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New susceptibility locus for rheumatoid arthritis suggested by a genome-wide linkage study

FRANÇOIS CORNÉLIS*†‡, SABINE FAURÉ†, MARIA MARTINEZ§, JEAN-FRANÇOIS PRUD'HOMME†, PIERRE FRITZ*†, COLETTE DIB†, HELENA ALVES¶, PILAR BARRERA‖, NIEK DE VRIES‖, ALEJANDRO BALSA**, DORA PASCUAL-SALCEDO**, KRISTIN MAENAUT††, RENÉ WESTHOVENS††, PAOLA MIGLIORINI‡‡, TUYET-HOA TRAN*, ARNAUD DELAYE*, NATHALIE PRINCE*, CAROLINE LEFEVRE*, GAËLLE THOMAS†, MURIELLE POIRIER†, STÉPHANE SOUBIGOU†, OLIVIER ALIBERT†, SANDRA LASBLEIZ†, SYLVAINE FOUIX†, CHRISTIANE BOUCHIER†, FRÉDÉRIC LIOTÉ*, MARIE-NOËLLE LOSTE§§, VIRGINIA LEPAGE§§, DOMINIQUE CHARRON§§, GABOR GYAPAY†, ANTONIO LOPES-VAZ¶, DANIEL KUNTZ*, THOMAS BARDIN*, AND JEAN WEISSENBACH†¶¶ FOR ECRAF

*Pôle Génétique des Maladies Auto-immunes, Laboratoire de Radiologie Expérimentale et de Physiopathologie Articulaire, Centre Viggo-Petersen, Hôpital Lariboisière, 75010 Paris, France; †Généthon-Centre National de la Recherche Scientifique Unité de Recherche Associée 1922, 91002 Evry, France; §Institut National de la Santé et de la Recherche Médicale U358, and §§Laboratoire d'Histocompatibilité, Hôpital Saint-Louis, 75010 Paris, France; ¶Hospital S Joao, 4200 Porto, Portugal; ‖Department of Rheumatology, NL6500 HB, Nijmegen, The Netherlands; **Hospital La Paz, 28046 Madrid, Spain; ††Katholieke Universiteit Leuven, 3212 Pellenberg, Belgium; ‡‡Instito Patologia Medica-56126 Pisa, Italy; and ¶¶ECRAF (The European Consortium on Rheumatoid Arthritis Families), which includes: T.B., D.C., F.C. (coordinator), S.F., D.K., M.M., J.F.P., J.W. (France); R.W., J. Dequeker (Belgium); A.B., D.P.-S. (Spain); M. Spyropoulou, C. Stavropoulos (Greece); P.M., S. Bombardieri (Italy); P.B., L. Van de Putte (The Netherlands); and H.A., A.L.-V. (Portugal)

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ABSTRACT **Rheumatoid arthritis (RA), the most common autoimmune disease, is associated in families with other autoimmune diseases, including insulin-dependent diabetes mellitus (IDDM). Its genetic component has been suggested by familial aggregation ($\lambda s = 5$), twin studies, and segregation analysis. *HLA*, which is the only susceptibility locus known, has been estimated to account for one-third of this component. The aim of this paper was to identify new RA loci. A genome scan was performed with 114 European Caucasian RA sib pairs from 97 nuclear families. Linkage was significant only for *HLA* ($P < 2.5 \cdot 10^{-5}$) and nominal for 19 markers in 14 other regions ($P < 0.05$). Four of the loci implicated in IDDM potentially overlap with these regions: the putative *IDDM6, IDDM9, IDDM13*, and *DXS998* loci. The first two of these candidate regions, defined in the RA genome scan by the markers *D18S68-D18S61-D18S469* (18q22–23) and *D3S1267* (3q13), respectively, were studied in 194 additional RA sib pairs from 164 nuclear families. Support for linkage to chromosome 3 only was extended significantly ($P = 0.002$). The analysis of all 261 families provided a linkage evidence of $P = 0.001$ and suggested an interaction between this putative RA locus and *HLA*. This locus could account for 16% of the genetic component of RA. Candidate genes include those coding for CD80 and CD86, molecules involved in antigen-specific T cell recognition. In conclusion, this first genome scan in RA Caucasian families revealed 14 candidate regions, one of which was supported further by the study of a second set of families.**

