



Universiteit
Leiden

The Netherlands

Functional analysis of genetic variants in PALB2 and CHEK2: linking functional impact with cancer risk

Boonen, R.A.C.M.

Citation

Boonen, R. A. C. M. (2023, April 4). *Functional analysis of genetic variants in PALB2 and CHEK2: linking functional impact with cancer risk*. Retrieved from <https://hdl.handle.net/1887/3590202>

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/1887/3590202>

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

**FUNCTIONAL ANALYSIS OF GENETIC VARIANTS IN *PALB2* AND
CHEK2: LINKING FUNCTIONAL IMPACT WITH CANCER RISK**

RICK BOONEN

The studies described in this thesis were performed at the Department of Human Genetics at the Leiden University Medical Centre, Leiden the Netherlands.

ISBN: 978-94-6483-006-4

The printing of this thesis was financially supported by the Leiden University Library.

Cover design: The cover and title pages have been designed by Rick A.C.M. Boonen

About the cover: With a bit of imagination, the little European robin that is carefully studied on the front cover is thought to depict a genetic variant (e.g., a variant of uncertain significance)

Thesis layout: Rick A.C.M Boonen

Printing: Ridderprint | www.ridderprint.nl

Copyright © by R.A.C.M. Boonen

All rights reserved. No parts on this book may be reproduced, stored in a retrieval system or transmitted in any form or by any means, without permission of the author.

**FUNCTIONAL ANALYSIS OF GENETIC VARIANTS IN *PALB2* AND
CHEK2: LINKING FUNCTIONAL IMPACT WITH CANCER RISK**

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 dinsdag 4 april 2023
klokke 15:00 uur
door

Ricky Antonius Cornelius Martin Boonen
geboren te Boxmeer
in 1983

Promotores

Prof. dr. H. van Attikum

Prof. dr. P. Devilee

Copromotor

Dr. M.P.G. Vreeswijk

Leden promotiecommissie

Prof. dr. ir. M.K. Schmidt

Prof. dr. J.M.M. Jonkers (Nederlands Kanker Instituut)

Prof. dr. H.P.J. te Riele (Nederlands Kanker Instituut)

Prof. dr. P.M. Knipscheer (Hubrecht Instituut)

For Isabella & Odin

CONTENTS

Chapter 1	General introduction	11
Chapter 2	Functional characterization of <i>PALB2</i> variants of uncertain significance: toward cancer risk and therapy response prediction	27
Chapter 3	<i>CHEK2</i> variants: linking functional impact to cancer risk	63
Chapter 4	Functional analysis of genetic variants in the high-risk breast cancer susceptibility gene <i>PALB2</i>	89
Chapter 5	Functional interpretation of <i>PALB2</i> missense variants and their association with breast cancer risk	141
Chapter 6	Functional analysis identifies damaging <i>CHEK2</i> missense variants associated with increased cancer risk	171
Chapter 7	Future perspectives	225
Chapter 8	Nederlandse samenvatting	238
	Curriculum Vitae	242
	Publications	244
	Dankwoord	248