false-positive SNPs in duplicated regions show the tell-tale sign of having 50% allele frequencies for both alleles in all populations. The only way to test for false-positive SNPs due to duplications is to check for mendelian inheritance of the alleles or assay the candidate SNP against a duplicated haploid genome such as the complete hydatidiform mole[5]. Based on the general experience that only approximately 5% of candidate SNPs that passed the computer filters for repetitive elements are due to low-copy duplications, global testing of candidate SNPs for duplications is not warranted.

Because a significant fraction of the SNPs in the public domain are found in repetitive regions, there is no guarantee that all SNPs can be amplified uniquely from the genome. Despite these limitations, the publicly available candidate SNPs from TSC and Washington University are likely to be useful to any researcher looking for SNPs in the public domain if they are selected judiciously. To make the marker set even more useful to the genome research community, our group at Washington University and several other groups will characterize more than 100,000 candidate SNPs by the end of 2001. With PCR assays designed for the SNPs and the allele frequencies of these SNPs determined, the average researcher can use these SNPs with a high degree of confidence that they are useful in their own populations.

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Genetic linkage of childhood atopic dermatitis to psoriasis susceptibility loci

We have carried out a genome screen for atopic dermatitis (AD) and have identified linkage to AD on chromosomes 1q21, 17q25 and 20p. These regions correspond closely with known psoriasis loci, as does a previously identified AD locus on chromosome 3q21. The results indicate that AD is influenced by genes with general effects on dermal inflammation and immunity.

AD (also known as eczema) commonly begins in infancy and early childhood, and is typified by itchy, inflamed skin. It affects 10–20% of children in Western societies and shows a strong familial aggregation[1,2]. Eighty percent of cases of AD have elevations of the total serum IgE concentration[3], and atopic mechanisms dominate current understanding of the pathogenesis of the disease[4].

We examined 148 nuclear families recruited through children with active AD (see Web Methods). The families contained 383 children and 213 sibling pairs; 254 children had physician-diagnosed AD, 153 had asthma and 139 had both. Children with AD were aged 6.9±4.4 years and 124 were male. The age of onset of disease was less than 2 years in 90% of children (geometric mean 1.5 y). We found that 51.5% of children had moderate disease and 28.6% had severe disease. The serum IgE concentration was much higher in children with AD and asthma together (geometric mean 880 IU/l; 95% CI 637–1,230 IU/l) than in children with asthma alone (mean 91; 95% CI 23–361 IU/l) or with AD alone (mean 171; 95% CI 106–277 IU/l).

We typed 385 microsatellite markers with an average marker spacing of 8.9 cM and an average information content greater than 65%. We tested four phenotypic models for linkage by non-parametric sib-pair methods. These were AD_{ao} (affected subjects only), AD_{au} (affected and unaffected subjects given equal weighting), $asthma_{au}$ (affected and unaffected subjects given equal weighting) and the total serum IgE analysed as a quantitative trait. We had insufficient subjects with asthma to analyse only affected sibpairs.

At the $P<0.001$ level, we identified linkage to AD on chromosomes 1q21 and 17q25, and linkage to asthma on 20p (Table 1). Linkage of chromosome 20p to children with both AD and asthma ($\chi^2=10.9$, $P=0.0005$) was not greatly different than that to children with asthma alone, indicating that the combination of AD and asthma may correspond to a genetic subtype of disease. The total serum IgE concentration was linked to chromosome 16q–tel. Weaker evidence for linkage was seen between the total serum IgE and *D5S2115* ($P=0.004$) within the chromosome 5 cytokine cluster,

