Genome-wide scan reveals association of psoriasis with IL-23 and NF-B pathways

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Genome-wide scan reveals association of psoriasis with IL-23 and NF-κB pathways

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Psoriasis is a common immune-mediated disorder that affects the skin, nails and joints. To identify psoriasis susceptibility loci, we genotyped 438,670 SNPs in 1,409 psoriasis cases and 1,436 controls of European ancestry. We followed up 21 promising SNPs in 5,048 psoriasis cases and 5,041 controls. Our results provide strong support for the association of at least seven genetic loci and psoriasis (each with combined \( P < 5 \times 10^{-8} \)). Loci with confirmed association include HLA-C, three genes involved in IL-23 signaling (IL23A, IL23R, IL12B), two genes that act downstream of TNF-α and regulate NF-κB signaling (TNIP1, TNFAIP3) and two genes involved in the modulation of Th2 immune responses (IL4, IL13). Although the proteins encoded in these loci are known to interact biologically, we found no evidence for epistasis between associated SNPs. Our results expand the catalog of genetic loci implicated in psoriasis susceptibility and suggest priority targets for study in other auto-immune disorders.

Psoriasis is a common inflammatory disease affecting ~1% of individuals. The most obvious cellular features of psoriasis are epidermal hyperplasia, altered keratinocyte differentiation and inflammation. Psoriasis susceptibility has a genetic component, partly explained by association between psoriasis and major histocompatibility complex (MHC) haplotypes bearing HLA-Cw6 (ref. 2) and SNPs near HLA-C loci \( P = 4 \times 10^{-53} \) and \( P = 5 \times 10^{-13} \) and IL23R \( P = 3 \times 10^{-7} \). Encouraged by these results, we selected 21 SNPs (representing 18 independent loci, see Methods) for genotyping in an additional 5,048 cases and 5,051 controls (see Table 1 and Supplementary Table 2 online). We found supporting evidence of association at 10 of these 18 loci \( P < 0.05 \) in the follow-up sample, direction of effect matches discovery sample; Table 2). Evidence for association was particularly compelling at seven of these loci \( P < 0.0005 \) in follow-up samples, combined \( P \) value \(<5 \times 10^{-8} \). Owing to the ‘winner’s curse’, odds ratios estimated in the discovery sample were larger than those...
of the IL-23 receptor): rs2082412 (risk allele frequency in controls (encoding the p19 subunit of IL-23) and IL12B susceptibility. First, three SNPs with strong evidence of association genotyped SNPs, increase disease risk by 4. An approach provides frequency 4.

Table 1 Summary description of the samples used in this study

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean age at onset</td>
</tr>
<tr>
<td>Discovery samples</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collection of J.T. Elder</td>
<td>480</td>
<td>23.0</td>
</tr>
<tr>
<td>Collection of G. Krueger</td>
<td>476</td>
<td>28.4</td>
</tr>
<tr>
<td>Collection of A. Bowcock</td>
<td>453</td>
<td>27.2</td>
</tr>
<tr>
<td>Discovery sample total</td>
<td>1,409</td>
<td>26.1</td>
</tr>
<tr>
<td>Follow-up samples</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collection of J.T. Elder</td>
<td>1,642</td>
<td>30.8</td>
</tr>
<tr>
<td>Collection of M. Weichenthal</td>
<td>718</td>
<td>25.1</td>
</tr>
<tr>
<td>Celera follow-up set 1, A. Begovich</td>
<td>498</td>
<td>29.4</td>
</tr>
<tr>
<td>Celera follow-up set 2, A. Begovich</td>
<td>483</td>
<td>26.8 (intronic)</td>
</tr>
<tr>
<td>Collection of D. Gladman</td>
<td>691</td>
<td>29.4</td>
</tr>
<tr>
<td>Collection of J. Fischer</td>
<td>346</td>
<td>19.0</td>
</tr>
<tr>
<td>Collection of A. Bowcock</td>
<td>302</td>
<td>28.0</td>
</tr>
<tr>
<td>Collection of P. Rahman</td>
<td>368</td>
<td>28.3</td>
</tr>
<tr>
<td>Follow-up sample total</td>
<td>5,048</td>
<td></td>
</tr>
</tbody>
</table>

