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A Genomewide Search for Quantitative-Trait Loci Underlying Asthma

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A genomewide screen for quantitative-trait loci (QTLs) that underlie asthma was performed on 533 Chinese families with asthma, by the unified Haseman-Elston method. Nine asthma-related phenotypes were studied, including forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), airway responsiveness as indicated by methacholine (MTCH)-challenge test, serum total immunoglobulin E (TIgE), serum-specific immunoglobulin E, eosinophil count in peripheral blood, and skin-prick tests with three different allergens (cockroach, *Dermatophagoides pteronyssinus,* and *D. farinae*). Our study showed significant linkage between airway responsiveness to MTCH and D2S1780 on chromosome 2 ($P < .00002$) and provided suggestive evidence ($P < .002$) for six additional possible QTLs: D10S1435 and D22S685, for FEV_1; D16S412, for FVC; D19S433, for airway responsiveness to MTCH; D1S518, for TIgE; and D4S1647, for skin reactivity to cockroach. No significant or suggestive evidence of linkage for the other four traits was found.

Introduction

Asthma (MIM 600807) is a common clinical syndrome of reversible-airflow obstruction, characterized by airway hyperresponsiveness, airway inflammation, epithelial damage, and airway smooth-muscle hypertrophy (Sheffer 1995). Susceptibility to asthma is determined by the interaction of an unknown number of genetic and environmental factors. The genetics of asthma has been the subject of several recent reviews (see Holloway et al. 1999; Cookson and Moffatt 2000; Palmer and Cookson 2000). Linkage analysis plays a pivotal role in the search for genes underlying asthma. Although clinical definitions play an important role in the diagnosis and treatment of asthma, it is quite conceivable that the best clinical definition does not coincide with the best definition for the mapping of genes that contribute to asthma. In comparison, intermediate phenotypes, in many cases, are quantitative, more reliable, and of less genetic heterogeneity, conferring better power in linkage studies. On the basis of the definition of asthma, the asthma-related intermediate phenotypes can be broadly divided into two groups: the first group is related to lung function, including forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and airway responsiveness to bronchorestrictors and to bronchodilators; the second group is related to inflammation and allergy, including serum total and serum-specific immunoglobulin E (TIgE and SIgE, respectively), skin-prick tests to aeroallergens, and peripheral-blood–eosinophil (EOS) count.

Previous genomewide linkage studies suggested that several loci are probably linked to asthma or to related phenotypes, although few linkages reached the stringent genomewide significance level (Daniels et al. 1996; the Collaborative Study on the Genetics of Asthma 1997; Ober et al. 1998, 2000; Wjst et al. 1999; Dizier et al. 2000; Yokouchi et al. 2000; Mathias et al. 2001). Furthermore, considerable inconsistency was observed among the previously published results, reflecting the complexity of asthma and, owing to relatively small sample sizes, the lack of power. In this study, we screened 2,551 subjects from 533 Chinese families with asthma, searching for loci linked to asthma-related intermediate phenotypes. To our knowledge, this is, thus far, the largest published whole-genome linkage study on asthma-related phenotypes.

Subjects and Methods

Study Samples

This study was conducted, in collaboration with Anhui Medical University and Anqing Health Bureau, in Anqing, China. The geographic characteristics of the Anqing population, as well as the procedure for ascer-

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taining the study samples, have been described elsewhere (Xu et al. 1999*a*). In brief, by screening the Anqing population, we ascertained 2,752 index families with asthma, with the following criteria: (1) presence of at least two siblings with physician-diagnosed asthma who were ⩾8 years old, (2) availability of both parents, and (3) history of asthma in no more than one parent. In addition, we ascertained, from the same population, 270 reference families who were selected from 1992 census records by a two-stage random-sampling technique, in which the village was the first-stage sampling unit and the household was the second-stage sampling unit. Our inclusion criteria for reference families were (1) family size of at least four, (2) availability of both parents, and (3) presence of at least two siblings who were ⩾8 years old. We used the reference families for assessing the effects that common covariates (e.g., age, gender, etc.) had on each asthma-related phenotype. A multiple linear-regression model developed on the basis of the reference families was then used, prior to linkage analysis, to adjust phenotypic values in the families with asthma for fixed effects of these covariates. From the 2,752 index families, we selected 533 for genomewide-linkage study. This study has been approved by the Human Subject Committees at Brigham and Women's Hospital and at the Harvard School of Public Health. Each enrolled subject or, in the case of children, the subject's parent or guardian has signed an informed-consent form.