Table 1 • Results of linkage analysis from genome screen

		AD_{ao}		AD_{au}		$Asthma_{au}$		IgE	
Marker	Location[a]	χ^2 (LR)[b]	P[c]	χ^2 (LR)	P	χ^2 (LR)	P	χ^2 (LR)	P
D1S252	155.1	4.74	0.015	7.54	0.003	–	–	3.45	0.03
D1S498	160.7	4.00	0.02	10.95	0.0005	–	–	3.04	0.04
D1S484	173.9	–	–	5.34	0.01	–	–	–	–
D16S520	123.3	–	–	–	–	–	–	10.25	0.0007
D17S784	117.7	11.04	0.0004	5.38	0.01	–	–	–	–
D17S928	128.7	8.23	0.002	4.78	0.015	–	–	–	–
D20S889	11.0	–	–	–	–	3.86	0.02	–	–
D20S115	20.9	–	–	–	–	10.63	0.0005	–	–
D20S186	33.2	–	–	–	–	6.67	0.01	–	–

Linkages with $P<0.001$ are shown, together with flanking markers with $P<0.05$. [a]Position in cM from top of chromosome linkage group. [b]Likelihood ratio χ^2. [c]Single marker significance, unadjusted for genome-wide scan.

Table 2 • Previously observed linkages to psoriasis

Chromosome	Study reference	Marker at peak of linkage	Location cM
1q21	8,15	*D1S498*	160.7
3q21	11	*D3S1269*	142.2
4q	12	*D4S1535*	198.5
6p (MHC)	10,14	*D6S273*	44.9
17q25	9,13,14	*D17S784*	117.7
20p	10,13	*D20S186*	33.2

which contains the important atopy candidate genes *IL4*, *IL13*, *IL5*, *CD14* and *SPINK5*.

We assessed the significance of our findings by simulations, using the four phenotypes and the pattern of marker data observed in the original genome scan. The results indicated that 0.86 linkages would be expected by chance. The probability that all 4 observed linkages were due to chance was 0.008.

Our results differ from another genome screen of similar modest size and power[5], which identified a single AD locus near *D3S3606* on chromosome 3q21. This study contained probands of similar age and age of onset to ours. Disease severity was classified differently, and could not be compared directly between studies. More of our subjects were asthmatic (60% versus 24%) and came from a tertiary referral center, and may represent a different spectrum of disease. Both studies used simulations to establish true genome-wide significance. The studies used different panels of markers and had limited power to exclude linkage to other loci. Together the results indicate that several genes influence AD.

Immune diseases are recognized to share linkage to a limited number of loci[6,7], indicating control by common susceptibility genes. Psoriasis is a chronic inflammatory skin disease that affects 1–2% of the population and has a genetic basis. Although AD is quite distinct from psoriasis, both diseases are characterized by dry, scaly skin, disturbed epidermal differentiation and an inflammation that is responsive to T-cell–specific agents. These two diseases rarely occur together in clinical practice.

Six major psoriasis loci are recognized[8–14]. Our chromosome 1q21, 17q25 and 20p loci are closely coincident with three of these regions[8–10] (Table 2). The probability of random coincidence of our 3 loci within ±25 cM of these 6 regions, estimated by further simulations, was 2.8×10^{-5}. The possibility of testing for coincidence with other inflammatory disorders might render this result less significant, but the ±25 cM window was very conservative, as our peaks of linkage actually shared markers with peaks for psoriasis loci (*D1S498*, *D17S784* and *D20S186*; Tables 1 and 2). It may not be coincidence that the 3q21 locus identified by Lee *et al.*[5] at position 146 cM closely overlaps another psoriasis locus[11] at position 142 cM (Table 2). The colocalization of AD to psoriasis loci seen in both studies indicates that AD is influenced by genes that modulate dermal responses independently from atopic mechanisms. The chromosome 1q21 locus is already known to contain a cluster of genes influencing epidermal differentiation[15].

The knowledge that two common diseases are influenced by the same loci may help positional cloning at the same time as emphasizing its scientific value. Although replication of our findings is necessary and positional cloning remains a formidable undertaking, the availability of genomic sequence and advances in linkage disequilibrium mapping make the discovery of genes for AD both desirable and feasible.

Note: supplementary information is available on the Nature Genetics web site (http://genetics.nature.com/supplementary_info/).

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