Reviewer’s report

Title: Association Analysis Identifies ZNF750 Regulatory Variants in Psoriasis

Version: 1 Date: 17 October 2011

Reviewer: Maartje Aukes

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Birnbaum and colleagues examined whether ZNF750 variants were associated with psoriasis in a large case-control population by sequencing the promoter and exon regions.

They found no evidence of association of common polymorphisms with disease. In subsequent haplotype analysis, two haplotypes were associated with psoriasis.

Additionally, they detected several rare, non-synonymous, coding variants in ZNF750 that were only present in cases and not in controls. In order to evaluate the possible association of these rare variants in ZNF750 with psoriasis, they used a weighted-sum approach. The promoter or 5' UTR of ZNF750 were enriched in the cases compared to controls.

Furthermore, they studied the functional impact of the 5' regulatory variants in a promoter activity assay. All 4 variants showed decreased promoter activity. However, in a segregation analysis, the 5' regulatory variants did not segregate with psoriasis.

The authors suggest two interpretations: 1) certain 5' regulatory variants in ZNF750 could serve as a genetic modifier of the psoriasis phenotype or act as an incremental risk modifier similar to the common susceptibility alleles previously identified. 2) there is no true association of 5' regulatory variants in ZNF750 with psoriasis. Based on phenotypic similarities between carriers of the 5' regulatory variants the authors suggest that the second interpretation is unlikely.

I have one major compulsory revision:

1. The type, medical status and recruitment of controls used is unclear. How were the cases and controls recruited? The paper now only mentions (section Methods, Patients) where DNA samples were collected (“collected form University of California, SF and Washington University”). Were the controls patients? Have they been screened for psoriasis? Using what methods? Please provide these details.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable
**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests