

University of Groningen

## Functional and clinical translation of asthma and allergy associated genetic variants in IL33 and IL1RL1

Ketelaar, Marlies

DOI:  
[10.33612/diss.171580070](https://doi.org/10.33612/diss.171580070)

**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:*  
2021

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Ketelaar, M. (2021). *Functional and clinical translation of asthma and allergy associated genetic variants in IL33 and IL1RL1*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen. <https://doi.org/10.33612/diss.171580070>

### 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).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

### Take-down policy

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.

**Functional and clinical translation of asthma  
and allergy associated genetic variants in *IL33*  
and *IL1RL1***

Maria Elizabeth Ketelaar

Images: Maria E. Ketelaar  
Cover: Ilse Modder | [www.ilsemodder.nl](http://www.ilsemodder.nl)  
Lay-out: Ilse Modder | [www.ilsemodder.nl](http://www.ilsemodder.nl)  
Print: Gildeprint | [www.gildeprint.nl](http://www.gildeprint.nl)

© 2021 M.E. Ketelaar. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without the prior permission in writing from the proprietor.

© 2021 M.E. Ketelaar. Alle rechten voorbehouden. Niets uit deze uitgave mag worden verveelvoudigd, opgeslagen in een geautomatiseerd gegevensbestand, of openbaar gemaakt, in enige vorm of op enigerlei wijze, hetzij elektronisch, mechanisch, door fotokopieën, opnamen, of op enige andere manier, zonder voorafgaande schriftelijke toestemming van de rechthebbende.



rijksuniversiteit  
groningen

# Functional and clinical translation of asthma and allergy associated genetic variants in *IL33* and *IL1RL1*

## Proefschrift

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

De openbare verdediging zal plaatsvinden op

maandag 14 juni 2021 om 11.00 uur

door

**Maria Elizabeth Ketelaar**

geboren op 20 februari 1986  
te Hoogezand-Sappemeer

## **Promotores**

Prof. dr. G.H. Koppelman

Prof. dr. M.C. Nawijn

Prof. dr. I. Sayers

## **Beoordelingscommissie**

Prof. dr. H.A.M. Kerstjens

Prof. dr. R.W. Hendriks

Prof. dr. I.M. Adcock

**“Juist  
van de weg af zie je meer”**



**“Next  
to the road there is more to experience”**



# Table of Contents

<b>Chapter 1</b>	General Introduction Translational research: a tailored prescription for patient, doctor and scientist?	11
<i>PART I "The role of the IL-33/IL1-RL1 pathway in asthma and allergic disorders: current evidence from genetic and clinical studies"</i>		25
<b>Chapter 2</b>	Decoding asthma: Translating genetic variation in <i>IL33</i> and <i>IL1RL1</i> into disease pathophysiology	27
<b>Chapter 3</b>	The role of the IL-33/IL-1RL1 axis in mast cell and basophil activation in allergic disorders	51
<i>PART II "Functional translation of IL33 and IL1RL1 genotypes into asthma pathophysiology"</i>		61
<b>Chapter 4</b>	Phenotypic and functional translation of <i>IL33</i> genetics in asthma	63
<b>Chapter 5</b>	Phenotypic and functional translation of <i>IL1RL1</i> locus poly morphisms in lung tissue and asthmatic airway epithelium	123
<b>Chapter 6</b>	Effects of IL-33 on differentiated human Th2 cells stratified for <i>IL1RL1</i> asthma risk haplotypes	171
<i>PART III "Clinical translation of the IL-33/IL-1RL1 pathway in asthma and allergy"</i>		203
<b>Chapter 7</b>	The challenge of measuring IL-33 in serum using commercial ELISA: lessons from asthma	205
<b>Chapter 8</b>	Predictive value of serum sST2 in preschool wheezers for development of asthma with high FeNO	213
<b>Chapter 9</b>	IL-1RL1a serum levels and <i>IL1RL1</i> SNPs in the prediction of food allergy	221
<i>PART IV "A bird's eye view"</i>		237
<b>Chapter 10</b>	Summary, general discussion and future perspectives	239
<b>Chapter 11</b>	Dutch summary   Nederlandse samenvatting	261
<b>References</b>		269
<b>Appendix</b>		289
	Word of thanks   Dankwoord	290
	Curriculum vitae of the author	296



