was chosen at random from the *n* possible contributions for that study at the *n* different locations ($n = 6$ for rodent and 13 for human). The *P* values from the *m* studies were combined using Fisher's method to give an overall test statistic for that replicate. Comparison of the observed Fisher's test statistic to that obtained using simulation allows an empirical *P* value for the observed statistic to be calculated. The $-(\log_{10})$ of these values were plotted at intervals of 10 cM (Fig. 3). This method relies on the assumption that at most locations, there is no linkage to disease. If a high proportion of the locations is, in fact, linked to disease, this method would give a conservative estimate of the empirical *P* value. Thus, in the case of the rodent meta-analysis in which there was a reasonable expectation of linkage of the 40- to 50-cM bin to disease (Fig. 2*A*), *P* values from the other five bins only (0–40 cM and 50 cM telomere) were used for a second permutation. The method would be anticonservative if the number of studies with missing information (in which the *P* value contribution was set to 1.0) was significantly smaller at the test location than at a random location. In our analyses, the test locations with higher Fisher's combined statistics did not have significantly fewer missing *P* values than other locations.

Genome search meta-analysis method. The genome search meta-analysis (GSMA) method (86) can be applied to a wide range of study designs and to studies that differ in family ascertainment, population sampled, phenotype definition, markers genotyped, and analysis method used. The method requires ranking the results (test statistics or *P* values) at *n* bins within each study. The test statistic at each location is the sum (over *m* studies) of the ranks. Ten-cM bins were used, meaning 6 bins for rodent chromosome 18 and 13 bins for human chromosome 18. The exact distribution of the ranked statistic may be calculated (86). The $-(\log_{10})$ of the *P* values were plotted at intervals of 10 cM along rodent and human chromosome 18. Because our analysis was on a specific chromosome rather than from a whole genome scan, and our bins were smaller in length (and thus more correlated) than the recommended 20-cM bins (86), the significance of the test statistics was also evaluated using a simulation/permutation approach as described above (plotted in Fig. 4). *P* values using this method were very similar to theoretical *P* values.

Analysis of allelic association and linkage. Transmission of two-marker haplotypes was assessed from heterozygous parents to both affected and unaffected offspring using the transmission disequilibrium test (TDT) (87). To take account of the lack of independence (owing to linkage) between siblings in multiplex families and obtain a valid estimate of association, the TDT-based statistic (T_{sp}) was used (88). T_{sp} has a χ^2 (1 df) distribution. When both parents were heterozygous for the same alleles at one marker in the haplotype, the family was removed from the analysis to prevent bias (89). Any families with missing parental data were also removed from the analysis to eliminate bias either from reconstruction of parental haplotypes or counting transmissions from a single parent (90,91). Transmission of haplotypes and T_{sp} were calculated assuming no recombination between 88,21 and 55,26. Percent *T* is the number of times an allele or haplotype was transmitted from heterozygous parents divided by the total of transmissions plus nontransmissions, expressed as a percentage. To assess linkage disequilibrium between haplotypes, D′ values were calculated (92). D′ values range from 1 (complete disequilibrium) through 0 (complete equilibrium) to –1 (alleles never found on same haplotype).

