

Atopy susceptibility and chromosome 19q13

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Atopy and atopic disease such as asthma show strongly familial characteristics, with heritability estimates varying between 36% and 79% (reviewed in Ref. (1)). Chromosomal region 19q13.1–13.3 has been identified as containing genes predisposing to atopy or asthma-related phenotypes (reviewed in Ref. (2)). A region at ~58 Mb has shown linkage to atopy and IgE phenotypes in a study of 111 Italian Caucasian families (3); however, the linkage peak was broad spanning several megabases. The aim of the current study was to replicate and further define this potential atopy locus using two independent UK cohorts.

In the first analyses, we utilized the Southampton asthma sibling pair cohort ($n = 341$ families) which has been extensively described (2) using total IgE, elevated specific IgE (0.35 kU/l) and positive skin prick test (> 3 mm diameter, SPT) phenotypes. Five microsatellite markers spanning the region D19S402 (56.9 Mbp), D19S601 (57.3 Mbp), D19S571 (57.9 Mbp), D19S180 (58.4 Mbp) and D19S572 (58.8 Mbp) were genotyped as described (2). Errors in genotyping were detected using the inheritance check in Family-Based Association

We have replicated and further defined an atopy susceptibility locus on chromosome 19q13.

Test (FBAT) software (4). Global FBAT analyses (additive model) identified association between D19S571 and number of specific IgE responses [spIgE(no.)] with borderline significance for total IgE levels (tIgE) and positive specific IgE (spIgE+) (Fig. 1A). Marker D19S180 was associated with tIgE, spIgE+, SPT+ with borderline association for spIgE(no.). These data identified D19S571 and D19S180 markers as showing significant association with total IgE and atopy traits. Our findings confirm the data of Venanzi et al. (3) and extends these analyses to localize the signal to two adjacent markers that are ~450 kb apart. In contrast to our analyses, Venanzi et al. found that the peak linkage signal was at marker D19S601 for atopy defined by elevated spIgE or SPT positivity (LOD 3.33, $P = 0.0005$) (3). In the current analyses, we did not see any association with D19S601. We also did not observe an association between any marker and asthma (data not shown) in keeping with Venanzi et al. (3). FBAT for these two markers in the bi-allelic mode identified key D19S571 and D19S180 alleles underlying the global association i.e. D19S571 alleles 234 (protection) and 240 (risk) and D19S180 alleles 152 (risk), 158 (protection) and 160 (risk) (Fig. 1B).

For replication, we used an adult UK population (mean age 42.2 years, 47.8% male, 37% SPT+, $n = 276$) composed of nonasthmatic controls ($n = 184$) and adult subjects ($n = 92$) of unknown asthma diagnosis recruited from the UK. Skin prick test response to common allergens including grass, house dust mite, cat, dog, *Alternaria* and tree allergens was determined. Case-control analyses [(SPT+ ($n = 88$) and SPT- ($n = 165$)), Fishers exact test] identified that D19S180 allele 152 was protective for atopy (OR 0.29 CI 0.10–0.83, $P = 0.009$), and D19S180 allele 158 was a risk factor for atopy (OR 2.10 CI

1.11–3.99, $P = 0.018$) (Fig. 1C). These data show the so-called allele ‘flip flop’ affect observed in other genetic studies and by ourselves (2). Importantly, the number of D19S180 alleles correlated with the number of positive skin prick tests; allele 152 [$n = 253$, coefficient -0.127 , $P = 0.043$] and 158 ($n = 253$, coefficient 0.156 , $P = 0.013$). Overall, the replication analyses provided further support for association between D19S180 alleles and atopy susceptibility.

Chromosome 19 has the highest gene density of all chromosomes (5) suggesting that identification of the causative gene will be a challenge. Investigation of the association region (D19S571–D19S180 interval ± 200 kb) suggests the presence of 30+ transcripts predominantly encoding Kruppel-related zinc finger transcription factors (Fig. 1D). It is tempting to speculate that altered transcription factor expression/activity underlies the association with atopy risk as suggested previously for PHF11 (6). In conclusion, we provide replication that chromosome 19q13 contains an atopy susceptibility locus and importantly further localize this signal.

