IS-10  Low RET mutation frequency and polymorphism analysis of the RET and EDNRB genes in patients with Hirschsprung disease in Taiwan

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Hirschsprung disease (HSCR), or congenital intestinal aganglionosis, is a relatively common disorder characterized by the absence of ganglion cells in the nerve plexuses of the lower digestive tract, resulting in intestinal obstruction in neonate. Mutations in genes of the RET receptor tyrosine kinase and endothelin receptor B (EDNRB) signaling pathways have been shown to be associated in HSCR patients. In this study we collected genomic DNA samples from 55 HSCR patients in central Taiwan and analyzed the coding regions of the RET and EDNRB gene by PCR amplification and DNA sequencing. In the 55 patients, an A to G transition was detected in two patients (identical twin brothers). The mutation was at the end of RET exon 19 at codon 1062 (Y1062C), a reported critical site for the signaling pathways. Single nucleotide polymorphisms (SNP) in exons 2, 7, 11, 13 and 15 of RET, and exon 4 of EDNRB in the HSCR patients or controls were detected. The differences between patients and controls in allele distribution of the five RET polymorphic sites were statistically significant. The most frequent genotype encompassing exons 2 and 13 SNP (the polymorphic sites with the highest percentage of heterozygotes) was AA/GG in patients, which was different from the AG/GT in the normal controls. Transmission disequilibrium was observed in exons 2, 7 and 13, indicating non-random association of the susceptibility alleles with the disease in the patients. This study represents the first comprehensive genetic analysis of HSCR disease in Taiwan.