Rheumatoid arthritis (RA), a chronic disease that leads to progressive joint destruction (1), is associated with other autoimmune diseases in families, such as thyroid diseases and insulin-dependent diabetes mellitus (IDDM) (2, 3). RA preferentially affects women (1), with a sex ratio of 2 to 4. Its mean age of onset is between 45 and 50 years of age, and its prevalence may be as high as 1% in adults (1). RA is believed to be a multifactorial disease resulting from a T cell-driven autoimmune process aimed primarily at the joints; its pathophysiology is unknown (4). Its genetic component has been suggested by familial aggregation (RA prevalence ratio of sibs to the general population: $\lambda s = 5$) (2, 5), twin studies (6–8), and segregation analysis (9). *HLA*, which is the only susceptibility locus known (10, 11), has been estimated to account for one-third of this component ($\lambda_{HLA}=1.8$) (12, 13). To identify new RA susceptibility loci, ECRAF (the European Consortium on Rheumatoid Arthritis Families) collected affected sib pair families for analysis by genome scanning, followed by further testing of suggested loci.

MATERIALS AND METHODS

Ascertainment of Families. Families were recruited through the two RA siblings and then extended to parents and eventually other siblings when one or two parents were unavailable, which is often the case in this disease of relatively late onset. Potential families either were identified by clinicians (all countries) or were self-reported after media announcements (France, Italy, Spain, and Belgium). At least two siblings in each family met the 1987 American College of Rheumatology criteria for RA (14), as reported by one of the rheumatologists participating in this study (The Netherlands and Belgium) or the clinician in charge of the patient (other countries) who completed a standardized questionnaire.

Genotyping. DNA was extracted from whole blood by standard methods in the various centers and used at Généthon for genotyping of microsatellite markers with the fluorescence-based technology on *ABI373* automatic sequencers (15), using the programs GENESCAN ANALYSIS 2.0.0 and GENOTYPER 1.1. The list of markers (with a mean heterozygosity of 77%) is available on request. The software interpretation of each allelic profile was checked by two different individuals before verification of Mendelian segregation. Any discrepancy was resolved by S.F. or C.D., or the data were excluded for the analysis. Three families from the first group of 100 families were excluded for non-Mendelian segregation, as was one unaffected sib from the additional 164 families. Molecular

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Abbreviations: IDDM, insulin-dependent diabetes mellitus; IBD, identity by descent; IBS, identity by state.

‡To whom reprint requests should be addressed at: Pôle Génétique des Maladies Auto-immunes, Centre Viggo-Petersen, 6 rue Patin, 75010, Paris, France. e-mail: francois.cornelis@lrb.ap-hop-paris.fr.

Table 1. Rheumatoid arthritis-affected sib-pair families

Families	Genome scan	Second set	Total
Two RA sibs	90	152	242
Three RA sibs	6	10	16
Four RA sibs	1	2	3
Total number of families	97	164	261
Families with parent(s) available	42	24	66
Individuals genotyped	460	561	1,021
Total number of sib pairs	114	194	308

These European Caucasian families were from France (all families in the genome scan and 88 in the second set), Italy (23 families), The Netherlands (22 families), Spain (12 families), Belgium (11 families), and Portugal (8 families). In most families, unaffected sibs were included to help deduction of parental genotypes because one or both parents were unavailable for genotyping.

HLA-DRB1 genotyping was performed with the Inolipa kit (Murex, Chatillon, France).

Analytical Methods. Affected sib pair analysis was conducted for the bipoint linkage analysis (one marker locus and the disease locus) with J. Terwilliger's ANALYZE package, using the program SIBPALNA 1.1 for autosomes and SIBPAIR 2.1 for the X chromosome. For the few families with multiple affected "sibships," we used all-possible pairs as if they were independent. The use of all-possible pairs has little effect on the *P* values under H0 (null hypothesis: no linkage) when the majority of the sample is independent sib pairs (16). Allele frequencies were estimated from the data with ILINK of the LINKAGE package (17). Multipoint linkage analysis (several marker loci and the disease locus) was performed with the program GENEHUNTER 1.1 (ref. 18).

HLA partition was done according to the identity by state (IBS) of genotypes available for 3 *HLA* markers (*TNFa*, *D6S276*, and *HLA-DRB1* typing), as an approximation of identity by descent (IBD), because most parents were unavailable for genotyping; *HLA*-concordant applies to the pairs with complete IBS, and *HLA*-discordant applies to the remaining pairs (only the first affected pair of each family was used in the analysis). Homogeneity between subsamples was tested by using a $\chi 2$ comparing the numbers of shared and unshared IBD alleles.

The parameter λ for a susceptibility locus M is defined as the ratio of the expected proportion of sib pairs sharing no alleles IBD (25%) to the observed proportion among affected sib pairs. For the markers with the best linkage evidence, this observed proportion was estimated with the program SIBPALNA. The relative contribution of locus M was computed assuming a multiplicative model for the interaction between M and other susceptibility loci ($\log\lambda_M/\log\lambda_s$) (19). From our data, the relative contribution of *HLA* and the chromosome 3 region (3.1) can be estimated to be 33% and 16%, respectively, using $\lambda_s = 5$ (ref. 1), $\lambda_{HLA} = 1.7$ (for *TNFa*), and $\lambda_{3.1} = 1.3$ (for *D3S3576*).

Table 2. Evidence for linkage ($P < 0.05$) from the RA genome scan performed with 309 markers outside of the *HLA* region

D number	AFM*	Position	Region	S	NS	*P*	pM
D1S228	196xb4	32.4	1.1/1p36-pter	89.5	56.8	0.0035	0.0065
D1S238	205xg1	206.7	1.2/1q31-32	94.2	68.5	0.022	0.099
D2S380	321xd9	88.0	2.1/2p13-pter	102.1	78.7	0.041	0.010
D2S377	319zf9	228.2	2.2/2q33-37	84.9	61.0	0.024	0.013
D2S2354	a046we1	235.0	2.2	91.1	58.9	0.0043	0.0054
D3S1267	116xh2	141.1	3.1/3q13	96.1	63.4	0.032	0.039
D3S1262	059xa9	207.2	3.2/3q27	97.0	75.0	0.046	0.11
D5S422	211yc7	163.9	5.1/5q32-33	99.5	75.2	0.033	0.045
D6S292	203za9	138.2	6.1/6q21-23	89.0	66.7	0.036	0.034
D8S1825	a055zg1	14.9	8.1/8p23-pter	89.0	67.1	0.040	0.10
D12S99	217xa7	13.9	12.1/12p13-pter	66.5	41.4	0.0077	0.083
D12S95	207ve1	97.7	12.2/12p13-q24	67.4	41.6	0.0067	0.043
D13S170	240wh2	65.4	13.1/13q31	92.9	70.4	0.039	0.015
D13S1315	a058xd5	105.2	13.2/13q32-qter	110.4	65.4	0.00035	0.0037
D14S285	319vf5	50.0	14.1/14q13-23	57.5	41.1	0.049	0.33
D16S420	238xb2	43.2	16.1/16p12	70.2	51.8	0.047	0.039
D16S401	025tg9	45.5	16.1	56.9	34.0	0.0080	0.028
D16S516	350vd1	98.3	16.2/16q24	75.7	55.4	0.038	0.11
D16S511	312xd1	108.4	16.2	108.6	85.6	0.049	0.11
D18S57	147yg7	63.2	18.1/18q12	101.2	73.5	0.018	0.033
D18S474	295xh1	71.3	18.1	84.5	63.0	0.038	0.012
D18S68	248yb9	94.4	18.2/18q22-23	97.1	72.9	0.032	0.020
D18S61	193yf8	102.8	18.2	108.6	69.3	0.0016	0.0098
D18S469	116yg11	109.0	18.2	79.7	50.6	0.0055	0.020
D20S864	a343xc9	0.0	20.1/20pter	63.7	44.2	0.030	0.11
D21S270	031xc5	41.3	21.1/21q22-qter	97.0	73.7	0.038	0.11
D21S268	260ze9	44.3	21.1	96.4	71.0	0.025	0.13
D22S264	—	0–9	22.1/22q11	74.6	51.4	0.019	0.0098
DXS1068	238yo11	56.2	X.1/Xp11-21	34.8	21.9	0.044	0.27
DXS998	224zg11	183.8	X.2/Xq27	35.3	17.7	0.0078	0.019