All cases and controls were of white European ancestry. *In the Celera case samples, subjects were only classified as psoriatic arthritis positive or negative ten years after disease onset. In follow-up set 1, 98 of 241 subjects followed-up for > 10 years had psoriatic arthritis. In follow-up set 2, 63 of 215 subjects met this criterion. Information on age at disease onset and age at exam was available for 293 cases and 292 controls, respectively.**Age information for controls in this sample set was not tracked electronically in the sample database and is not readily accessible.

estimated in the follow-up samples. To minimize this effect, we use follow-up sample odds ratios in the discussion that follows. Figure 1 summarizes the results of the association scan, with the seven regions of confirmed association detailed in Figure 2. Overall, our approach provides ~70% power to detect loci that are well tagged by genotyped SNPs, increase disease risk by >1.35-fold and have a frequency >20%.

The results highlight the role of several key pathways in disease susceptibility. First, three SNPs with strong evidence of association map near IL23B (encoding the p40 subunit of IL-23 and IL-12), IL23A (encoding the p19 subunit of IL-23) and IL23R (encoding a subunit of the IL-23 receptor): rs2082412 (risk allele frequency in controls fcontrol = 0.80, odds ratio in follow-up samples ORfollow-up = 1.44, combined P value PC0mmbined = 2 × 10−28), rs2066808 (fcontrol = 0.93, ORfollow-up = 1.34, Pcombined = 1 × 10−9) and rs2201841 (fcontrol = 0.29, ORfollow-up = 1.13, Pcombined = 3 × 10−8). Genetic variants in the IL23A locus are implicated in psoriasis and autoimmune disease susceptibility for the first time by our study. IL-23 signaling promotes cellular immune responses by promoting the survival and expansion of a recently identified subset of T cells expressing IL-17 that protects epithelia against microbial pathogens. Dysregulated IL-23 signaling could predispose certain individuals to inappropriate chronic immune responses that target epithelial cells and ultimately result in psoriasis.

Second, loci including TNFAIP3 (TNF-α induced protein 3) and TNIP1 (TNFAIP3 interacting protein 1), whose gene products work downstream of TNF-α to regulate NF-κB, show strong association

Table 2 Loci with strongest evidence of association with psoriasis in the combined sample, including discovery and follow-up samples