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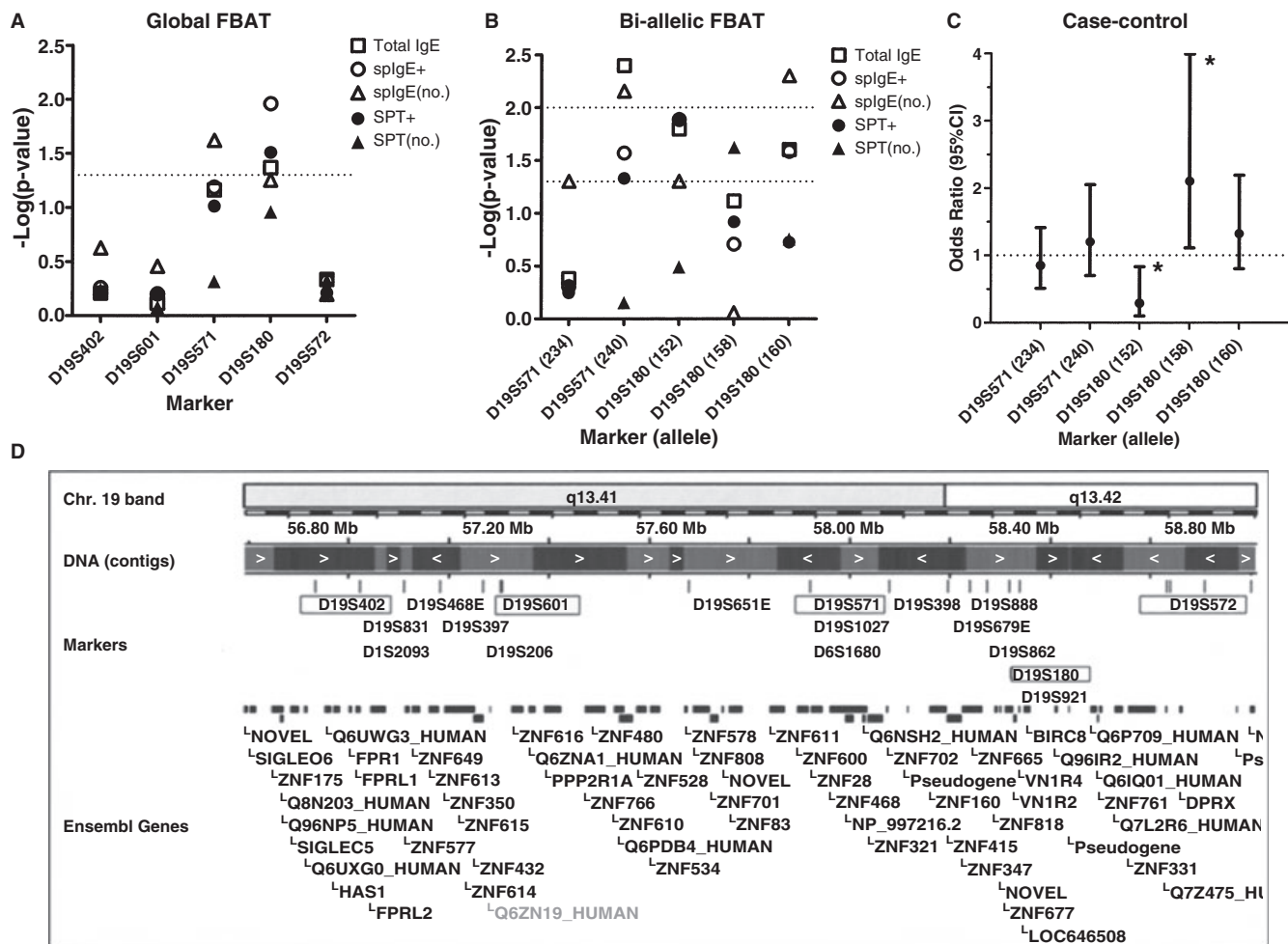


Figure 1. Association between 19q13 markers and atopy phenotypes in family and case-control analyses. Global (A) and bi-allelic (B) Family-Based Association Test (FBAT) analyses (additive model) in 341 asthma families identified marker D19S571 and D19S180 atopy risk alleles. Case-control analyses in the replication cohort ($n = 276$) confirms the role of D19S180 152 and 158 alleles in conferring risk to develop atopy defined by SPT. Ensembl representation of the initial atopy linkage region on chromosome 19q13 (D). Illustrated are the position of microsatellite markers used in the current association analyses and known genes in the region. The association with atopy localized to markers D19S571 and D19S180, a region containing a large number of predicted transcription factors of unknown function. In (A) a $P < 0.05$ is highlighted, and in (B) both $P < 0.05$ and $P < 0.01$ are highlighted. In (C) a $*P < 0.05$ is shown.

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