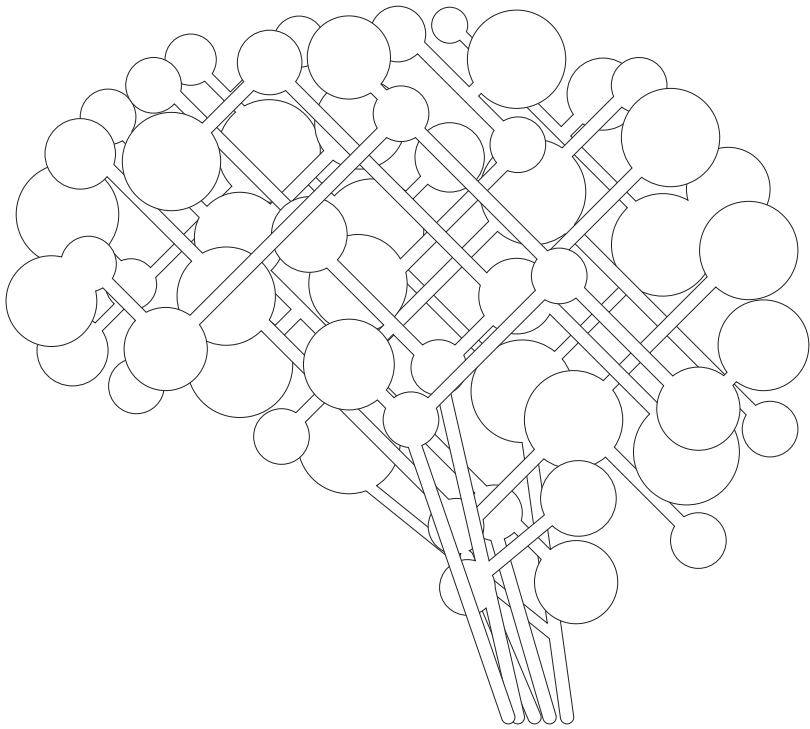


# FROM SINGLE GENES TO GENE-NETWORKS

cellomics meets neurodegenerative diseases



SASJA HEETVELD

Leescommissie: prof.dr. E.M. Hol  
prof.dr. M. Verhage  
dr. W.D.J. van de Berg  
dr. W.M.C. van Roon  
dr. W. Scheper

Paranimfen: Iris E. Jansen  
Margherita Francescatto

Cover design & layout: Design Your Thesis / [www.designyourthesis.com](http://www.designyourthesis.com)  
Printing: Ridderprint B.V. / [www.ridderprint.nl](http://www.ridderprint.nl)  
ISBN: 978-94-6299-915-2

**Copyright © Sasja Heetveld, 2018**

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 holder of the copyright.

Printing of this thesis was financially supported by: Sylics (Synaptologics BV), Parkinson Vereniging, Stichting Alkemade-Keuls and Alzheimer Nederland.

 Sylics



VRIJE UNIVERSITEIT

# From single genes to gene-networks: cellomics meets neurodegenerative diseases

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor  
aan de Vrije Universiteit Amsterdam,  
op gezag van de rector magnificus  
prof.dr. V. Subramaniam,  
in het openbaar te verdedigen  
ten overstaan van de promotiecommissie  
van de Faculteit der Bètawetenschappen  
op woensdag 13 juni 2018 om 11.45 uur  
in de aula van de universiteit,  
De Boelelaan 1105

door

Sasja Heetveld  
geboren te Deventer

promotoren:

prof.dr. A.B. Smit  
prof.dr. P. Heutink

*Voor mijn ouders*



# TABLE OF CONTENTS

<b>Chapter 1</b>	General Introduction	9
<b>Chapter 2</b>	<i>C9orf72</i> is differentially expressed in the central nervous system and myeloid cells and consistently reduced in <i>C9orf72</i> , <i>MAPT</i> and <i>GRN</i> mutation carriers	39
<b>Chapter 3</b>	Regulation of <i>MAPT</i> exon 10 splicing: a shRNA screen of the human spliceosome	97
<b>Chapter 4</b>	RNA-based technologies to modulate alternative splicing of endogenous <i>MAPT</i> exon 10	127
<b>Chapter 5</b>	Discovery and functional prioritization of Parkinson's disease candidate genes from large-scale whole exome sequencing	157
<b>Chapter 6</b>	Summary and General Discussion	225
<b>Addendum</b>	Nederlandse samenvatting	247
	Dankwoord	251
	Publications	255
	About the author	257