Stellingen behorende bij het proefschrift

Genetic and Functional Studies of Hirschsprung Disease

1. *De novo* mutations in Hirschsprung disease patients implicate central nervous system genes in enteric nervous system development, thereby supporting the idea of common factors in the gut-brain axis *(this thesis)*.

2. In complex diseases such as Hirschsprung disease, many different rare and common genetic variants in concert contribute to the diseased phenotype in the same family *(this thesis)*.

3. Our studies on multigenerational Dutch family have highlighted the role of Hedgehog signaling in Hirschsprung disease *(this thesis)*.

4. Overexpression of *ATP5O* affects enteric nervous system development in zebrafish and could explain the causative link between Hirschsprung disease and Down syndrome *(this thesis)*.

5. Unbiased *in silico* prediction of the pathogenic effects of newly identified genes in Hirschsprung disease is not sufficient to prove their causality, but *in vivo* functional analysis using the zebrafish model provides a quick and efficient tool for screening enteric nervous system directly *(this thesis)*.

6. Disease-causing regulatory mutations at enhancer sequences are increasingly recognized, drawing attention to their importance in complex diseases, such as Hirschsprung disease.

7. "We may be RARE, but we've got ROAR" (*Julie Flygare*).

8. Decoding the human genome sequence is the most significant undertaking that we have mounted so far in an organized way in all of science. I believe that reading our blueprints, cataloguing our own instruction book, will be judged by history as more significant than even splitting the atom or going to the moon *(Francis Collins).*

9. I don't know if the optimists or the pessimists are right. But, the optimists are going to get something done *(Craig Venter).*

10. We are sitting at the cusp of a new revolution in NGS technologies, rather than being a novelty, NGS technologies are now a routine part of biological research and becoming more widespread in the clinical sector *(Goodwin et al., 2016, Nature Reviews Genetics).*

11. "कालोऽस्मि लोकक्षयकृत्प्रवृद्धो..... (I am Time, the great destroyer of the world ~Bhagavad Gita 11.32)".

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