

Genetic factors implicated in aromatic anti-epileptic drug induced hypersensitivity reactions

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Background: Carbamazepine can induce hypersensitivity reactions ranging in severity from mild to potentially life threatening. Previous studies have shown associations between genetic variants in human leukocyte antigens (HLA) and hypersensitivity reactions. However, due to the complexity of genetic and non-genetic factors, the presence of HLA variants does not fully predict an individual's susceptibility. Whole genome sequencing of 28 cases and 20 controls identified novel six single nucleotide polymorphisms (SNPs) that could also contribute to hypersensitivity predisposition;

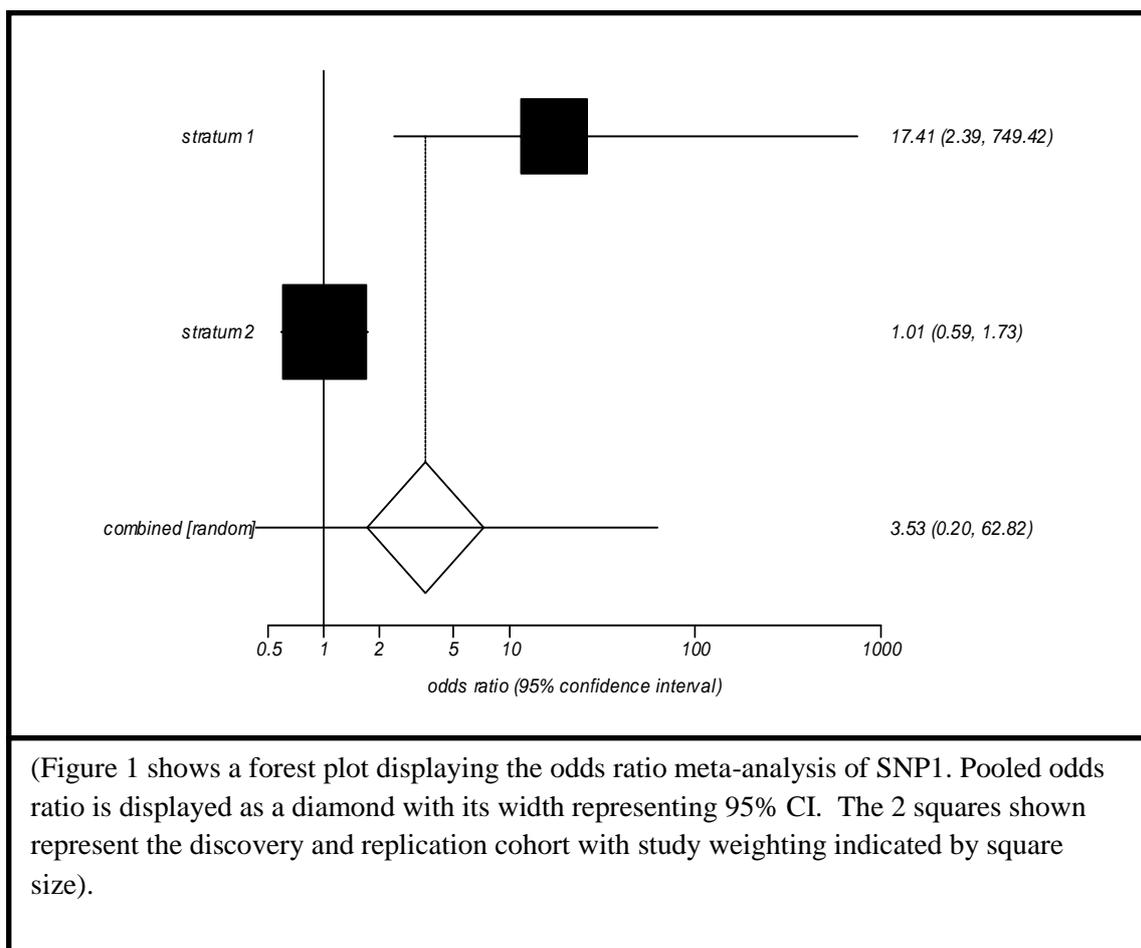
- SNP1 in the TATA box binding protein associated factor 13 (TAF13) gene.
- SNP2 and SNP3 located in the intragenic region of the SOCS5 (suppressor of cytokine signalling) gene.
- SNP4 and SNP5 were found to be located in the intragenic and intergenic region of the vacuolar protein sorting 13 homolog A (VPS13A) gene respectively.
- SNP6 located in an unidentifiable gene.

Aims: To validate findings produced in the previously sequenced discovery cohort; 28 cases and 20 controls with severe hypersensitivity reactions (SJS, TEN, and drug reaction with eosinophilia and systemic symptoms complex (DRESS)) and to reproduce findings in a validation cohort; 93 controls and 101 cases (48 cases: transient maculopapular exanthema (MPE) , 53 cases: severe hypersensitivity reactions (DRESS, SJS or TEN)).

Methods: Patients were recruited from the Liverpool research department and through collaboration with the International Serious Adverse Event Consortium (iSAEC).

242 samples were genotyped using the real-time PCR 7900HT fast sequence detection system to determine the genotype and allelic frequency of six SNPs. Results were statistically analysed using StatsDirect2.7.9.

Results: Findings obtained in the discovery cohort were all statistically significant when analysed alone and were consistent with sequencing results. However results were not reproduced in the replication cohort and meta-analysis results were statistically insignificant in all six SNPs.



Conclusion: In conclusion, results obtained in the discovery cohort were consistent with findings from sequenced data. However an association between genotype and phenotype in all the SNPs were no longer evident when discovery cohort results were grouped with statistically insignificant results obtained from the replication data. This suggests that SNPs identified as having an association with CBZ-induced hypersensitivity during sequencing were potentially false positive findings. However, predisposition to CBZ-induced

hypersensitivity may act in a manner that is specific to ethnicity and severity of DISI which may have produced less favourable results in the replication cohort. A larger cohort may provide more statistically significant findings although given the rarity of this syndrome, recruitment of a larger sample size would be a very challenging process.