Complex Genetic Disorders, Genetic Susceptibility to Infections

AB099. Joint effects of *RET* and *SEMA3* polymorphisms in Hirschsprung disease

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Background: *RET* and Semaphorin 3 (*SEMA3*) common variants have been associated with Hirschsprung disease (HSCR), but their genetic interactions for development of HSCR is not established yet. To determine the joint effects of *RET* gene, rs2435357, and *SEMA3* gene with three markers; rs1583147, rs12707682, and rs11766001 polymorphisms in Indonesian HSCR patients.

Methods: Sixty HSCR patients and 115 non-HSCR controls were included in this study. Four genetic markers of the *RET* and *SEMA3* were examined in 175 DNAs using TaqMan Genotyping assay. Case-control analysis and transmission disequilibrium test (TDT) were used to determine an association between four genetic markers and HSCR. We used a P value of <0.013 for a significant association.

Results: There was a strong association between *RET* rs2435357 marker and HSCR either by case-control analysis (OR =4.46, P=2.5×10^{-8}) or TDT (P=4.2×10^{-6}), but not *SEMA3* rs1583147 (OR =1.9, P=0.023 and P=0.11, respectively) and rs12707682 (OR =1.5, P=0.06 and P=0.041, respectively). Two locus analyses of variants revealed that *RET* rs2435357 (TT), in combination with *SEMA3* rs1583147 (CT) or rs12707682 (CC), were associated with the augmented disease risks of HSCR (OR =2.88, P=0.016 and OR =19.9, P=0.005, respectively) compared with a single variant of *SEMA3* rs1583147 or rs12707682. Moreover, the *SEMA3* rs11766001 frequencies in HSCR patients and non-HSCR subjects were 1.7% and 0.8 % (P=0.48), respectively.

Conclusions: The genetic effects of *SEMA3* genotypes are epistatic to *RET*. The rarity of *SEMA3* rs11766001 in Indonesia could be explained by the founder effect.

Keywords: Hirschsprung disease; *RET*; Semaphorin 3; polymorphisms; rare variant

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