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Differences in Gene-Gene Interactions in Graves' Disease Patients Stratified by Age of Onset

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Abstract

Background

Graves' disease (GD) is a complex disease in which genetic predisposition is modified by environmental factors. Each gene exerts limited effects on the development of autoimmune disease (OR = 1.2–1.5). An epidemiological study revealed that nearly 70% of the risk of developing inherited autoimmunological thyroid diseases (AITD) is the result of gene interactions. In the present study, we analyzed the effects of the interactions of multiple loci on the genetic predisposition to GD. The aim of our analyses was to identify pairs of genes that exhibit a multiplicative interaction effect.

Material and Methods

A total of 709 patients with GD were included in the study. The patients were stratified into more homogeneous groups depending on the age at time of GD onset: younger patients less than 30 years of age and older patients greater than 30 years of age. Association analyses were performed for genes that influence the development of GD: *HLADRB1*, *PTPN22*, *CTLA4* and *TSHR*. The interactions among polymorphisms were analyzed using the multiple logistic regression and multifactor dimensionality reduction (MDR) methods.

Results

GD patients stratified by the age of onset differed in the allele frequencies of the *HLADRB1*03* and *1858T* polymorphisms of the *PTPN22* gene (OR = 1.7, p = 0.003; OR = 1.49, p = 0.01, respectively). We evaluated the genetic interactions of four SNPs in a pairwise fashion with regard to disease risk. The coexistence of *HLADRB1* with *CTLA4* or *HLADRB1* with *PTPN22* exhibited interactions on more than additive levels (OR = 3.64, p = 0.002; OR = 4.20, p < 0.001, respectively). These results suggest that interactions between these pairs of genes contribute to the development of GD. MDR analysis confirmed these interactions.

Conclusion

In contrast to a single gene effect, we observed that interactions between the *HLADRB1/PTPN22* and *HLADRB1/CTLA4* genes more closely predicted the risk of GD onset in young patients.