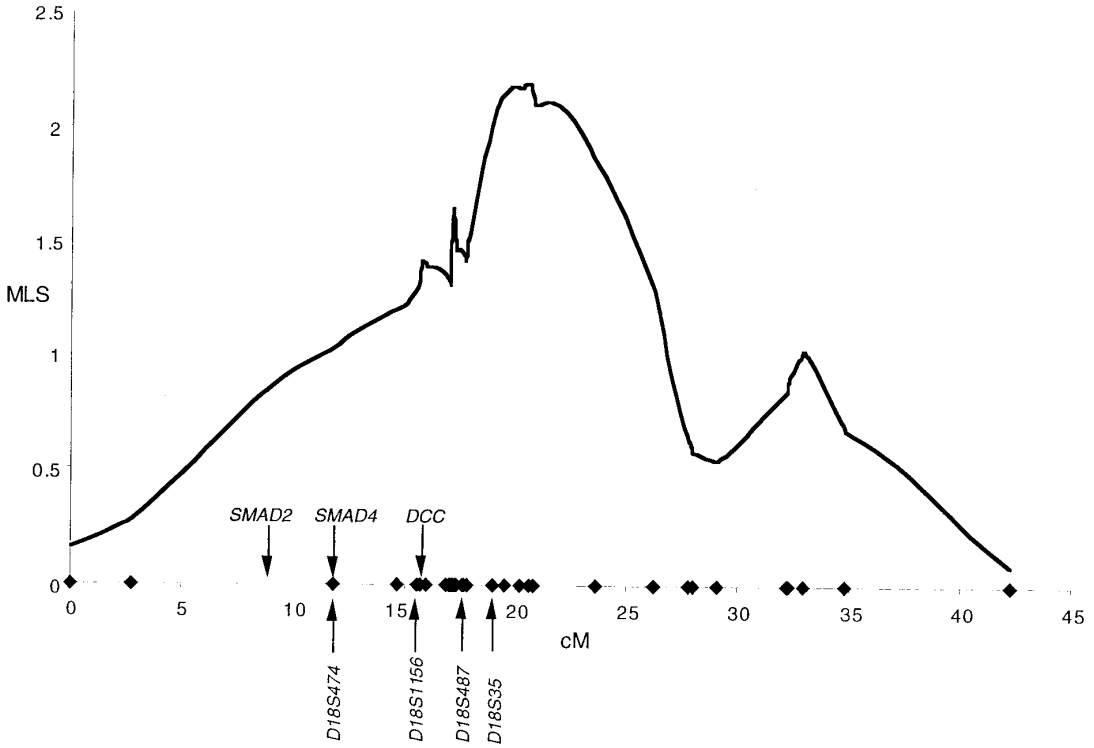

FIG. 1. Linkage of human chromosome 18q to type 1 diabetes in 882 affected sib-pair families. The approximate positions of *SMAD2*, *SMAD4*, and *DCC* are shown. *SMAD2* has been colocalized to YAC clones positive for *D18S460*, *SMAD4* to YAC clones positive for *D18S474*, and *DCC* to YAC clones positive for *D18S1156* (95). Microsatellite markers (represented by ◆) are listed, centromeric to telomeric, in RESEARCH DESIGN AND METHODS.

For the linkage analysis, up to 33 microsatellite markers spanning a 42-cM region of 18q12-q21 were typed in 882 affected sib-pair families from six populations. Centromeric to telomeric, these were as follows: *D18S57*, *D18S454*, *D18S474*, *D18S484*, *D18S1156*,88,21,55,26,114,1,30T7,129,6,129,12,129,11, IO43,56, *D18S487*, A181,2,49,12,49,22, *D18S35*, *D18S69*, *D18S39*, *D18S41*, *D18S1152*, *D18S1129*, *D18S64*, *D18S38*, *D18S1134*, *D18S1148*, *D18S68*, *D18S42*, *D18S55*, *D18S483*, *D18S465*, and *D18S61*. The 10 framework markers *D18S454*, *D18S474*, *D18S487*, *D18S35*, *D18S69*, *D18S39*, *D18S41*, *D18S64*, *D18S38*, and *D18S42* were typed in all of the populations except the 39 Norwegian families. A further 11 of the 33 markers were typed in the Danish, Italian, and Norwegian data sets and 13 additional microsatellites were typed in the Finnish and U.S. data sets. All 33 were typed in the U.K. families. Markers were ordered with the Genome Analysis System (http://users.ox.ac.uk/~ayoung/gas.html). When a physical map existed (13), it was used to order markers instead. Intermarker distances were calculated using the Aspex software (ftp://lahmed.stanford.edu/pub/aspex/index.html) using all available family material. Multipoint MLS values were produced using Mapmaker/Sibs (ftp://ftp-genome.wi.mit.edu/distribution/software/sibs).

RESULTS

Previously, we cloned and physically mapped 10 microsatellite markers within a 650-kb region surrounding *D18S487* on

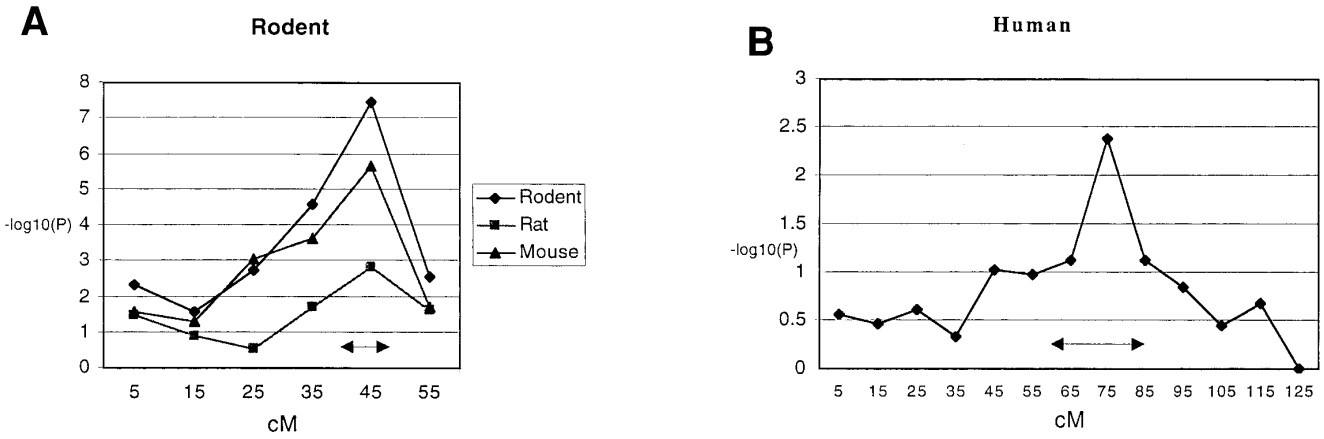

FIG. 2. Linkage of chromosome 18 to an autoimmune phenotype in (*A*) rodent and (*B*) human by Fisher's method of combining *P* values. Plotted points were taken from Tables 2 and 3, respectively, and are $-\log_{10}(P)$ of total *P* values represented at the bottom of each table. Separate mouse and rat curves were plotted in Fig. 2*A* by summing appropriate *P* values, obtaining a combined *P* value, and plotting $-\log_{10}(P)$. The region of synteny to human chromosome 18q12-q21 is marked (↔) on the rodent chromosome 18 curve, and the 18q12-q21 region is marked (↔) on the human chromosome 18 curve.

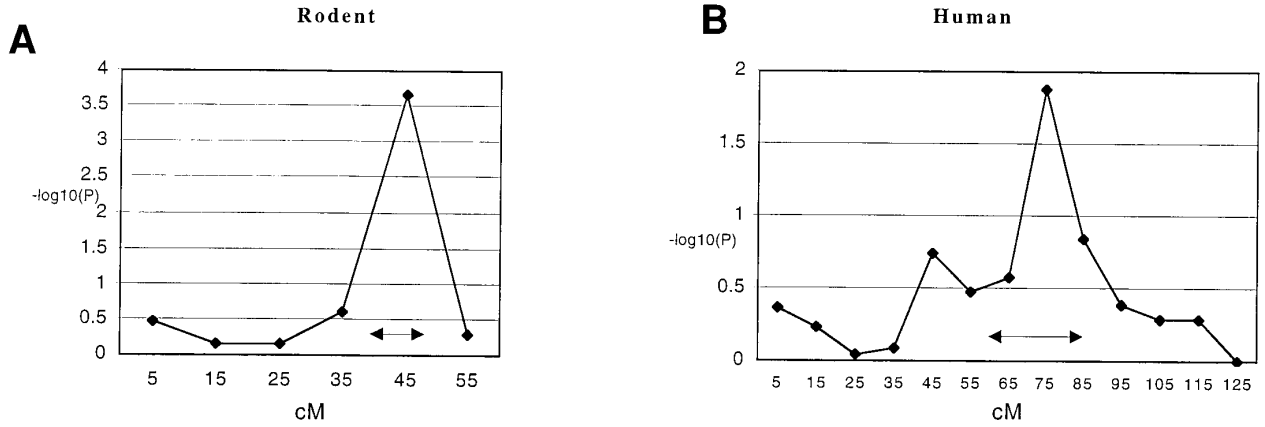

FIG. 3. Empirical significance of the Fisher's test statistics. Permutation on data in Tables 2 and 3 was performed as described in RESEARCH DESIGN AND METHODS, excluding the 40- to 50-cM bin in rodent, and -log$_{10}$(P) of the permuted P values were plotted for (A) rodent and (B) human. The region of synteny to human chromosome 18q12-q21 is marked (↔) on the rodent chromosome 18 curve, and the 18q12-q21 region is marked (↔) on the human chromosome 18 curve.