Position on the chromosome is provided in cM from the telomere of the short arm, based on the Généthon linkage map (20). Candidate regions are numbered consecutively for each chromosome. Clusters of markers adjacent in the scan are assigned to a single region. The number of alleles IBD in affected sib pairs reported for each marker and the associated *P* value are calculated by the program SIBPALNA (S for shared, NS for not shared). The *P* value calculated by the multipoint analysis program GENEHUNTER (pM) is provided. The raw data for the genome scan are available on Généthon's web site.

*Ref. 20.

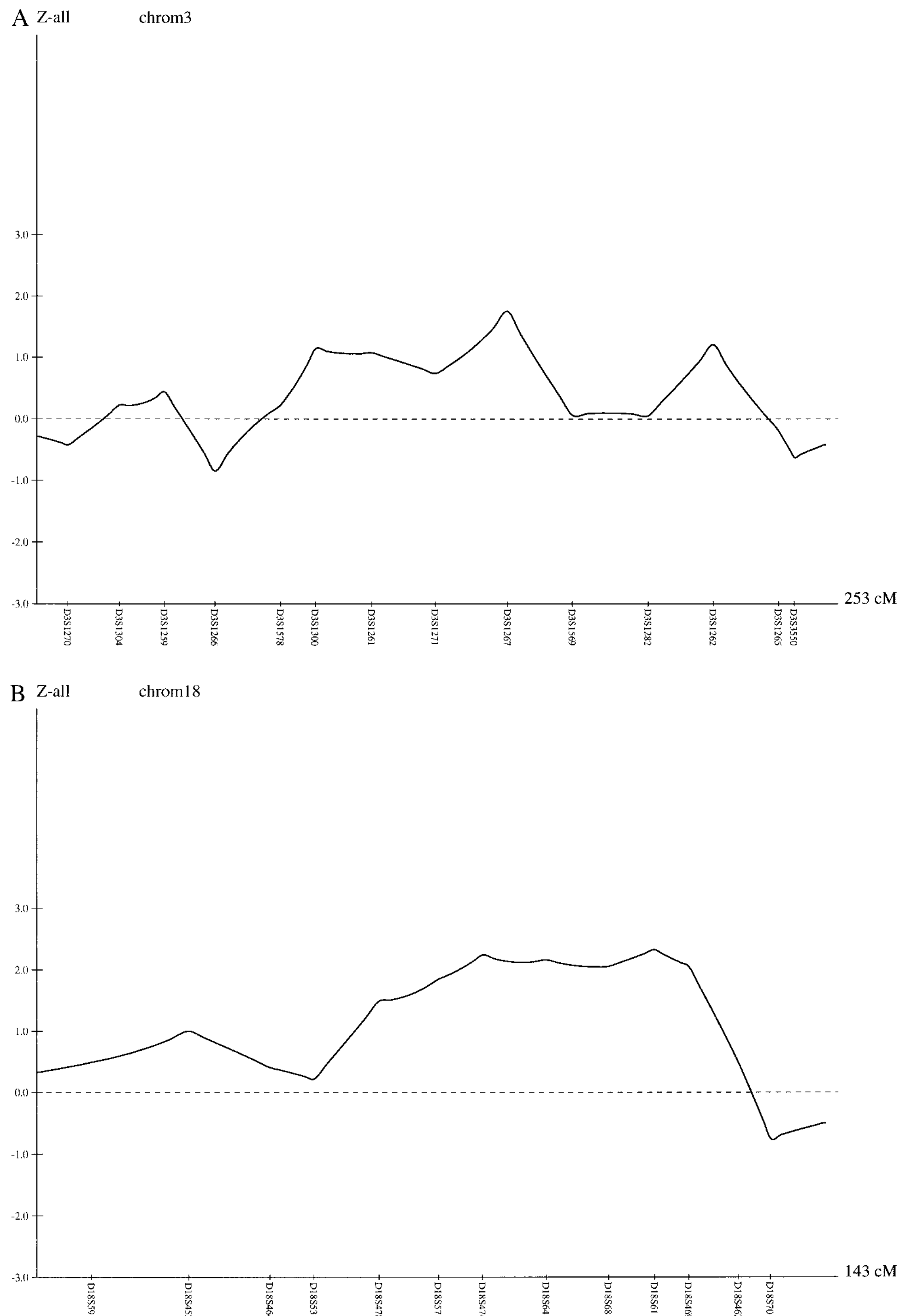

FIG. 1. Multipoint analysis of the chromosomes 3 and 18 scan. The genetic map is plotted on the *x* axis, and the likelihood ratio score calculated by the GENEHUNTER program is plotted on the *y* axis. The associated linkage *P* value is reported for the most linked markers in Table 2. The figures for other chromosomes are available on request.

RESULTS

A genome scan was performed outside of the *HLA* region with 114 sib pairs from 97 nuclear families (Table 1) with a mean spacing of 12 cM, using 309 microsatellite markers. In the *HLA* region, 17 markers spanning a 43-cM interval (*D6S443–D6S282*) were used. Linkage to *HLA* was significant ($P = 2.0 \times 10^{-5}$ for the *TNFa* microsatellite marker). Evidence for linkage to *HLA* ($P < 0.05$) was observed in a region spanning 31 cM, illustrating the power of the 12-cM scan. Outside of the *HLA* region, using bipoint linkage analysis, 30 markers showed nominal evidence of linkage to RA ($P < 0.05$), defining 23 candidate regions (Table 2).