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SINGLE NUCLEOTIDE POLYMORPHISMS ASSOCIATIED WITH ELEVATED SERUM VIRAL LOAD OF HEPATITIS B VIRUS IN PATIENTS WITH CHRONIC HEPATITIS B: A GENOME-WIDE ASSOCIATION STUDY IN TAIWAN

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Background and aims: Serum hepatitis B virus (HBV) load (HBV DNA level) is the most import risk predictor of liver disease progression in patients with chronic hepatitis B (CHB). There exists an extreme inter-individual variation in serum HBV DNA levels among CHB patients without antiviral treatment. This study aimed to investigate human single-nucleotide polymorphisms (SNPs) associated with elevated HBV load using a two-stage genome-wide association study.
Methods: Participants with extremely high ($\geq 10^8$ copies/mL; n=560) and low (< 300 copies/mL; n=560) baseline viral load were selected from the R.E.V.E.A.L.-HBV cohort. Their genomic DNA was extracted and genotyped for the first stage analysis using Affymetrix Genome-Wide Human SNP Array 6.0, which features more than 900,000 SNP markers. After stringent quality filtering on both samples and markers, a total of 660,337 SNPs in 279 high viral load cases and 278 low viral load controls was processed in the association analysis. Chi-square test was used to test phenotype-genotype association for each SNP based on three (allelic, dominant, and recessive) genetic models. The association analysis was also applied to a subset of sample, in which age-matching was performed between case and control groups.
Results: Based on the minimal P value merging results from three genetic models and combining all and age-matching data sets, there were 1, 3, 35, and 195 SNPs that had P values < 10^{-8}, 10^{-8}-< 10^{-7}, 10^{-7}-< 10^{-6}, and 10^{-6}-< 10^{-5}, respectively. The 5 SNPs showing the smallest P values are located at chromosome 5p15.1 within a 22-kb region including *FAM134B*. Ten SNPs located at chromosome 6p21.32 spanning *HLA-DQA1, -DQA2, -DRB1*, and *DRB5* were shown to have small P values (10^{-6}-< 10^{-5}) as well. The 234 SNPs that had had the smallest P values (< 10^{-5}) was selected for the second stage analysis, which is genotyping on additional samples from 470 cases and 470 controls using Illumina VeraCode GoldenGate Genotyping Assay.
Conclusions: Genetic variants might be associated with natural diversity of serum HBV DNA level in patients with chronic HBV infection. The second stage validation and external replications are required to narrow down and consolidate our findings.

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