S8 – Uncovering the Genetic Lesions Underlying the Most Severe Form of Hirschsprung (HSCR) Disease by Whole Genome Sequencing (WGS): A Pilot Study in 8 Family Trios

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Introduction and objectives: Hirschsprung disease (HSCR; aganglionic megacolon) is a complex genetic disorder characterised by the absence of enteric neurons along a variable length of the distal intestine. It is attributed to a failure in the migration of the enteric neurons precursors. HSCR is a relatively rare congenital disorder with significant population variation in incidence with that in Chinese being the highest in the world. The disease presents mainly sporadically although it can be familial (5-20% of the patients).

Only a fraction of the HSCR patients are explained by deleterious **rare** DNA variants (RV) affecting coding sequences (CDS) of genes encoding protein members of the signalling pathways that govern the development of the **enteric nervous system (ENS)**, the most important being *RET*. Also *RET* and *NRG1* common variants (CV; present in >1% of the population) are strongly associated with HSCR although their contribution to the disorder is relatively small. Our and others' data indicate that while HSCR-associated CV contribute to the most common and milder HSCR forms (male, S-HSCR, sporadic), deleterious RV are more likely to underlie the less common and more severe forms (female, L-HSCR, familial). Yet many patients affected with severe aganglionosis are unaccounted for by mutations in known HSCR genes.

Our aim is to understand the genetic architecture underlying HSCR and, for this, the study of sporadic HSCR patients with severe aganglionosis should be the starting point as such phenotype is likely to result from a relatively simple genetic model (de novo or recessively inherited RV in either coding –CDS- or non-coding –NCDS- regions).

Methods: Trios (unaffected parents and affected probands) were scrutinized by whole genome sequencing (WGS). WGS data was also used to detect insertions and deletions larger than 1 kilobase, i.e. copy number variants (CNV).

Results: Amidst the genetic heterogeneity, we sought to find a common "niche" for all RV detected. Pathway analysis of genes with RV indicated that the **E**xtra**C**ellularMatrix-receptor pathway was significantly shared by HSCR patients ($p=1.5x10^{-11}$).

Conclusions: Pronounced genetic heterogeneity (inter and intra-familial) indicates that genetic counselling is not yet advisable. On a more positive note, a molecule common to the main "mutated" pathway/s will eventually be found and such molecule could be used as a therapeutic target. This is the first WGS study in HSCR and has been instrumental for the establishment of a WGS pipeline in HKU.

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