<table>
<thead>
<tr>
<th>SNP</th>
<th>Chr. (Mb)</th>
<th>N</th>
<th>Mean age at onset</th>
<th>Male (%)</th>
<th>Psoriatic arthritis (%)</th>
<th>PC0mmbined</th>
<th>ORfollow-up</th>
<th>Pcombined</th>
<th>ORfollow-up</th>
<th>Pcombined</th>
<th>Notable nearby genes (relative position)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs12191877</td>
<td>6 (31.36)</td>
<td>0.313</td>
<td>0.141</td>
<td>2.79</td>
<td>4 × 10−53</td>
<td>0.301</td>
<td>0.147</td>
<td>2.64</td>
<td>&lt;10−100</td>
<td>&lt;10−100</td>
<td>HLA-C (−13 kb)</td>
</tr>
<tr>
<td>rs2082412</td>
<td>5 (158.65)</td>
<td>0.856</td>
<td>0.792</td>
<td>1.56</td>
<td>5 × 10−10</td>
<td>0.848</td>
<td>0.798</td>
<td>1.44</td>
<td>3 × 10−20</td>
<td>2 × 10−28</td>
<td>IL12B (+24 kb)</td>
</tr>
<tr>
<td>rs17728338</td>
<td>5 (150.46)</td>
<td>0.093</td>
<td>0.056</td>
<td>1.72</td>
<td>2 × 10−7</td>
<td>0.087</td>
<td>0.054</td>
<td>1.59</td>
<td>6 × 10−15</td>
<td>1 × 10−20</td>
<td>TNIP1 (−12 kb)</td>
</tr>
<tr>
<td>rs20541</td>
<td>5 (132.02)</td>
<td>0.832</td>
<td>0.783</td>
<td>1.37</td>
<td>6 × 10−6</td>
<td>0.827</td>
<td>0.790</td>
<td>1.27</td>
<td>1 × 10−10</td>
<td>5 × 10−15</td>
<td>IL13 (nonsynonymous)</td>
</tr>
<tr>
<td>rs610604</td>
<td>6 (138.24)</td>
<td>0.374</td>
<td>0.318</td>
<td>1.28</td>
<td>1 × 10−5</td>
<td>0.360</td>
<td>0.320</td>
<td>1.19</td>
<td>7 × 10−8</td>
<td>9 × 10−12</td>
<td>TNFAIP3 (intronic)</td>
</tr>
<tr>
<td>rs2066808d</td>
<td>12 (55.02)</td>
<td>0.958</td>
<td>0.931</td>
<td>1.68</td>
<td>2 × 10−5</td>
<td>0.947</td>
<td>0.932</td>
<td>1.34</td>
<td>5 × 10−6</td>
<td>1 × 10−9</td>
<td>IL23A (+3.7 kb)</td>
</tr>
<tr>
<td>rs2201841</td>
<td>1 (67.47)</td>
<td>0.350</td>
<td>0.286</td>
<td>1.35</td>
<td>3 × 10−7</td>
<td>0.325</td>
<td>0.295</td>
<td>1.13</td>
<td>4 × 10−4</td>
<td>3 × 10−8</td>
<td>IL23R (intronic)</td>
</tr>
<tr>
<td>rs1076160</td>
<td>6 (139.80)</td>
<td>0.520</td>
<td>0.463</td>
<td>1.26</td>
<td>2 × 10−5</td>
<td>0.496</td>
<td>0.475</td>
<td>1.09</td>
<td>4 × 10−3</td>
<td>6 × 10−6</td>
<td>TSC1 (intronic)</td>
</tr>
<tr>
<td>rs12983316</td>
<td>10 (9.98)</td>
<td>0.186</td>
<td>0.144</td>
<td>1.32</td>
<td>2 × 10−5</td>
<td>0.159</td>
<td>0.147</td>
<td>1.09</td>
<td>0.027</td>
<td>8 × 10−5</td>
<td>SMARCA4 (intronic)</td>
</tr>
<tr>
<td>rs3972111</td>
<td>2 (113.60)</td>
<td>0.718</td>
<td>0.677</td>
<td>1.21</td>
<td>1 × 10−3</td>
<td>0.709</td>
<td>0.696</td>
<td>1.08</td>
<td>0.025</td>
<td>4 × 10−4</td>
<td>IL1RN (+0.5 kb)</td>
</tr>
</tbody>
</table>

*Frequency of the risk allele. **All P values are two-tailed. +Position of each SNP relative to notable nearby genes is given. Plus (+) and minus (−) signs indicate whether the SNP is upstream (+) or downstream (−) of the transcription start site. SNPs that overlap the gene are labeled as ‘intronic’, ‘synonymous’ or ‘nonsynonymous’. *Genotypes for rs2066808 were imputed using MaCH. The distribution of imputed posterior probabilities for each genotype was then compared between cases and controls. Similar evidence for association was observed at rs2066807 (combined P = 2 × 10−10), which maps nearby and was genotyped in discovery and follow-up samples. Boldface rows indicate loci achieving a genome-wide level of significance (P < 5 × 10−8) in the combined analysis.
with psoriasis. In these two regions, markers rs610604 (\(f_{\text{control}} = 0.32\), \(OR_{\text{follow-up}} = 1.19\), \(P_{\text{combined}} = 9 \times 10^{-12}\)) and rs17728338 (\(f_{\text{control}} = 0.05\), \(OR_{\text{follow-up}} = 1.59\), \(P_{\text{combined}} = 1 \times 10^{-20}\)) were sites of replicated association. TNFAIP3 encodes A20, a TNF-\(\alpha\)-inducible zinc-finger protein that temporally limits immune responses by inhibiting NF-\(\kappa\)B activation and terminating NF-\(\kappa\)B mediated responses\(^8\). Symptoms in a mouse model of psoriasis induced by administration of IL-23 are ameliorated by blocking of TNF-\(\alpha\) and systemic lupus erythematosus (for example, rs5029939, \(P_{\text{value}} = 0.01\)). These results endorse a search for additional psoriasis susceptibility alleles within the MHC, we implemented a forward-selection procedure to select a set of disease-associated variants in each locus (see Methods). This analysis resulted in a model with three imputed SNPs (Supplementary Table 3 online). The first two of these (rs12204500 and rs13191343, forward-selection value \(P = 8 \times 10^{-57}\) and \(2 \times 10^{-10}\), respectively) are close to and in strong LD with HLA-Cw6 (\(r^2 = 0.78\) and 0.52, respectively), whereas the third one (rs2022544, \(P = 10^{-21}\)) maps closer to the HLA-DR gene cluster and shows only weak LD with HLA-Cw6 (\(r^2 = 0.01\)). These results endorse a search for additional psoriasis susceptibility loci within the MHC.