[a] A second analysis of the results was performed with a multipoint analysis program (Fig. 1). This showed similar trends, but nominal evidence was obtained for only 19 of 30 markers (Table 2). No additional regions were

[a]The candidate regions 3.1, 1.1, and X.2 (Table 2) were referred to as *RA2, RA3*, *and RA4* loci (retaining *RA1* for the *HLA* locus) at the American Society of Human Genetics, the American College of Rheumatology, and the Société Française de Rhumatologie 1997 meetings. However, these names, even if provisional, could be confusing, as none of these loci has been definitively linked to RA susceptibility.

Table 3. Evidence for linkage to chromosome 18 region 18.2 and chromosome 3 region 3.1 (Table 2) in genome scan families

Locus	Marker	cM	S	NS	IBD	*P*
Chromosome 18 region 18.2						
D18S64	212xg5a	12	67.4	58.6	53%	0.22
D18S68	248yb9	5	97.1	72.9	57%	0.03
D18S465	260yh1	5	92.6	49.1	65%	0.00013
D18S61	193yf8	2	108.6	69.3	61%	0.0016
D18S1125	b304yb9	1	84.3	64.4	57%	0.051
D18S485	330yd9	4	89.6	63.4	59%	0.017
D18S469	116Yg11	1	79.7	50.6	61%	0.0055
D18S486	333wd5	3	47.8	26	65%	0.0057
D18S1161	a085y1	2	82.9	63.9	56%	0.058
D18S1009	a037zc9	3	72.2	64.2	53%	0.25
D18S1115	b01xf5	1	44.7	35.3	56%	0.15
D18S554	296wd5	1	84.2	68.8	55%	0.11
D18S462	079xb3	—	74.2	69.2	52%	0.34
Chromosome 3 region 3.1						
D3S1303	225yd6	1	89.7	71.5	56%	0.076
D3S3513	217xb4	1	88.5	83.7	51%	0.356
D3S3576	a210ye9	1	78.6	61.9	56%	0.079
D3S1267	116xh2	0	86.1	63.4	58%	0.032
D3S3720	a072ya5	3	96.8	73.1	57%	0.035
D3S1589	290zf1	—	80.7	64.4	56%	0.089

