

Complex Genetic Disorders, Genetic Susceptibility to Infections

AB087. Synergistic genetic effects of *RET* and *NRG1* susceptibility variants in Hirschsprung disease

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Background: Hirschsprung disease (HSCR) is a complex genetic disorder, which characterized by absence of ganglion cells along variable lengths of the intestines in neonates, with the *RET* and *NRG1* are reported as the most common susceptible genes for HSCR development. Here, we investigated three common genetic markers: *RET* rs2506030 and *NRG1* rs7835688 and rs16879552, to determine their potential interactions to the susceptibility of HSCR in Indonesian population.

Methods: We ascertained 60 HSCR subjects and 118 non-HSCR controls. Three genetic markers of the *RET* and *NRG1* were examined using TaqMan assay. Case-control association tests between three genetic markers and HSCR were performed using the χ^2 (chi square) statistic

and 2x2 contingency tables. We analyzed the family based association in duos and trios using the transmission disequilibrium test (TDT) for the variants using PLINK.

Results: There was association between *NRG1* rs7835688 (4.3×10^{-3}) variant and HSCR, but not *RET* rs2506030 ($P=0.042$) and *NRG1* rs16879552 ($P=0.097$). TDT of 33 HSCR families demonstrates no genetic effect either at *RET* rs2506030 ($P=0.034$) or *NRG1* rs7835688 ($P=0.18$) and rs16879552 ($P=0.28$). Two locus analyses of polymorphisms demonstrated that *RET* rs2506030 (GG), in combination with *NRG1* rs7835688 (CC) or rs16879552 (CC), were associated with the increased disease risks of HSCR (OR =6.22, $P=0.028$ and OR =3.34, $P=6.0 \times 10^{-4}$, respectively) compared with a single variant of either *RET* or *NRG1*.

Conclusions: Our study shows that *RET* and *NRG1* polymorphisms are common genetic risk factors for Indonesian HSCR. These results also imply that synergistic effects of *RET* and *NRG1* is necessary for normal ganglionosis.

Keywords: Hirschsprung disease (HSCR); *RET*; *NRG1*; Indonesia

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