chromosome 18q21 (13). In 1,708 families, we showed that a haplotype ("10-2-4") of three of these markers (129, 11-IO43, 56-*D18S487*) showed some positive evidence of association with type 1 diabetes ($P = 2 \times 10^{-4}$) (13). Here, in an attempt to replicate this association, we typed the three markers in an independent set of 627 type 1 diabetes families and examined transmission of the 10-2-4 haplotype from heterozygous parents to affected offspring. The three-marker haplotype was negatively transmitted in these families (33 T vs. 53 NT), although there was evidence for linkage of the two markers to disease in the 140 multiplex family subset of the 627 (MLS = 1.2, $P = 0.02$). In the combined 2,335 families, there were 249 T vs. 199 NT (%T = 55.6, $P = 0.02$). In the context of genome-wide levels of statistical significance for allelic association of $P < 5 \times 10^{-8}$ (93), this is highly unlikely to be a true positive. This Bonferroni-based threshold may be too stringent, however, if there is prior evidence of linkage of a chromosome region with disease. We, therefore, reevaluated the evidence of linkage. Not only did we analyze linkage of chromosome 18q in 882 type 1 diabetic sib-pairs, but we also meta-analyzed linkage of the orthologous region of rodent chromosome 18 to type 1 diabetes. First, we typed up to 33 polymorphic microsatellite markers covering a 44-cM region (*D18S57* to *D18S61*) in 882 type 1 diabetes–affected sib-pair pedigrees and tested for linkage to disease (Fig. 1). There was a peak MLS of 2.2 (λs = 1.2; $P = 0.001$), 3 cM telomeric to *D18S487*, suggestive evidence for linkage to disease (94).

On the basis of this result, we sought additional support for the possibility that chromosome 18q21 contains a diabetes gene by meta-analysis of the published evidence for linkage of the orthologous region to type 1 diabetes in rodent models of disease. A 25-cM segment of human chromosome 18q12-q21 is orthologous with an 8-cM segment of mouse chromosome 18, and mouse and rat chromosome 18 are also conserved. Gene order is conserved between *SMAD2* (65 cM on human chromosome 18q12.3 and 48 cM on mouse chromosome 18) and *FECH* (90 cM on human chromosome 18q21.3 and 40 cM on mouse chromosome 18). The content and order of mapped genes is also conserved between mouse and rat chromosome 18 along the entire length, except for *Gja1* (which maps at 59 cM on rat chromosome 18 and 29 cM on mouse chromosome 10). Four independent genome scans of rodent type 1 diabetes, with at least three markers along chromosome 18, have been published. The distal portion of rodent chromosome 18 (40–50 cM), orthologous with human chromosome 18q12-q21, showed evidence of linkage to type 1 diabetes ($P = 9 \times 10^{-4}$; Table 2).

Human 18q12-q23 has also been reported as being linked to Graves' disease, SLE, and RA (65,70,85), and the orthologous region on distal rodent chromosome 18 has been linked to EAE (39,95), to Theiler's virus-induced demyelination in mouse (a model of MS) (96), and in the murine model of lupus (45). To test the hypothesis that the distal end of rodent chromosome 18 and the orthologous region on human chromosome 18q12-q21 was linked to a phenotype of autoimmunity rather than to just a single autoimmune disease such as type 1 diabetes, the meta-analysis was extended to all published genome scans of autoimmune disease, beginning with the rodent model. Scans for linkage in rodent models of type 1 diabetes, EAE, lupus, arthritis, orchitis, gastritis,

TABLE 4
Transmission of the 2-10 haplotype of markers 88,21 and 55,26 from heterozygous parents to affected offspring in Caucasian autoimmune data sets