Genetic distances to the next locus (in cM) are based on the Genethon linkage map (20). The number of alleles IBD in affected sib pairs and the associated *P* value are calculated by the program SIBPALNA (S for shared, NS for not shared).

suggested by the multipoint analysis. Altogether, 14 regions showed consistent nominal evidence of linkage. Four of the loci implicated in IDDM (21–25) potentially overlap with these regions: the putative *IDDM6, IDDM9, IDDM13,* and *DXS998* loci with the regions 18.2, 3.1, 2.2, and X.2 defined by the markers *D18S68-D18S61-D18S469, D3S1267, D2S377-D2S2354, DXS1068,* and *DXS998*, respectively (Table 2).

The first two regions (18.2 and 3.1) on chromosome 18q22–23 and chromosome 3q13 (Fig. 1) were studied further. Additional markers in both regions were analyzed in the same families, which increased the evidence for linkage only for the 18.2 region ($P = 10^{-4}$) (Table 3). Markers from both regions then were studied in 194 new sib pairs from 164 nuclear families (Table 1). A small excess of allele sharing was observed in the chromosome 18 region, which did not reach significance ($P = 0.08$) (Table 4). Evidence for RA linkage to the chromosome 3 region was found ($P = 0.002$), providing strong support for a new RA locus, although the overall evidence from all families was only suggestive [$P = 0.001$, Table 4, the proposed threshold for significance (26) is 2.5×10^{-5}]. Multipoint analysis was consistent with these results (Table 5).

To search for possible interactions with the *HLA* locus, an analysis of all families was then performed after partition for *HLA* (see *Materials and Methods*). The results revealed a higher evidence for linkage in the *HLA*-concordant RA sib pairs for the chromosome 3 region ($P = 0.001$) compared with the remaining RA pairs ($P = 0.08$) (Table 4). No consistent trend was observed in the chromosome 18 region (Table 4).

We believe that our data support RA linkage to chromosome 3, but not chromosome 18, placing more emphasis on consistency than on *P* value. We hypothesize that RA and IDDM could share a putative chromosome 3 autoimmunity factor. However, definitive proof must await further evidence for linkage or discovery of the underlying genetic factor. Interestingly, obvious candidate genes are located in this region. They code for the antigen-presenting cell molecules CD80 and CD86, which interact with T cell molecules CTLA-4 and CD28 in the costimulatory pathway that determines the

Table 4. Study of a second set of families for chromosome 18 and 3 regions (18.2 and 3.1, Table 2) and search for interaction with *HLA*

