

LETTER TO THE EDITOR

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**IL-13 Gene Polymorphisms and Their Association with
Atopic Asthma and Rhinitis in Pakistani Patients**

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To the editor:

Recently, we read with great interest the article by Shazia et al, which was published in your journal.¹ The aim of the study was to evaluate the role of IL-13 SNPs in the Pakistani patients with atopic asthma and allergic rhinitis (AR). The results indicated that the IL-13A-1512C polymorphism was a risk factor for asthma and AR. After carefully reading the article, we noted some issues which should be considered an additional exploration.

First, the authors overlooked an important issue of ethnically matched cases and controls, as Pakistani population has ethnic, religious and language barriers reflecting different sub-casts and tribes. These subdivisions predictably exert genetic effects and thus influence the strength of genetic association studies in this region.² The authors appeared to have missed the calculation of Hardy-Weinberg equilibrium in the control population. It is standard practice when examining data to test Hardy-Weinberg Equilibrium proportion in cases and separately in controls as this is very important quality control check in case-control analysis;³ therefore, no allowance is made for the deviation of Hardy-Weinberg equilibrium in the controls for IL-13A1512C polymorphism in the context of Pakistani population.

Second, the authors documented the association of variant allele A at IL-13-1512 with asthma and AR with an odd ratio of 2.4 and 3.4, respectively. In this case-control analysis, the risk of asthma and particularly AR was quite large as compared to the recent genome-wide association studies.^{4,5}

Therefore, this SNP-disease gene association is remarkably strong and is looking exceptional in the context of common disease/common variant association detected in genome-wide or other large scale SNPs experiments.⁴

Due to strict traditional values in Pakistan, there are 40-60% consanguineous marriages.² In the article by Shazia and colleagues, the increased homozygosity of studied SNPs indicates the low genetic variability and may be due to increased consanguinity rates as described elsewhere.⁶ Moreover, regarding IL-13A-1512C genotype,¹ the expected heterozygosity was more than observed in the control population attributing the deviation from Hardy-Weinberg to forces such as inbreeding and selection pressure.²

Genome-wide association studies (GWAS) has led to the identification of hundreds of SNPs as risk variants for common disease while acknowledging that most of the heritability for these common traits remained to be explained.⁷ The consistency in odd ratio across the different populations is not always observed as most of the GWASs are reported from the European ancestry.⁴ Recently, a group of scientists reported a genomic region susceptible for the inflammatory conditions in multi-

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ethnic populations. The risk allele was more common in the subjects from Asian population, and this was high with an odd ratio of 5.42 as compared to European ancestry. The greater risk in the Asian population as compared to European populations raises the possibility that it tags some rare unknown causative variants through linkage disequilibrium (LD) that is stronger in the Asian than in European population.⁸ The underlying biology of complex diseases studied in genetic association studies, however, is expected to involve multiple SNPs and non-genetic factors. With the existence of multiple causal or associated factors (rare genetic variants, ethnicity, population diversity, LD and environmental factors), the estimated odd ratio of the disease defined for one of the causal factors would not represent accurately the extent and mechanism of the underlying disease mechanism involving the factor.⁹ Therefore, the strong association between the IL-13A-1512 may be due to the tight linkage of this SNP with causative rare genetic variants in study population. Although the exact biological mechanism of this association remains to be explored, however, the suggested explorations will support the credible evidence of association between genetic variation of IL-13 and atopic asthma and AR, respectively.¹

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