Data set (n)	T	N	%T	T_{sp}	P
U.K. (618)	346	299	54.8	2.5	0.1
U.S. (241)	157	145	52.0	0.6	0.5
Sardinian (241)	64	55	53.8	0.7	0.4
Finnish (263)	92	76	54.8	1.5	0.2
Romanian (204)	74	55	57.4	2.8	0.09
Canadian (87)	19	7	73.1	4.8	0.03
Italian (126)	40	34	54.1	0.4	0.5
Norwegian (420)	151	107	58.5	7.0	0.008
Danish (159)	78	72	52.0	0.2	0.6
Type 1 diabetes (2,359)	1,021	850	54.6	14.0	2×10^{-4}
Sardinian-MS (229)	79	52	60.3	6.4	0.01
U.K.-MS (667)	174	156	52.7	1.0	0.3
MS (896)	253	208	54.8	4.7	0.03
U.K.-RA (125)	58	42	58.0	2.8	0.09
Total (3,380)	1,332	1,100	54.8	20.8	5×10^{-6}

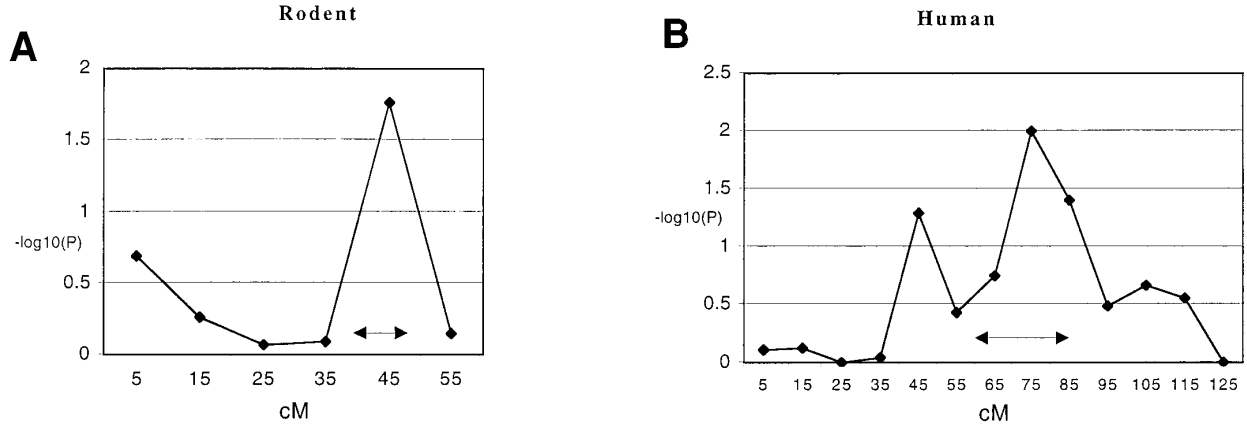

FIG. 4. Linkage of chromosome 18 to an autoimmune phenotype in (*A*) rodent and (*B*) human by GSMA. Plotted points are $-\log_{10}(P)$ of simulated (empirical) *P* values calculated as described in RESEARCH DESIGN AND METHODS, using data from Tables 2 and 3. The region of synteny to human chromosome 18q12-q21 is marked (↔) on the rodent chromosome 18 curve, and the 18q12-q21 region is marked (↔) on the human chromosome 18 curve.

sialadenitis, and uveoretinitis were available (Table 2; Fig. 2*A*). Strongest linkage was observed to the 40- to 50-cM portion of chromosome 18 ($P = 2 \times 10^{-8}$). When plotted separately, the rat and mouse curves were similar, with linkage peaking in the 40- to 50-cM window for each (Fig. 2*A*; $P = 2 \times 10^{-6}$ and $P = 0.001$, respectively). Meta-analysis of human chromosome 18 was then performed on published human autoimmune disease genome scans of type 1 diabetes, inflammatory bowel disease, psoriasis, MS, RA, SLE, and Graves' disease. Peak $P = 0.004$ was obtained in the chromosome 18q21 region (Table 3; Fig. 2*B*). Note that three type 1 diabetes studies (2,3,11) were excluded owing to overlap in families used.

Genome scans using families or animal cohorts of small size (Tables 2 and 3) may increase the chance of type 1 error owing to the possibility of the respective test statistics not being continuous. Therefore, we repeated the human and rodent analyses excluding the five smallest studies from each. *P* values by Fisher's method were 0.004 for the 70- to 80-cM bin of human chromosome 18 and 4×10^{-9} for the 40- to 50-cM bin of rodent chromosome 18. Excluding these studies did not greatly affect the combined statistic.

