



University of Groningen

#### Genetics of Hirschsprung disease

Schriemer, Duco

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version Publisher's PDF, also known as Version of record

Publication date: 2016

Link to publication in University of Groningen/UMCG research database

*Citation for published version (APA):* Schriemer, D. (2016). Genetics of Hirschsprung disease: Rare variants, in vivo analysis and expression profiling [Groningen]: Rijksuniversiteit Groningen

Copyright Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

## **GENETICS OF HIRSCHSPRUNG DISEASE**

Rare variants, in vivo analysis and expression profiling

Duco Schriemer

Genetics of Hirschsprung disease – Rare variants, *in vivo* analysis and expression profiling Duco Schriemer

The work presented in this PhD thesis was mostly conducted at the Department of Neuroscience, section Medical Physiology and the Department of Genetics of the University of Groningen, University Medical Center Groningen. Part of this work was conducted on behalf of The International Hirschsprung Disease Consortium.

The research in this thesis was financially supported by grants from ZonMW (TOP-subsidie 40-00812-98-10042 and the Maag Lever Darm stichting (W009-62).

Printing	Ipskamp Drukkers
Cover design	Duco Schriemer, image of zebrafish gut by William Cheng
Financial support	Printing of this thesis was financially supported by the University of Groningen, University Medical Center Groningen (UMCG) and the Groningen University Institute for Drug Exploration (GUIDE).
ISBN (printed version)	978-90-367-8900-4
ISBN (electronic version)	978-90-367-8899-1

Copyright © 2016 by Duco Schriemer. All rights reserved. No part of this thesis may be reproduced, stored in a retrieval system, or transmitted in any form or by any means without prior permission of the author.



# **Genetics of Hirschsprung disease**

Rare variants, in vivo analysis and expression profiling

### Proefschrift

ter verkrijging van de graad van doctor aan de Rijksuniversiteit Groningen op gezag van de rector magnificus prof. dr. E. Sterken en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

maandag 20 juni 2016 om 14.30 uur

door

### **Duco Schriemer**

geboren op 27 maart 1987 te Leeuwarden

#### Promotor

Prof. dr. R.M.W. Hofstra

#### Copromotor

Dr. B.J.L. Eggen

### Beoordelingscommissie

Prof. dr. J.D. Laman Prof. dr. P.K.H. Tam Prof. dr. ir. J.A. Veltman

#### Paranimfen

Koen van Zomeren Hiske van Duinen

#### **TABLE OF CONTENTS**

Chapter 1	General introduction	
Chapter 2	<i>De novo</i> mutations in Hirschsprung patients link Central Nervous System genes to the development of the Enteric Nervous System	39
Chapter 3	Regulators of gene expression in Enteric Neural Crest Cells are putative Hirschsprung disease genes	87
Chapter 4	Removing the maximum assigned value of the Genotype Quality score allows specific detection of <i>de novo</i> mutations in Next-Generation Sequencing data	111
Chapter 5	Combined strategies to identify diseases associated genes for rare complex diseases: Hirschsprung disease as a model	129
Chapter 6	Overexpression of the chromosome 21 gene <i>ATP50</i> results in fewer enteric neurons: the missing link between Down syndrome and Hirschsprung disease?	157
Chapter 7	General discussion	181
Chapter 8	Summary	196
	Nederlandse samenvatting	200
	List of abbreviations	204
	Dankwoord / Acknowledgements	206