Evaluation of Phenotypes

The following procedures were performed on the basis of protocols that are in accordance with those used in the National Institutes of Health Collaborative Study on the Genetics of Asthma (CSGA).

Questionnaire administration.—A modified American Thoracic Society (ATS) Division of Lung Disease questionnaire was administered specifically to assess respiratory history and symptoms, occupational and smoking histories, home environment, and family history of asthma or other chronic diseases. The questionnaire was divided into two forms—one for adults (aged >14 years) and one, to be completed by parents, for children (aged ⩽14 years).

Pulmonary-function tests.—Standardized spirometry was performed on ATS "Snowbird Guideline"–approved equipment (Schiller). Each subject was seated, with nose clip, and performed five to eight maneuvers, to obtain three acceptable tracings. For both FEV_1 and FVC, the maximum of the three accepted measurements was believed to be more reproducible than the means (Tager et al. 1976) and was used as a quantitative phenotype in our subsequent analyses.

Airway methacholine (MTCH)-challenge test.—MTCH-challenge test was performed for all subjects with FEV_1 >60% of the predicted value, by a modified Chatham protocol (Chatham et al. 1982). In brief, each subject was challenged with the following five combinations of number of breaths and MTCH concentrations, in sequential order: one breath of 1 mg/ml, one breath of 5 mg/ml, four breaths of 5 mg/ml, one breath of 25 mg/ml, and four breaths of 25 mg/ml. At each dose, two satisfactory spirometry maneuvers were obtained. Again, the greater of the two measurements was used in analyses. The test terminated either at the dose that produced a ⩾20% FEV_1 drop (PD_{20}) from the baseline FEV_1 or at the final dose. The individual airway responsiveness to MTCH was measured in dose-response–slope percentage (DRSP) defined as $(FEV_1^b - FEV_1^t)/(FEV_1^b \cdot [MTCH]_t)$, where FEV_1^b is the baseline FEV_1, FEV_1^t is FEV_1 at the terminating dose of MTCH test, and $[MTCH]_t$ is the cumulative dosage of MTCH inhaled during the test. The $\log_{10}$ transformation of DRSP, logDRSP, was approximately normally distributed in the general population and was used in our subsequent linkage analysis. For a small number of subjects, whose FEV_1 did not drop during the test, logDRSP values were fixed at -4.5.

Skin-prick test.—Skin-prick test was performed by a slightly modified semiquantitative puncture method developed by Santilli et al. (1980). In addition to histamine and saline controls, the following antigens were applied to the forearm of each subject: cockroach, *Dermatophagoides pteronyssinus, D. farinae,* house dust, mixed trees, mixed grass, tobacco leaf, polyvalent molds, artemisia, and silk. The diameters of the wheals were recorded; any subject with either a >2-mm wheal in response to the saline control or a <2-mm wheal in response to the histamine control was excluded from analyses. Of the 10 allergens tested in the population that we studied, cockroach, *D. pteronyssinus,* and *D. farinae* caused large wheals much more frequently than did the other 7 allergens. The population mean of the diameters of the wheals was >1.1 mm for cockroach, *D. pteronyssinus,* and *D. farinae* but <0.4 mm for the other allergens. For this reason, only skin reactions to cockroach, to *D. pteronyssinus,* and to *D. farinae* were selected for subsequent linkage analysis.

Measurement of serum immunoglobulin E levels.—TIgE levels were measured using a UniCAP system (Pharmacia Diagnostics). SIgE levels were determined using the Phadiatop kit (Pharmacia Diagnostics). The $\log_{10}$ transformation of TIgE, logTIgE, was approximately normally distributed in the general population and was used in our subsequent linkage analysis.

EOS count.—EOS count was performed by use of a Coulter counter. The $\log_{10}$ transformation of EOS, logEOS, was approximately normally distributed in the general population and was used in our subsequent linkage analysis.