Locus	cM	Families	S	NS	IBD	*P*
Chromosome 18 region 18.2						
D18S465	5	Second set	152.9	133.2	53%	0.12
		Total	245.8	182.3	57%	0.0011
		HLA concordant	99.3	54.5	64%	0.00015
		HLA discordant	146.6	127.8	53%	0.13
D18S61	7	Second set	153.8	145.4	51%	0.31
		Total	260.4	214.6	55%	0.018
		HLA concordant	102.8	77.9	57%	0.032
		HLA discordant	157.6	136.7	54%	0.11
D18S469	1	Second set	109.8	93.6	54%	0.13
		Total	187.2	144.3	56%	0.0091
		HLA concordant	76.4	58.0	57%	0.057
		HLA discordant	110.8	86.2	56%	0.040
D18S486	—	Second set	67.2	52.0	56%	0.081
		Total	117.0	77.1	60%	0.0021
		HLA concordant	47.1	33.3	58%	0.061
		HLA discordant	69.7	43.8	61%	0.0075
Chromosome 3 region 3.1						
D3S3576	1	Second set	155.9	108.4	59%	0.0018
		Total	236.5	174.3	58%	0.0011
		HLA concordant	103.6	63.7	62%	0.0010
		HLA discordant	132.9	110.6	55%	0.077
D3S1267	<1	Second set	156.7	127.5	55%	0.042
		Total	254.6	196.9	56%	0.0034
		HLA concordant	107.0	78.2	58%	0.017
		HLA discordant	147.6	118.7	55%	0.039
D3S3720	—	Second set	156.4	134.1	54%	0.095
		Total	253.4	209.2	55%	0.020
		HLA concordant	104.8	73.9	59%	0.010
		HLA discordant	148.6	135.3	52%	0.21

Loci studied in the second set of families are shown, followed by genetic distance to the next locus (based on the Genethon linkage map), families used for the analysis [second set, total, *HLA* concordant (96 families) or discordant (165 families)], number of alleles identical by descent shared (S) or not shared (NS) by affected sib pairs calculated by the programs SIBPALNA, the percentage of shared alleles (IBD), and the associated *P* value.

fate of T cells (27). A model involving this pathway has been proposed recently for RA, IDDM, and other autoimmune diseases (28).

The initial evidence for the chromosome 18 locus was either spurious, or was a chance finding that revealed a minor RA locus. Indeed, the recent refinement of the *IDDM6* locus (just centromeric to the 18.2 region) at the level of allelic association will permit testing the implication of this locus in RA (29).

From our data, the relative contribution of *HLA* and the chromosome 3 region (3.1) can be estimated to be 33% and 16%, respectively (see *Materials and Methods*). To search for the remaining factor(s), the other candidate regions (Table 2) deserve high priority. Confirmation of some of these regions would rely on further testing in additional families. While this paper was under revision, two of the regions reported here on chromosome 1 and chromosome X (regions 1.1 and X.2, Table 2) were implicated in Japanese RA families (30).

Conclusion. We reported a genome scan in Caucasian RA families. It showed similarities with the associated autoimmune disease, IDDM (21, 22), with no other locus than *HLA* showing significant linkage, but 14 regions with nominal evidence. Additional study for one of these candidate regions on chromosome 3 provided further support for a new RA locus.

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Table 5. Multipoint affected sib-pair analysis

Marker	cM	97 families	164 families	261 families
		Chromosome 18 region		
D18S465	0	0.000309	0.157416	0.001211
	1	0.000706	0.159597	0.001917
	2.01	0.00143	0.161912	0.00282
	3.01	0.002506	0.163662	0.003871
	4.01	0.004016	0.164866	0.004996
D18S61	5.02	0.005777	0.165538	0.006086
	6.43	0.006143	0.1673	0.005682
	7.84	0.006419	0.169388	0.005249
	9.24	0.006677	0.170971	0.004785
	10.65	0.006812	0.172235	0.004304
D18S469	12.06	0.006822	0.173587	0.003821
	12.26	0.006404	0.174271	0.003875
	12.46	0.00601	0.175646	0.003929
	12.66	0.005631	0.176608	0.003983
	12.86	0.005276	0.177066	0.004033
D18S486	13.06	0.004937	0.178374	0.004086
		Chromosome 3 region		
D3S3576	0	0.06831	0.009921	0.001724
	0.5	0.05661	0.011876	0.001646
	1	0.045512	0.014072	0.001535
	1.5	0.035642	0.016656	0.001402
D3S1267	2	0.027129	0.019497	0.001258
	2.5	0.035701	0.026592	0.001804
D3S3720	3	0.046432	0.035497	0.002528

Genetic distances between markers were estimated from the data and the *P* values calculated by the program GENEHUNTER 1.0.

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