GENETICS, BIOINFORMATICS & SYSTEMS BIOLOGY COLLOQUIUM

THURSDAY, May 27th
12:00-1:00 PM
Held on Zoom

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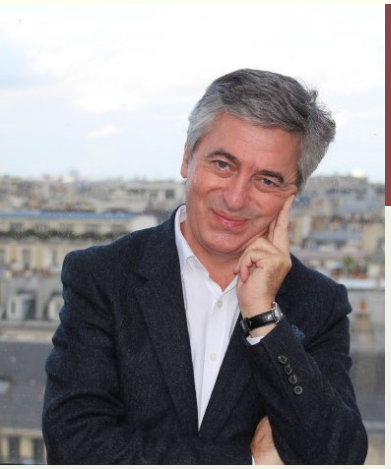
Meeting Password: Genetics



Stanislas Lyonnet, MD

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The genetics of Hirschsprung disease: Transethnic analyses of isolated cases and new candidate genes for syndromic cases

Hirschsprung disease (HSCR) is characterized by the absence of enteric ganglia in the intestinal tract. Whether the ENS above the aganglionic segment is normal has long been controversial and a "transitional zone" has been described. Most patients feature an isolated HSCR, either sporadic (80%) or familial (20%), and the more recent data of our International HSCR Consortium value the role of non-coding variants at predisposing loci depending on the ancestry background.

Regarding syndromic cases (30%), as an example, we recently studied patients presenting HSCR, neuronal chronic intestinal pseudo-obstruction (CIPO), progressive sensorimotor peripheral neuropathy and dysautonomia, without intellectual deficiency. By trio WES we identified compound heterozygous missense substitutions in the pseudokinase domain of the erb-b2 receptor tyrosine kinase 3 (ERBB3, MIM 190151). International collaborations allowed the recruitment of ive additional cases with recessively inherited ERBB3 variants, from unrelated families. The weak genotype-phenotype correlation raises the question of modifying factors. Ongoing in vitro analysis, aimed at studying differences in signalling for different alleles, may explain part of the broad spectrum of clinical manifestations. Thus far, ERBB3 has not been considered as an HSCR candidate gene, despite trans-ethnic GWAS showing an association at the NRG1 locus (MIM 142445, the ligand of ERBB3). Our results now show that ERBB3 dysfunction can lead to a severe intestinal phenotype that combines HSCR and CIPO.

Faculty Host: Joseph Gleeson

Presented by:

IGM Institute for Genomic Medicine

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