Statistical methods for analysing complex genetic traits

El Galta, Rachid

Statistical methods for analysing complex genetic traits

Rachid el Galta

Statistical methods for analysing complex genetic traits

PROEFSCHRIFT

ter verkrijging van de graad van Doctor
aan de Universiteit Leiden,
op gezag van de Rector Magnificus Dr. D. D. Breimer,
hoogleraar in de faculteit der Wiskunde en Natuurwetenschappen
en die der Geneeskunde,
volgens besluit van het College voor Promoties
te verdedigen op woensdag 27 september 2006
klokke 13:45 uur

door

Rachid el Galta

geboren te Elkbab, Marokko, in 1972

PROMOTIECOMMISSIE

PROMOTORES:	Prof. dr. J. C. van Houwelingen Prof. dr. T. Stijnen · *Erasmus Medical Center, Rotterdam*
CO-PROMOTOR:	Dr. J. J. Houwing-Duistermaat
REFERENT:	Prof. dr. H. Bickeböller · *University of Göttingen, Göttingen*
OVERIGE LEDEN:	Prof. dr. C. M. van Duijn · *Erasmus Medical Center, Rotterdam* Prof. dr. E. P. Slagboom Prof. dr. F. R. Rosendaal

This work was financially supported by a Program Grant from the Netherlands Organization for Scientific Research (NWO 912-03-014). Publication of this thesis was supported by the department of Medical Statistics, LUMC.

Contents

1 Introduction **1**
- 1.1 Introduction . . . 1
- 1.2 Familial Correlation . . . 1
- 1.3 Linkage analysis . . . 3
- 1.4 Association studies . . . 6
- 1.5 Scope of this thesis . . . 8

2 Score test for proband-family design **11**
- 2.1 Introduction . . . 12
- 2.2 Methods . . . 14
- 2.3 Simulation study . . . 17
- 2.4 Discussion . . . 20
- 2.5 Appendix . . . 24

3 Global tests for linkage **25**
- 3.1 Introduction . . . 26
- 3.2 Methods . . . 27
- 3.3 Simulation . . . 30
- 3.4 Discussion . . . 35
- 3.5 Appendix . . . 37

4 Score test for genetic association **41**
- 4.1 Introduction . . . 42
- 4.2 The maximising approach . . . 44
- 4.3 The averaging approach . . . 45
- 4.4 Simulation study . . . 48
- 4.5 Application to real data . . . 52
- 4.6 Discussion . . . 53
- 4.7 Appendix 1 . . . 55
- 4.8 Appendix 2 . . . 56

5 Methods for testing genetic association **59**
5.1 Background 60
5.2 Material and Methods 61
5.3 Results 62
5.4 Discussion 63

6 Generalizing Terwilliger's likelihood approach **67**
6.1 Introduction 68
6.2 Methods 70
6.3 Results 71
6.4 Discussion 74

7 Phenotypic Subtypes in ADHD **79**
7.1 Introduction 80
7.2 Methods 81
7.3 Results 83
7.4 Discussion 84
7.5 Appendix 87

8 Summary **91**

9 Samevatting **95**

Bibliography **99**

Curriculum Vitae **111**