When we applied the same forward-selection strategy to the other loci, two independent SNPs (\(r^2 < 0.01\)) were selected in the IL12B and IL23R regions. Although only one SNP was selected in the four other regions (Supplementary Table 3), it is likely that independent disease-associated alleles exist in additional loci such as TNIP1 where rs884520 (a SNP only \(\sim 6\) kb away from the peak of association at rs17728338) was suggestively associated with psoriasis (\(P = 9 \times 10^{-5}\) unadjusted, \(P = 0.051\) after conservative adjustment for 565 independent tests) in our conditional analyses. Fully characterizing the impact of these loci on psoriasis susceptibility will require characterization of the full spectrum of allelic variation at each locus in large case-control samples.

As the loci implicated here are involved in regulation of immune responses, and several of the proteins they encode interact physically (for example, IL-12B/p40 and IL-23/p19 form a heterodimer that binds to IL-23R, and TNIP1 interacts with TNFAIP3) we assessed evidence of epistasis in our data. We considered all 21 possible pairings of the seven lead SNPs, testing for deviation from a log-additive risk is <0.01), but IBD5 does show modest evidence for association with psoriasis (rs10077785, \(P = 0.03\)), suggesting that it could be another locus that contributes to both diseases.

SNP rs12191877, the genotyped marker showing strongest association with psoriasis (\(f_{\text{control}} = 0.15\), \(f_{\text{case}} = 0.30\), \(OR_{\text{follow-up}} = 2.64\), \(P_{\text{combined}} = 2 \times 10^{-10}\)), was in LD with HLA-Cw6 (\(r^2 = 0.63\)). In a subset of cases and controls in which HLA-Cw6 genotypes were available, HLA-Cw6 was more strongly associated with psoriasis than any genotyped or imputed SNP, but could not fully account for all observed association signals (data not shown). To assess the evidence for multiple psoriasis susceptibility alleles within the MHC, we considered all 21 possible pairings of the seven lead SNPs, testing for deviation from a log-additive risk
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model. Only the pairing involving rs12191877 near HLA-C and rs610604 near TNFAIP3 showed any evidence for epistasis under this model \( (P = 0.02 \) in combined sample). It is possible that tests of interaction will be more powerful once the causal variants at each loci have been identified, but it is notable that even when proteins encoded by the associated loci interact physically no significant evidence for epistasis was detected (a similar situation occurs for height\(^2\), among other traits).

To evaluate evidence for heterogeneity in the effect sizes at each of the seven replicated loci, we calculated \( F \) and \( Q \) statistics for a meta-analysis of follow-up samples (Supplementary Table 4 online). We observed no evidence for heterogeneity at non-MHC loci, and only

![Figure 2](image_url)

**Figure 2** Evidence for association in confirmed loci. The figure summarizes evidence of association (in the discovery sample) in each region of confirmed association. Test statistics at the SNP selected for follow-up (typically, the genotyped SNP showing strongest evidence for association in each locus) are highlighted with a square. Test statistics for other SNPs are drawn as circles and color coded according to the degree of linkage disequilibrium with the SNP selected for follow-up.
modest evidence for heterogeneity at rs12191877 in the MHC (P = 0.007, Supplementary Table 4)—potentially reflecting sample differences in the proportion of familial cases and psoriatic arthritis. At several of the confirmed loci, we found modest differences in association signal strength for psoriatic arthritis compared to purely cutaneous psoriasis (Supplementary Table 5 online), supporting epidemiologic evidence for differences in genetic architecture of the two conditions21. In other stratified analyses, we found no evidence for heterogeneity between males and females (all P > 0.15) or between younger and older individuals (all P > 0.15, cases and controls stratified around median ages).