Family Selection for Genome Scan and Genotyping

Of the 2,752 enrolled families, 533 were selected for the genome scan; of these, 471 had at least two siblings with a PD_{20} and 52 had one sibling with a PD_{20}. The scan covered 22 autosomal chromosomes with 422 highly polymorphic microsatellite markers, with an average spacing of 7–8 cM. In brief, genomic DNA was extracted from whole blood by use of a commercially available kit (Gentra Systems). The genotyping was performed, by a fluorescent-based detection method, at Millennium Pharmaceuticals, by use of ABI377XL automated sequencers (Perkin-Elmer). Each genotype was double scored—that is, scored once by an expert technician (i.e., a human scorer) and once by a proprietary software package. Incongruities between the two scores were resolved by the human scorer. Marker data for each pedigree were checked for Mendelian inheritance. Raw data for all observed deviations were reevaluated. Genotyping errors resulting in rare double recombination were cleaned up by the `sib_clean` program included in the ASPEX package (Schwab et al. 1995). The chromosomal orders and the intervals of markers were obtained from Weber's linkage map (Center for Medical Genetics, Marshfield Medical Research Foundation) and were fine-tuned by the `sib_map` program included in the ASPEX package.

Linkage Analysis

The phenotypes tested for linkage included FEV_1, FVC, logDRSP, logTIgE, SIgE, logEOS, and wheal size in skin-prick test with three allergens (i.e., cockroach, *D. pteronyssinus*, and *D. farinae*). All the phenotypes were quantitative, with the exception of SIgE, which was treated as pseudoquantitative with values 0 and 1. Effects that factors such as age, gender, height, weight, and pack-years of smoking had on each phenotype were examined in a collection of 270 reference families who were randomly selected from the same community as were the families with asthma. In the reference population, the five aforementioned factors accounted for ~75% of the variance in FEV_1 and FVC but accounted for only ⩽5% of the variance in the other seven traits. For both FEV_1 and FVC, a trait-prediction model was constructed by multiple linear regression, by use of the observations from the reference families, to adjust for the aforementioned covariates. The standardized residuals of FEV_1 and FVC were then computed on the basis of data on the members of the families with asthma and were used in subsequent linkage analyses. The other seven traits were standardized using the mean and variance of the reference population prior to linkage analysis. The identical-by-descend (IBD) probabilities between a sib pair, at any arbitrary chromosomal location, were estimated by GENEHUNTER version 2 (Kruglyak et al. 1996). Linkages to the asthma intermediate phenotypes were then analyzed by a unified Haseman-Elston (HE) method, by the computer program XWXW (Xu et al. 2000). The information content (I_c) of IBD estimates varies according to marker heterozygosity, marker density, and family structure. For any IBD distribution in which z_0, z_1, and z_2 are the probabilities of sharing 0, 1, and 2 alleles IBD, respectively, the portion of IBD sharing has an expected value $\hat{\pi} = (z_1/2) + z_2$ and a variance $\text{var}(\hat{\pi}) = \Sigma_{i=0}^{2} z_i[(i/2) - \hat{\pi}]^2$. The variance is 0 when a marker is fully informative and is .125 under the null distribution (no marker genotype is available). The I_c value for an estimate of IBD distribution was defined as $I_c = 1 - \text{var}(\hat{\pi})/.125$. I_c takes the maximum value of 1 when an IBD estimate is unambiguous, and is 0 when no marker data are available. In our linkage analysis, we used sib-pair observations only when the I_c values of IBD estimates were ⩾.1.

Results

Our genome scan included 2,551 subjects from 533 families with asthma, from Anqing, China. Of the 533 families with asthma, only 15 are nonnuclear families who include either three generations or two marriages by one person (table 1). The phenotypic characteristics of these families with asthma, as well as of the reference families included in the construction of models for the prediction of phenotypic traits, are summarized in table 2. The distributions of the standardized traits in the nonfounders of the scanned families are depicted in figure 1.

