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. 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, we have developed a more complete centromere-based genome map of chromosome 5 and plan to make it widely available. 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.

Acknowledgments

Wethank E.P.H. Yap for the Asian samples; M. Boyce-Jacino for the Caucasian and African American samples; R. Sachidanandam and L. Stein for TSC sequence information; and S. Sherry and E.H. Lai for discussion. This work is funded in part by grants from the National Human Genome Research Institute (HG01720) and the SNP Consortium.

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 16q–tel. Weaker evidence for linkage was seen between the total serum IgE concentration and an average information content greater than 65%. We tested four phenotypic models for linkage by non-parametric sib-pair methods. These were ADo (affected subjects only), ADo (affected and unaffected subjects given equal weighting), asthmaO (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

<table>
<thead>
<tr>
<th>Marker</th>
<th>Location</th>
<th>ADo</th>
<th>AsthmaO</th>
<th>IgE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$\chi^2$ (LR)</td>
<td>$P$</td>
<td>$\chi^2$ (LR)</td>
</tr>
<tr>
<td>D1S252</td>
<td>155.1</td>
<td>4.74 0.015</td>
<td>7.54 0.003</td>
<td>3.45 0.03</td>
</tr>
<tr>
<td>D1S498</td>
<td>160.7</td>
<td>4.00 0.02</td>
<td>10.95 0.0005</td>
<td>3.04 0.04</td>
</tr>
<tr>
<td>D1S498</td>
<td>173.9</td>
<td>- -</td>
<td>5.34 0.01</td>
<td>- -</td>
</tr>
<tr>
<td>D1S520</td>
<td>123.3</td>
<td>- -</td>
<td>- -</td>
<td>- -</td>
</tr>
<tr>
<td>D1S157</td>
<td>117.7</td>
<td>11.04</td>
<td>0.0004</td>
<td>3.86</td>
</tr>
<tr>
<td>D1S528</td>
<td>128.7</td>
<td>8.23 0.002</td>
<td>4.78 0.015</td>
<td>10.63 0.0005</td>
</tr>
<tr>
<td>D2OS889</td>
<td>11.0</td>
<td>- -</td>
<td>- -</td>
<td>6.67 0.01</td>
</tr>
<tr>
<td>D2OS115</td>
<td>20.9</td>
<td>- -</td>
<td>- -</td>
<td>- -</td>
</tr>
<tr>
<td>D2OS186</td>
<td>33.2</td>
<td>- -</td>
<td>- -</td>
<td>- -</td>
</tr>
</tbody>
</table>

Links with P<0.001 are shown, together with marker flanking markers with P=0.05. *Position in cM from top of chromosome linkage group. **Single marker significance, unadjusted for genome-wide scan.
which contains the important atopy candidate genes IL4, IL13, ILS, 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, 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, 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.18–11. Our chromosome 1q21, 1q25 and 20p loci are closely coincident with three of these regions8–10 (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 locus11 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 differentiation15.

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/complementary_info/).

Acknowledgments
Wetstein J.A. Faux for IgE estimations and L.R. Cardon for helpful comments on the linkage analyses. This study was funded by the Wellcome Trust.

William O.C.M. Cookson1, Baljinder Ubhi1, Robert Lawrence1, Goncalo R. Abecasis3, Andrew J. Walley1, Helen E. Cox3, Rosemary Coleman4, Nicholas I. Leaves5, Richard C. Trembath3, Miriam F. Moffatt2 & John I. Harper2

1Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK. 2Great Ormond Street Hospital and the Institute for Child Health, London, UK. 3Department of Genetics, University of Leicester, Leicester, UK. Correspondence should be addressed to W.O.C.M.C. (e-mail: william.cookson@ndm.ox.ac.uk)

Received 26 January; accepted 5 March 2001.