# (T1294) MULTI-ANCESTRY GENOME-WIDE ASSOCIATION META-ANALYSIS REVEALS NEW HIRSCHSPRUNG'S DISEASE GENES

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**Abstract**: Hirschsprung's disease (HSCR) is a rare, congenital disorder of the colon in children. Abnormal development of the enteric nervous system (ENS) is known to be involved in its pathogenesis. The disease is caused by multiple genetic factors, but only a few causal genes are reported until now. In this study, we performed the largest multi-ancestry meta-analysis of genome-wide association study (GWAS) involving 1,250 HSCR cases and 7,140 controls and identified four novel HSCR-susceptibility loci, with three loci (JAG1, HAND2 and ZNF25) reaching genome-wide significance and one putative locus (UNC5C) prioritized by functional relevance. Single-cell transcriptomic data and immunofluorescence staining results suggested that four novel candidate genes were expressed in migratory enteric neural crest cells (ENCCs) and/or neurons. In vitro, disruption of HAND2 and ZNF25 in the SK-N-SH cell line caused abnormal migration behaviors. In vivo, CRISPR/Cas9-mediated candidate genes knockout in zebrafish displayed abnormal ENS development. Conclusively, our study showed that JAG1, HAND2, ZNF25 and UNC5C are four novel risk genes for HSCR, and genetic dysregulation of these candidate genes may disrupt ENCCs migration and impair ENS development.

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