To further evaluate the significance of the meta-analysis–based linkage obtained using Fisher's method, we applied a simulation method to the data (Fig. 3). For rodents, $P = 2 \times 10^{-4}$ (with a reasonable expectation of linkage of the 40- to 50-cM region to disease, this region was excluded from the permutation, $P = 0.005$ when this region was included) was obtained for linkage of the 40- to 50-cM bin of chromosome 18 to autoimmunity and $P = 0.01$ for linkage of human chromosome 18q12-q21 to autoimmunity. If any of the other positions used for the permutation are, in fact, linked to disease, then $P = 2 \times 10^{-4}$ will be a conservative estimate of the empirical level of significance in rodent. The permutation accounts for any residual linkage present on chromosome 18 and indicates that the linkages observed using Fisher's method are unlikely to have occurred owing to chance.

A separate method of meta-analysis, the GSMA method (86), was applied to the data (Fig. 4). This analysis supported the results obtained using Fisher's method of combining *P* values, with linkage observed both to the distal end of rodent chromosome 18 (40- to 50-cM portion, $P = 0.03$) and the chromosome 18q12-q21 region in humans (70- to 80-cM portion, $P = 0.02$). Simulated *P* values were 0.02 and 0.01, respectively (Fig. 4). The GSMA *P* values are less significant than the Fisher's *P* values (Fig. 2), probably because the GSMA method does not take into account the actual *P* values obtained in the individual studies.

At this stage of the investigation, we concluded that there was sufficient justification to commence a functional candidate gene approach to finding the disease locus (or loci) in the potentially linked region. As a first step, we chose the DCC gene because it has been well characterized at the genomic level, its product functions in apoptosis (97), and apoptosis defects can cause autoimmune disease. Using two microsatellite markers (88,21 and 55,26) cloned from within introns of *DCC*, we tested *DCC* for association with autoimmunity in the 2,359 type 1 diabetes families (Table 1), 896 MS families, and 125 RA families ($n = 3{,}380$; Table 4). All four haplotypes with a frequency >5% in parental chromosomes (2–10 [19.5%], 2–11 [10.9%], 7–1 [9.2%], and 2–12 [5.8%]) were tested for association with autoimmunity in the 3,380 families. The T_{sp} statistics were 20.8 (1,332 T, 1,100 NT; $P = 5 \times 10^{-6}$), 1.2 (821 T, 780 NT; $P = 0.28$), 1.0 (674 T, 643 NT; $P = 0.32$), and 0.0 (432 T, 500 NT; $P = 1.0$), respectively. Thus, only 2-10, the most common haplotype, showed some positive association with autoimmunity ($P = 5 \times 10^{-6}$; $P_c = 2.1 \times 10^{-4}$). A correction factor of 42 takes account of the 38 independent tests done in previous association analyses of the region (12,13) and the four separate 88,21–55,26 haplotypes tested here. Even if we anticipate 5,000 tests within this 20-cM chromosome 18q region, corrected *P* would still be <0.05. Association between the 2-10 haplotype and the separate autoimmune phenotypes was also tested (Table 4). Evidence for association with type 1 diabetes ($P = 2 \times 10^{-4}$) and with MS ($P = 0.03$) but not with RA ($P = 0.09$) was obtained. Transmission of the 2-10 haplotype to unaffected siblings did not differ from random expectations in the 3,380 families (633 T and 595 NT; % T = 51.5, $P = 0.28$).

DISCUSSION

A multifaceted approach to study of a non-MHC type 1 diabetes susceptibility locus on chromosome 18q21 that incorporates all currently available clinical resources and data is presented here. On the basis of suggestive evidence for linkage of the

chromosome 18q12-q21 region with type 1 diabetes in 882 families (Fig. 1; $P = 0.001$), a meta-analysis was undertaken providing evidence for linkage of the orthologous region in rodent to type 1 diabetes ($P = 9 \times 10^{-4}$). Evidence for linkage of the same region to an autoimmune phenotype in both rodent and human ($P = 2 \times 10^{-8}$ and 0.004, respectively, simulated $P = 2 \times 10^{-4}$ and 0.01, respectively) was obtained by further meta-analyses. Finally, with use of a positional candidate gene approach, association of microsatellite markers within the DCC gene was demonstrated to an autoimmune phenotype in humans (3,380 families, $P = 5 \times 10^{-6}$; $P_c = 2.1 \times 10^{-4}$).