Our linkage analysis suggested seven quantitative-trait loci (QTLs) ($P < .002$) for FEV_1, FVC, logDRSP, logTIgE, and skin reactivity to cockroach but did not suggest any QTLs for logEOS, SIgE, and skin reactivity to *D. pteronyssinus* and to *D. farinae*. The suggestive QTLs are as follows: D10S1435 and D22S685, at chromosomes 10 and 22, respectively, for FEV_1; D16S412, at chromosome 16, for FVC; D2S1780 and D19S433, at chromosomes 2 and 19, respectively, for logDRSP;

Table 1

Structure of 533 Genome-Scanned Families

Category	No.
Nuclear family:	
2 sibs	241
3 sibs	177
4 sibs	66
5 sibs	16
6 sibs	13
7 sibs	1
8 sibs	2
9 sibs	2
Nonnuclear family	15
Total	533

Table 2

Phenotypic Characteristics of Genome-Scanned and Reference Families

Variables	Mean ± SD [Total No.]	
	Asthma Index Family	Random Control Family
Sex (% male)	48.8 [2,551]	50.6 [1,021]
Age (years)	30.7 ± 16.4 [2,549]	30.3 ± 15.5 [1,021]
Height (m)	1.52 ± .15 [2,547]	1.54 ± .13 [1,021]
Weight (kg)	47.0 ± 13.4 [2,547]	48.0 ± 12.4 [1,021]
BMI (kg/m^2)	19.8 ± 3.20 [2,547]	19.8 ± 3.07 [1,021]
Asthma[a] (% replying yes)	25.7 [2,542]	2.75 [1,018]
FEV_1 (liters)	2.55 ± .90 [2,510]	2.83 ± .79 [960]
logDRSP (%/mg)	−2.10 ± .86 [2,229]	−2.70 ± .73 [922]
logEOS ($cells/mm^3$)	2.02 ± .49 [2,542]	1.99 ± .46 [1,020]
logTIgE (IU)	2.16 ± .68 [2,488]	1.96 ± .72 [236]
SIgE (% positive)	44.7 [2,501]	36.7 [237]
Skin reactivity (mm) to:		
Cockroach	1.67 ± 2.15 [2,099]	1.67 ± 2.02 [1,021]
D. pteronyssinus	1.74 ± 2.33 [2,099]	1.71 ± 2.06 [1,021]
D. farinae	1.09 ± 1.82 [2,099]	1.31 ± 1.83 [1,021]

[a] Asthma was defined as a yes in reply to both "Have you ever had asthma?" and "Was the asthma diagnosed by a physician?"

D1S518, at chromosome 1, for logTIgE; and D4S1647, at chromosome 4, for skin reactivity to cockroach. The complete linkage-test results for these five traits are shown in figure 2, and the suggested QTLs are summarized in table 3. It is noteworthy that the linkage between logDRSP and D2S1780 ($P = .00002$) reaches the stringent genomewide significance level (Lander and Kruglyak 1995).

Discussion

The present study, which includes 2,551 subjects from 533 families, is the largest genomewide linkage study of asthma-related phenotypes thus far reported. In addition to the large sample size, our study takes advantage of extensively documented intermediate phenotypes related to asthma and of an improved HE linkage-analysis method. We also believe ours is the first report of a genomewide linkage study of pulmonary function (e.g., FEV_1 and FVC).

Phenotype assessment is critical in gene-mapping studies of complex disease. The lack of a standardized definition of the asthma phenotype makes this phenotype sensitive to misclassification and relatively unreliable for genetic studies. This is especially true in the sample that we studied, since the asthma statuses of the subjects were initially defined by local village physicians whose criteria for diagnosis of asthma may have substantially differed from one another's. We have studied several algorithms for classification of asthma phenotypes in the Chinese population, on the basis of a combination of respiratory symptoms, increased airway responsiveness, and a physician's diagnosis of asthma (Celedon et al. 2000). However, it is not clear which algorithm is optimal for linkage analysis of our study sample. In comparison, the quantitative intermediate phenotypes in each subject were measured by the same team or laboratory and by the same procedures and instruments; hence, they are more reliable for linkage study.

According to simulation studies and our own research experience, adjustment of traits with important covariates that are not related to the QTL of interest substantially improves the power to detect linkage (Xu et al. 1999*b*). Although a few methods to directly adjust covariates in sib-pair linkage analysis have been suggested (Elston et al. 2000), they are ad hoc methods and are problematic in the presence of ascertainment bias. Alternatively, covariates can be adjusted prior to linkage analysis, if a good predictive model is available. By including reference families who were randomly selected from the same population as our study sample, we were able (1) to obtain unbiased estimates of the effects that covariates such as age, gender, height, weight, and smoking had on each trait of interest and (2) to make a corresponding adjustment to the trait. We applied this approach to the linkage analyses of both FEV_1 and FVC, for which these covariates account for ~75% of the total variance in the reference population. Without covariate adjustments, the significance levels of the three suggested QTLs for FEV_1 and FVC were substantially lower in the linkage test.

