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## Gene-Gene Interaction of Susceptibility Genes for IgA Nephropathy in the Chinese Han Population

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**Objectives :** IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide. Previous genome-wide association studies (GWAS) have identified multiple susceptibility genes for IgAN. Gene-gene interaction might have more influence on the susceptibility of IgAN and improve our understanding of the genetic pathogenesis of IgAN. This study aims to investigate the correlation between the gene-gene interaction and IgAN susceptibility.

**Methods :** The study enrolled 1,000 IgAN patients and 1,000 healthy controls. Genotyping 63 SNPs of five susceptibility genes (TNFSF13, ITGAX-ITGAM, FCRL3, ST6GAL1 and CARD9) by using MassARRAY platform. Data quality control and filtering were conducted using PLINK 1.90, and the frequency distribution of genotypes and alleles was calculated. Multifactor dimensionality reduction (GMDR) method was used to analyze the multi-step gene interactions.

**Results :** The GMDR analysis revealed that the interaction of TNFSF13 (rs4968210), FCRL3 (rs11264793), and ST6GAL1 (rs2284750, rs7634389) was significantly associated with the risk of IgAN ( $P=0.01$ ,  $OR=2.88$ ). The association analysis of clinicopathological phenotypes showed that the interaction of TNFSF13 (rs3803800), FCRL3 (rs11264794), ITGAM (rs4597342) and ST6GAL1 (rs7634389) was correlated with the serum creatinine level in IgAN patients ( $P=0.01$ ,  $OR=6.12$ ), while the interaction of TNFSF13 (rs3803800), FCRL3 (rs11264793, rs7528684), ITGAX (rs11150619) and ST6GAL1 (rs6784233, rs7634389) was associated with the eGFR in IgAN patients ( $P=0.01$ ,  $OR=14.03$ ). Additionally, association between TNFSF13 (rs3803800), FCRL3 (rs11264793, rs7528684), ITGAX (rs11150614), and ST6GAL1 (rs7634389) was correlated with low density lipoprotein in IgAN patients ( $P=0.01$ ,  $OR=4.81$ ). Furthermore, the interaction of TNFSF13 (rs3803800), FCRL3 (rs11264793, rs7528684), ITGAX (rs7190997) and ST6GAL1 (rs6784233, rs7634389) was associated with hematuria in IgAN patients ( $P=0.001$ ,  $OR=29.66$ ).

**Conclusions :** The study indicated that the interaction of ITGAX-ITGAM, TNFSF13, FCRL3 and ST6GAL1 genes was significantly associated with risk of IgAN. Additionally, it may also influence lipid levels, the incidence of hematuria, and the progression of renal function in patients.