The markers within *DCC* associated with autoimmunity (88,21 and 55,26) are within one megabase of *D18S487* (98), which is part of the three-marker 129, 11-IO43, 56-*D18S487* haplotype ("10-2-4") that we had previously found to be weakly associated with type 1 diabetes. The associated 2-10 haplotype of markers 88,21 and 5,26 was not in linkage disequilibrium with any of the five most common haplotypes, including the weakly associated 10-2-4 haplotype, at 129, 11-IO43, 56-*D18S487*. The D′ values were between –0.19 and 0.21 in the diabetes families. The 10-2-4 haplotype was positively transmitted to affected offspring in the 1,708 families previously studied ($T_{sp} = 12.0$; $P = 5 \times 10^{-4}$) (13) but was negatively transmitted in the second independent set of 627 type 1 diabetes families studied here (33 T, 53 NT). In contrast, the 2-10 haplotype was associated with disease in both sets of families ($P = 0.003$ and 0.01, respectively). The results for the 129, 11-IO43, 56-*D18S487* markers may represent either a false-positive association, or weaker linkage disequilibrium with the same locus detected by the *DCC* markers, or a very weak disease association distinct from that detected at *DCC*.

Our conclusion that there is suggestive evidence supporting association and linkage of human chromosome 18q12-q21 and its orthologue on rat and mouse chromosome 18 with multiple autoimmune phenotypes was reached only when considering the sum of the analyses presented here. Considering the conservation between human, mouse, and rat of association and linkage with autoimmunity, the results presented here are unlikely to be artifactual but rather indicate involvement of one or—more likely—more than one gene on chromosome 18 in susceptibility to autoimmunity. It is important to note that when examining each of the individual analyses in isolation (*DCC* association study in human and the rodent and human meta-analyses), none provides convincing evidence for involvement of chromosome 18 in autoimmunity—only the type 1 diabetes linkage analysis (Fig. 1) can be considered to provide "stand alone" suggestive evidence. For a number of reasons, however, our finding of possible involvement of chromosome 18 in autoimmune susceptibility is unlikely to be a false positive. $P = 2 \times 10^{-8}$ for linkage to rodent autoimmunity was obtained in the 40- to 50-cM portion of distal chromosome 18 (Table 2; Fig. 2*A*, empirical $P = 2 \times 10^{-4}$); the separate mouse and rat chromosome 18 meta-analyses were similar (Fig. 2*A*); linkage to rodent autoimmunity was replicated in the 70- to 80-cM orthologous region of human chromosome 18q21 (Fig. 2*B*; Table 3, $P = 0.004$; Fig. 3*B*, empirical $P = 0.01$). The GSMA method (Fig. 4) also supported linkage of the 40- to 50-cM portion of rodent chromosome 18 and 70- to 80-cM portion of human chromosome 18, to autoimmunity ($P = 0.03$ and 0.02, respectively). In addition, markers within *DCC* (which maps at 74 cM on human chromosome 18q21) are associated with autoimmune disease (Table 4; $P = 5 \times 10^{-6}$, $P_c = 2.1 \times 10^{-4}$), and there is suggestive evidence for linkage of chromosome 18q21 to type 1 diabetes (Fig. 1; $P = 0.001$).

Several caveats concerning the meta-analyses need to be discussed. Possibly the most significant problem is the methodology used when combining data from heterogeneous sources. For example, the rodent meta-analysis combined data from backcrosses and intercrosses between 17 and 10 independent mouse and rat crosses, respectively. This represents 22 separate strains, with an unknown number and origin of allele(s) at the putative chromosome 18 autoimmunity locus (or loci). Because of this heterogeneity, to obtain an estimate of the true significance of the combined data, it was necessary to combine *P* values by Fisher's method (22), rather than combine raw data. It should be noted that, if possible, it is preferable to combine raw data or parameter estimates; combining *P* values tends to cause more false-positive results and miss more true-positive loci than other approaches (99,100). In addition, we were unable to control for the fact that genome scan data might have higher marker density in regions of interest (for example, *IDDM6* may be considered a region of interest in an autoimmune genome scan), thus biasing the meta-analysis. It is not possible to state whether evidence supporting linkage of chromosome 18 to autoimmunity in the meta-analyses reached either suggestive or significant levels; this would require modeling of the meta-analysis methods presented here, in addition to performing a genome-wide meta-analysis. Our study took into account all genome-wide studies irrespective of the significance of the chromosome 18 linkage data. It does not select positive results, as in the work of Becker et al. (4), and is unlikely to be affected by publication bias of positive results, since the data for chromosome 18 come from whole genome scan studies. We excluded available unpublished data from the following individuals: D. Baker, showing linkage of the 40- to 50-cM region of mouse chromosome 18 to cyclophosphamide-induced diabetes in (ABH × NOD) × NOD (personal communication; $P = 0.0015$); R. Holmdahl, showing linkage to EAE of markers syntenic to the mouse 40- to 50-cM region in a (E3 × DA)F2 rat intercross ($P = 0.02$); J. Otto, showing linkage of proteoglycan-induced arthritis to the mouse 40- to 50-cM region in a (C3H × C57Bl/6)F2 intercross (personal communication; $P = 4 \times 10^{-4}$); and D. Kono and C. Teuscher (personal communication), showing no evidence for linkage of the 40- to 50-cM region of mouse chr 18 to SLE in (BXSB × NZW)F2 ($P = 0.93$) and to EAE in (SJL/J × B10.S)F1 × B10.S ($P = 0.63$), respectively. These unpublished data were excluded from our meta-analysis to remove any bias owing to the possibility of preferentially obtaining positive chromosome 18 data over negative data. If these *P* values were combined (using Fisher's method) with the total *P* values presented in Table 2, and published data not included in the chromosome 18 meta-analysis owing to availability of only some chromosome 18 data (see RESEARCH DESIGN AND METHODS), then *P* for the 40- to 50-cM portion of rodent chromosome 18 would be 7×10^{-13}. Similarly, adding $P = 0.001$ from the partial linkage map of chromosome 18 in human diabetes (Fig. 1), in addition to other partial human chromosome 18 data (85), to the data presented in Table 3 gives $P = 6 \times 10^{-6}$ supporting linkage of the 70- to 80-cM portion of human chromosome 18 to autoimmunity.

Although microsatellites are informative markers for association mapping, their typing in very large data sets is problematic owing to the failure to fully automate allele scoring. Therefore, single nucleotide polymorphisms, because their scoring can be automated in a robust and accurate way, should improve the feasibility of further characterizing the contribution of human chromosome 18 to autoimmune susceptibility. Our results also indicate the importance of animal models in mapping of disease genes. Congenic mapping will allow further investigation of the role of chromosome 18 in rodent autoimmunity.

ACKNOWLEDGMENTS

This work was funded by the Wellcome Trust, the British Diabetic Association, the U.K. Medical Research Council, the Juvenile Diabetes Foundation International (JDFI), the Arthritis Research Campaign, and the New Zealand Health Research Council. We thank the Finnish Childhood Registry Group, the Novo Nordisk Foundation, the Finnish Academy, and National Institutes of Health for their support for the Finnish part of the study. T.R.M. was a JDFI Postdoctoral Fellow and is currently a Wellcome Trust–New Zealand Health Research Council Overseas Postdoctoral Fellow. I.A.E was the recipient of a Wellcome Trust Prize Studentship, and J.A.T. was a Wellcome Trust Principal Research Fellow.

We acknowledge the following people who generously shared their data for this study: Marie-Claude Babron, David Baker, Alan Baxter, Elizabeth Blankenhorn, Jean-Francois Bureau, Russell Butterfield, Judy Cho, Francoise Clerget-Darpoux, Ingrid Dahlman, Dave Dyment, George Ebers, John Harley, Michelle Haywood, Jennifer Kelly, Brian Kotzin, Ed Leiter, Joseph Michalski, John Mordes, Bernie Morley, Jeffrey Otto, Miles Parkes, Luc Reininger, Elaine Remmers, Marie-Paule Roth, Jennifer Salström, Jack Satsangi, Pablo Silveira, Cory Teuscher, Yaron Tomer, Richard Trembath, Colin Veal, and Michael Weil. We also thank all authors who made their entire genome-wide linkage data publicly available, either in the relevant publication or electronically. Helen Yates and the Arthritis Research Campaign Epidemiology Research Unit are thanked for recruiting RA families. Frank Dudbridge is thanked for help in data analysis.

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