Psoriatic and uninvolved skin show significantly different expression for hundreds of genes, involved in both immune response and in the regulation of cellular differentiation and proliferation22. We reasoned that altered expression of genes in the loci implicated by our study might also be a molecular trigger in disease progression. Therefore, we examined expression of the genes in the loci showing replicated evidence of association in skin biopsies from 64 GWAS controls and in biopsies of involved and uninvolved skin from 58 GWAS cases (Supplementary Table 6 and Supplementary Fig. 1 online). Together, these results show that four of the genes investigated (HLA-C, IL12B, TNIP1 and IL23A) show highly significant differences in expression between involved and uninvolved skin (all with P < 10^{-9}). Two of these (IL23A, TNIP1) also showed differences in expression when we compared normal skin from controls and uninvolved skin from cases (P < 0.0003). The results are consistent with the hypothesis that the expression of particular HLA-C alleles and of IL23A and IL12B (encoding the two subunits of IL-23) in psoriatic skin are key events in disease progression. However, the dosage of risk alleles at the seven psoriasis-associated SNPs did not correlate with transcript levels for nearby genes in either involved, uninvolved or normal skin. It remains possible that association between these SNPs and gene expression patterns is stronger at specific time points during development, disease progression or in specific cell types.

Although this study represents a significant advance in our understanding of the genetic underpinnings of psoriasis, much work remains to be done. The association signals identified here account for a sibling recurrence risk (P_{sib}) of <1.35 (including ~1.25 due to HLA); consequently, much of the overall sibling recurrence risk for psoriasis, which has been estimated at approximately three- to sixfold23, remains unexplained. Still, the rapid pace of advance in psoriasis genetics is encouraging. In the past 18 months, the number of independent genetic loci confidently associated with psoriasis has increased from one (HLA-Cw6 and other MHC variants) to at least ten, including the seven association signals reported in this paper, copy number variants in the beta-defensin24 and late cornified envelope (LCE) gene regions25, and a signal near RNF114, a potential regulator of T-cell activation26. The RNF114 signal is supported by our data (see Supplementary Table 7 online for analysis of previously reported GWAS26,27 signals in our data). Although we did not systematically characterize copy number variation, we note that rs4112788, a SNP proxy for the LCE deletion25,27, is associated with disease in our discovery sample (P = 0.001). In each of the loci identified here, fine-mapping and resequencing efforts together with further functional studies are required to pinpoint and characterize causal variants, confirm the identity of the implicated genes, and accurately quantify the contribution of the locus to disease susceptibility. In parallel, follow-up analyses with larger numbers of SNPs, execution of genome-wide association scans in larger sample sets, meta-analyses of genome-wide scan results, and large scale analyses of rarer variants should lead to identification of additional susceptibility loci.

**METHODS**

**Informed consent.** All participating subjects gave informed consent and protocols were reviewed and approved by local institutional review boards.

**Genotyping.** Perlegen Sciences genotyped discovery samples using four proprietary, high-density oligonucleotide arrays. SNPs on the arrays were selected to tag common variation in samples of European ancestry. Cases and controls from the same collection were genotyped together, and arranged to ensure similar proportions of cases and controls in each plate. Follow-up samples were genotyped using either Applied Biosystems Taqman assays, Sequenom single base extension assays, or allele-specific kinetic PCR. The 21 SNPs selected for follow-up included 19 SNPs selected to represent loci with strongest evidence for association in our initial scan (including 2 SNPs per locus for hits near IL13, IL23A and PRKRIP1) and two SNPs in loci that included strong functional candidates (IL1RN and CNTNS) but more modest evidence of association (rs397211, P = 1 × 10^{-4}, and rs12807920, P = 1 × 10^{-4}).

