



Universiteit
Leiden
The Netherlands

Genetic and clinical pharmacology studies in GBA1-associated Parkinson's disease

Heijer, J.M. den

Citation

Heijer, J. M. den. (2022, March 30). *Genetic and clinical pharmacology studies in GBA1-associated Parkinson's disease*. Retrieved from <https://hdl.handle.net/1887/3281326>

Version: Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/3281326>

Note: To cite this publication please use the final published version (if applicable).

GENETIC AND CLINICAL PHARMACOLOGY STUDIES IN *GBA1*-ASSOCIATED PARKINSON'S DISEASE

PROEFSCHRIFT

ter verkrijging van

de graad van doctor aan de Universiteit Leiden,

op gezag van rector magnificus prof.dr.ir. H. Bijl,

volgens besluit van het college voor promoties

te verdedigen op woensdag 30 maart 2022

klokke 16:15 uur

DOOR

Jonas Matthias den Heijer

geboren te Roermond

in 1991

PROMOTORES

Prof. dr. G.J. Groeneveld

Prof. dr. J.J. van Hilten

LEDEN PROMOTIECOMMISSIE

Prof. dr. F. Baas

Prof. dr. J.M.A. van Gerven

Dr. W.D.J. van de Berg, Amsterdam UMC

Dr. B.P.C. van de Warrenburg, Radboud UMC

DESIGN: Caroline de Lint, Den Haag (caro@delint.nl)

COVER: Folkert van Meurs (FvMeurs@chdr.nl)

Photography used under the Unsplash License, for cover design: ('African fish eagle lunching' by Birger Strahl; 'Lioness staredown' by Harshil Gudka; 'Woman' by Icons8 Team).

Publication of this thesis was financially supported by the foundation Centre for Human Drug Research (CHDR) in Leiden, the Netherlands

Chapter 1	Introduction; adapted and updated version of ‘New insights into the pathobiology of Parkinson’s disease and possibilities for pharmacotherapy’ – 8
Chapter 2	A large-scale full <i>GBA1</i> gene screening in Parkinson’s Disease in the Netherlands – 12
Chapter 3	False negatives in <i>GBA1</i> sequencing due to polymerase dependent allelic imbalance – 22
Chapter 4	Experience in genetic counseling for <i>GBA1</i> variants in Parkinson’s Disease – 58
Chapter 5	Intronic haplotypes in <i>GBA</i> modify age at diagnosis of Parkinson’s: Replication in a subgroup – 66
Chapter 6	Preparing for <i>GBA1</i> -targeting Parkinson’s disease trials: a biomarker study in patients with <i>GBA1</i> -Parkinson’s disease and healthy controls – 72
Chapter 7	A randomized single and multiple ascending dose study in healthy volunteers of LTI-291, a centrally penetrant glucocerebrosidase activator – 104
Chapter 8	A phase 1B trial in <i>GBA1</i> -associated Parkinson’s disease of LTI-291, a centrally-penetrant glucocerebrosidase activator – 130
Chapter 9	Discussion – 154
Chapter 10	Summary in Dutch – 160
Appendices	Curriculum Vitae – 165 List of publications – 166 Dankwoord – 168