



Genetic Determinants of Non-syndromic Hearing Impairment

Genetische determinanten van
niet-syndromale slechthorendheid

Regie Lyn Pastor Santos



Printing of this thesis was realized with financial support from the Laboratory of Statistical Genetics (Leal Laboratory), Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas USA.

GENETIC DETERMINANTS OF NON-SYNDROMIC HEARING IMPAIRMENT
Santos, Regie Lyn Pastor
Thesis, Erasmus Medical Center, Erasmus University Rotterdam
With summary in English and Dutch



© Regie Lyn Pastor Santos, 2006

No part of this thesis may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, mechanical, photocopying, recording or otherwise, without written permission from the author. Several chapters are based on published articles, which were reproduced with permission from the co-authors and publishers. Copyright of these articles remains with the publishers.

Cover design and layout: Dennis A. Santos

Printed by RainTree Trading & Publishing Inc., Quezon City, Philippines





Genetic Determinants of Non-syndromic Hearing Impairment

Genetische determinanten van niet-syndromale slechthorendheid

Proefschrift

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de rector magnificus
Prof.dr. S.W.J. Lamberts
en volgens besluit van het College voor Promoties

De openbare verdediging zal plaatsvinden op
donderdag 14 september 2006 om 11 uur

door

Regie Lyn Pastor Santos

geboren te Caloocan City, Philippines



PROMOTIECOMMISSIE

Promotor: Prof.dr. C.M. van Duijn

Overige leden: Prof.dr. A. Uitterlinden
Prof.dr. J.G.G. Borst
Prof.dr. G. van Camp

Co-promotoren: Prof.dr. S.M. Leal
Dr. Y.S. Aulchenko



Para kay Mama --

*The enemy was cut off,
lost the chance to stare and grope at it.*

*I felt the knife sear,
though it is not my body
but my genes.*

*Did we win the DNA lottery?
Only time will tell.*

Contents

Chapter 1	INTRODUCTION	1
Chapter 2	NOVEL HEARING IMPAIRMENT LOCI	
2.1	A novel autosomal recessive non-syndromic hearing impairment locus (<i>DFNB47</i>) maps to chromosome 2p25.1-p24.3. <i>Hassan MJ, Santos RLP, Rafiq MA, Chahrour MH, Pham TL, Wajid M, Hijab N, Wambangco M, Lee K, Ansar M, Yan K, Ahmad W, Leal SM.</i> <i>Hum Genet</i> 2006 Jan; 118(5): 605-610.	13
2.2	Localization of a novel autosomal recessive non-syndromic hearing impairment locus <i>DFNB55</i> to chromosome 4q12-q13.2. <i>Irshad S, Santos RLP, Muhammad D, Lee K, McArthur N, Haque S, Ahmad W, Leal SM.</i> <i>Clin Genet</i> 2005 Sep; 68(3): 262-267.	25
2.3	The mapping of <i>DFNB62</i> , a new locus for autosomal recessive non-syndromic hearing impairment, to chromosome 12p13.2-p11.23. <i>Ali G, Santos RLP, John P, Wambangco MAL, Lee K, Ahmad W, Leal SM.</i> <i>Clin Genet</i> 2006 May; 69(5): 429-433.	34
2.4	Localization of a novel autosomal recessive non-syndromic hearing impairment locus <i>DFNB65</i> to chromosome 20q13.2-q13.32. <i>Tariq A, Santos RLP, Khan MN, Lee K, Hassan MJ, Ahmad W, Leal SM.</i> <i>J Mol Med</i> 2006 Mar; 84(3): 226-231.	43
2.5	<i>DFNB68</i> , a novel autosomal recessive non-syndromic hearing impairment locus at chromosomal region 19p13.2. <i>Santos RLP, Hassan MJ, Sikandar S, Lee K, Ali G, Martin PE, Wambangco MAL, Ahmad W, Leal SM.</i> <i>Hum Genet</i> 2006 Aug; 120(1): 85-92.	54
Chapter 3	FUNCTIONAL VARIANTS IN KNOWN HEARING IMPAIRMENT GENES	
3.1	Low prevalence of Connexin 26 (<i>GJB2</i>) variants in Pakistani families with autosomal recessive non-syndromic hearing impairment. <i>Santos RL, Wajid M, Pham TL, Hussan J, Ali G, Ahmad W, Leal SM.</i> <i>Clin Genet</i> 2005 Jan; 67(1): 61-68.	67



3.2	Novel sequence variants in the <i>TMCI</i> gene in Pakistani families with autosomal recessive hearing impairment.	81
	<i>Santos RLP, Wajid M, Khan MN, McArthur NM, Pham TL, Bhatti A, Lee K, Irshad S, Mir A, Yan K, Chahrour MH, Ansar M, Ahmad W, Leal SM.</i>	
	<i>Hum Mutat 2005 Oct; 26(4): 396.</i>	
3.3	Novel sequence variants in the <i>TMIE</i> gene in families with autosomal recessive non-syndromic hearing impairment.	93
	<i>Santos RLP, El-Shanti H, Sikandar S, Lee K, Bhatti A, Yan K, Chahrour MH, McArthur NM, Pham TL, Mahasneh AA, Ahmad W, Leal SM.</i>	
	<i>J Mol Med 2006 Mar; 84(3): 226-231.</i>	
Chapter 4	CORRELATION OF GENOTYPE WITH AUDIOMETRIC PHENOTYPE	
4.1	Hearing impairment in Dutch patients with Connexin 26 (<i>GJB2</i>) and Connexin 30 (<i>GJB6</i>) mutations.	103
	<i>Santos RLP, Aulchenko YS, Huygen PLM, van der Donk KP, de Wijs IJ, Kemperman MH, Admiraal RJ, Kremer H, Hoefsloot LH, Cremers CWRJ.</i>	
	<i>Int J Pediatr Otorhinolaryngol 2005 Feb; 69(2):165-174.</i>	
4.2	Phenotypic characterization of <i>DFNA24</i> : Prelingual progressive sensorineural hearing impairment.	119
	<i>Santos RLP, Haefner FM, Huygen PLM, Linder TE, Schinzel AA, Spillmann T, Leal SM.</i>	
	<i>Audiol Neurotol 2006 May; 11(5): 269-275.</i>	
Chapter 5	DISCUSSION	130
Chapter 6	SUMMARY AND CONCLUSIONS	157
	SAMENVATTING	162
	WORDS OF APPRECIATION	166
	AUTHOR'S DESCRIPTION	168