The HE method and the variance-component (VC) method are the two methods widely used for testing linkage to quantitative traits. We chose the unified HE method for our linkage study, for the following three reasons: First, the sample distributions of many traits that we analyzed deviate substantially from normal; it has been shown that the HE method is more robust than the VC method when a trait is not normally distributed (Allison et al. 2000). Second, the VC method usually has more power than the HE method when multigeneration pedigrees are studied; since nuclear families

Table 3

Significance of Linkage at Suggestive QTLs

Chromosome (Marker)[a]	Pointwise *P*				
	FEV_1	FVC	logDRSP	logTIgE	Cockroach
1 (D1S518)	.03	.007	…	<u>.001</u>	…
2 (D2S1780)	.006	.07	<u>.00002</u>	…	…
4 (D4S1647)	…	…	…	.04	<u>.0003</u>
10 (D10S1435)	<u>.0009</u>	.05	…	…	…
16 (D16S412)	…	<u>.0006</u>	.02	…	…
19 (D19S433)	…	.09	<u>.002</u>	.06	…
22 (D22S685)	<u>.002</u>	.03	…	…	…

[a] The most significant linkage at a particular location is underlined.

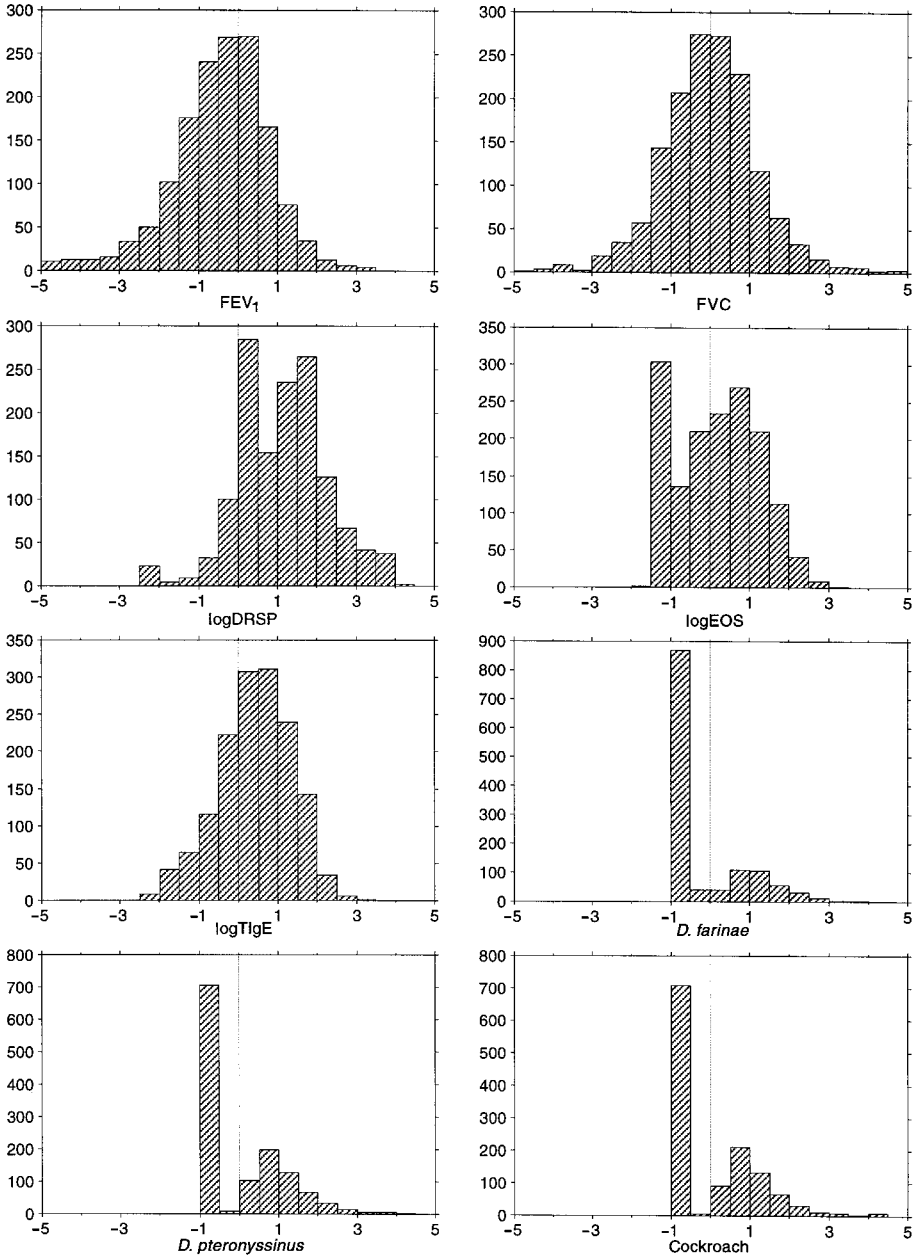

Figure 1 Distributions of standardized phenotypes in nonfounder members of genome-scanned families. The *Y*-axis is the count of nonfounder members.

constitute the majority of our study samples, the advantages of using the VC method are limited. Third, compared to other versions of HE methods, the unified HE method allows for multiple sib pairs in a family and has greater power (Xu et al. 2000). Because of differences in marker heterozygosity, in marker density, and in family structure, the accuracy of sib-pair IBD estimates varies. Although we initially thought that weighing the sib-pair observations by their I_c value might increase power, our simulations showed that giving the same weight to all observations with $I_c > .1$ has slightly better power in many situations (data not shown). As a result, we chose to include, in our linkage analysis, all sib-pair observations in which $I_c > .1$ with equal weights.

Our study demonstrates significant linkage of D2S1780 to airway responsiveness, as measured in logDRSP, and suggestive ($P < .002$) linkage of six other chromosomal loci to one of the five quantitative traits FEV_1, FVC, logDRSP, logTIgE, and skin reactivity to cockroach (table

