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| Title | Generation of patient-specific iPSCs for Hirschsprung's disease modelling |
| Author(s) | Yung, JSY; Chow, KHM; Tse, HF; Tam, PKH; Ngan, ESW |
| Citation | The 2011 Meeting of the Days of Molecular Medicine (DMM), Hong Kong, 10-12 November 2011. |
| Issued Date | 2011 |
| URL | http://hdl.handle.net/10722/144694 |
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## [6] Generation of Patient-Specific iPSCs for Hirschsprung's Disease Modelling

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Hirschsprung's (HSCR) disease is a congenital disorder of the colon in which certain nerve cells are absent due to incomplete colonization of bowel with enteric neural crest (NC) cells, causing chronic constipation. *RET* gene encodes for a tyrosine kinase receptor and is highly implicated in the neural crest development. Mutations or genetic variants in *RET* have accounted for most of the HSCR cases. In particular, a single nucleotide polymorphisms (SNP, rs2435362) residing in the intron one of *RET* gene are predominantly found in HSCR, which may cause a reduced *c-RET* expression in patient. In this study, a HSCR patient carrying a risk allele T in rs2435362 of *RET* gene and exhibiting a short segment aganglionosis and atrial/ventricular septal defects (ASD/VSD) was selected to establish a human model for HSCR. We reprogrammed patient's fibroblast cells into iPS cells by ectopic expression of four reprogramming factors. Three patient-specific iPS cell lines were currently obtained. They were ES-like, expressing the pluripotency markers and with low DNA methylation levels of CpG sites in the promoter regions of *NANOG* and *OCT3/4*. Importantly, they could generate teratoma comprising all three germ layers when they were injected in SCID mice, further corroborating the cells had acquired pluripotency. Subsequent differentiation experiments revealed that these HSCR iPS cells were able to differentiate into NC cells of a comparable capacity as that of the control iPS cells (IMR90). In addition, these iPS-derived NC cells were multipotent and could commit to both neurogenic and smooth muscle lineages under defined differentiation conditions. Nevertheless, in general, all the HSCR-iPS cells showed a lower competency to form neurons and smooth muscle cells, suggesting that differentiation defects of NC may represent a cause of HSCR and other NC-associated disorders. Taken together, these results substantiate the potential use of our patient-specific model to study the etiology of HSCR and other NC-associated diseases.