**Sample quality control.** Eighteen samples failed genotyping for technical reasons. Among the remaining samples, we excluded those with call rates <95% (8 samples) and with outlier heterozygosities of <31% or >34% (24 samples; the average heterozygosity for all samples was 32.6% with s.d. of 0.4%). We also excluded one individual from each pair of unexpected duplicates, first- or second-degree relatives (36 individuals). This resulted in a dataset with 1,359 cases and 1,400 controls.

**Quality control of genotype data.** Perlegen Sciences called > 50% of genotypes for 556,383 SNPs. Before analysis, we excluded markers with <95% genotype call rates (99,963 SNPs), with minor allele frequency <1% in the combined dataset (6,106 SNPs), with HWE P value <10^{-6} (2,962 SNPs), with >2 mismatches among 48 duplicate pairs (62 SNPs) or with >2 mendelian inconsistencies among 27 trios (41 SNPs). In total, 447,249 SNPs passed the quality control filters (average call rate of 99.2%). Here, we present analyses of 438,670 autosomal SNPs.

**Genotype imputation.** As previously described28, we used information on patterns of haplotype variation in the HapMap CEU samples (release 21)29 to infer missing genotypes ‘in silico’. We only analyzed SNPs that were genotyped or could be imputed with relatively high confidence (estimated r^2 between imputed SNP and true genotypes >0.3, so that patterns of haplotype sharing between sampled individuals and HapMap samples consistently indicated a specific allele).

**Assessment of genotyping and imputation quality.** A single plate containing 90 study samples was re-genotyped for 906,600 SNPs using the Affymetrix 6.0 chip. Comparison of 15,844,334 genotypes for 218,039 SNPs overlapping between the Perlegen and Affymetrix platforms resulted in an observed discrepancy rate of 0.25% per genotype (0.12% per allele). Comparison of 57,747,244 imputed and experimentally derived genotypes for 661,881 non-Perlegen SNPs present in both our imputed SNP set and the Affymetrix 6.0 array resulted in a discrepancy rate of 1.80% per genotype (0.91% per allele). Overall, the average r^2 between imputed genotypes and their experimental counterparts, which provides an estimate of the relative power of analysis relying on imputation instead of direct genotyping, was 0.93. This r^2 statistic exceeded 0.80 for >90% of SNPs, suggesting excellent coverage of common variation in the genome.

**Association analyses.** To evaluate the evidence for association between each genotyped or imputed SNP and psoriasis, we first calculated a single r^2 statistic that contrasted observed or imputed allele counts between cases and controls. The 832 follow-up samples collected by J. Fischer (Table 1) and colleagues were analyzed using a family-based approach30. To combine statistics across different samples, we first selected an arbitrary reference allele for each marker and then calculated a z statistic characterizing the evidence for association in each study (summarizing both the P value, in its magnitude, and the direction of effect, in its sign). We then calculated an overall z statistic as a weighted average of the individual statistics and calculated the corresponding P value. Weights were proportional to the square root of the number of individuals examined in each sample and were selected such that the squared weights sum to 1.0.

**Forward selection procedure.** We first selected the SNP that showed strongest association in each region. Then, conditioning on this SNP, we searched for the
Skin. This independent dataset did not suggest differential expression of
uninvolved skin from 16 individuals gave results consistent with those reported
here, suggesting that
involved and uninvolved skin from affected individuals). Comparisons
of normal skin from controls and psoriatic skin from cases gave similar results
(but slightly more significant P values) to paired comparisons of involved and
uninvolved skin from 16 individuals gave results consistent with those reported
here, suggesting that
expression was contrasted between different groups of samples using two sample t-tests (for comparisons involving skin from normal controls and individuals with psoriasis) or paired t-tests (for comparisons involving involved and uninvolved skin from affected individuals). Comparisons of normal skin from controls and psoriatic skin from cases gave similar results (but slightly more significant P-values) to paired comparisons of involved and uninvolved skin from affected individuals.

Accession codes. dbGAP: genotype and phenotype data described in this
manuscript have been deposited with accession code phs000019.v1.p1. NCBI GEO: microarray data have been deposited under accession number GSE13355.

Note: Supplementary information is available on the Nature Genetics website.

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AUTHOR CONTRIBUTIONS

COMPETING INTERESTS STATEMENT
The authors declare competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturegenetics/.

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