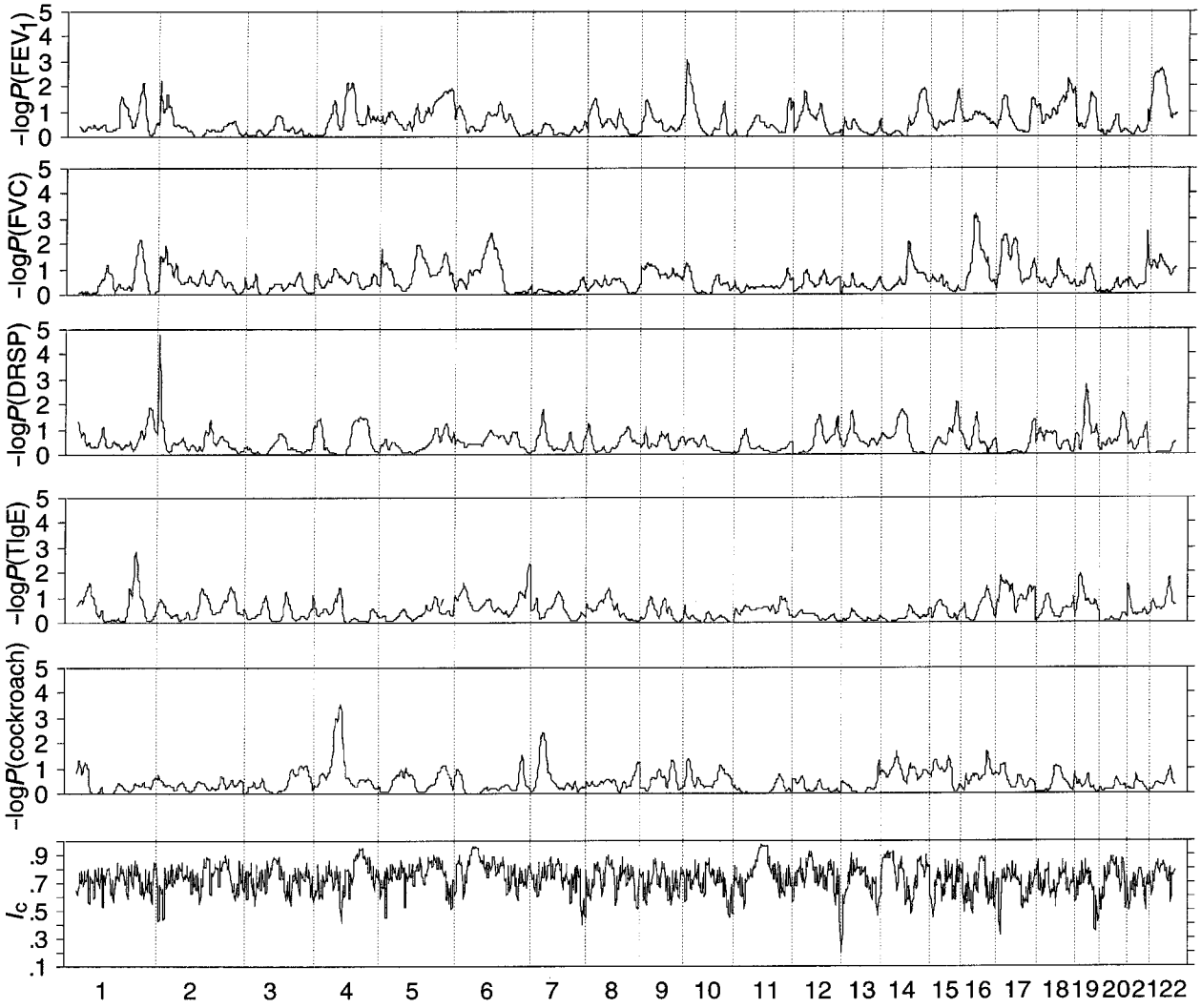

Figure 2 Complete genomewide-linkage–test results for five quantitative traits. The *Y*-axis is the −log*P* of the linkage result; the vertical dotted lines separate the 22 autosomes indexed at the bottom. I_c was calculated by GENEHUNTER.

3). For some of these suggestive QTLs, there is suggestive evidence of linkage not only to a single trait but also to other related traits, albeit at a reduced significance level; for example, there is suggestive evidence that D1S718 is linked not only to TIgE level ($P = .001$) but also to FEV_1 ($P = .03$) and to FVC ($P = .007$). A number of genome scans for asthma and asthma-related phenotypes have been previously reported (Daniels et al. 1996; the Collaborative Study on the Genetics of Asthma 1997; Ober et al. 1998, 2000; Wjst et al. 1999; Dizier et al. 2000; Yokouchi et al. 2000; Mathias et al. 2001). However, the results of these studies show considerable inconsistency, which presumably is due to differences in phenotypic definitions and study populations and, more likely, to a lack of power resulting from insufficient sample size. Such inconsistency also exists between our results and those previously reported. In our comparison, we regarded a previously reported result to be "consistent" with our result if a previously reported linkage peak with $P <$ .01 was, regardless of the asthma traits tested, <20 cM from one of the seven QTLs reported in this study; by this criterion, our suggested QTLs on chromosomes 1, 10, and 19 are consistent with results reported by Wjst et al. (1999), Dizier et al. (2000), and the Collaborative Study on the Genetics of Asthma (1997) and Ober et al. (2000), respectively. We emphasize here that these "consistent" linkages, although very encouraging, should not be regarded as positive replications, since comparison was made among many genome scans with different asthma-related traits and since, more important, few linkages reached the suggested genomewide significance level (Lander and Kruglyak 1995).

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Electronic-Database Information

The accession number and URLs for data in this article are as follows:

ASPEX Package, The: Affected Sib-Pair Exclusion Mapping, ftp://lahmed.stanford.edu/pub/aspex/doc/usage.html

Center for Medical Genetics, Marshfield Medical Research Foundation, http://research.marshfieldclinic.org/genetics/ (for Weber's linkage map)

FBAT Web Page, The, http://www.biostat.harvard.edu/~fbat/default.html (for XWXW)

GENEHUNTER, http://www.fhcrc.org/labs/kruglyak/Downloads/

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for asthma [MIM 600807])

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