# Genetics and epigenetics of repeat derepression in human disease

Peter E. Thijssen

Lay out & cover design: Peter Thijssen

Printing: Publisher BOXPress || Proefschriftmaken.nl

ISBN: 9789462954250



Publication of this thesis was financially supported by the department of Human Genetics and the Leiden University Medical Center

# Genetics and epigenetics of repeat derepression in human disease

**Proefschrift**

ter verkrijging van de graad van Doctor aan de Universiteit Leiden
op gezag van Rector Magnificus prof.mr.C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op donderdag 1 september 2016
klokke 13:45

door

Peter Evert Thijssen

geboren te Zoetermeer in 1983

| | |
|---|---|
| Promotores: | Prof. Dr. Ir. S.M. van der Maarel<br>Prof. Dr. P.E. Slagboom |
| Leden promotiecommissie: | Prof. Dr. A.M. Aartsma-Rus<br>Prof. Dr. J.H.L.M. van Bokhoven[1]<br>Prof. S. Tapscott, MD, PhD[2] |

1: UMC Radboud, Nijmegen, The Netherlands
2: Fred Hutchinson Cancer Research Center, Seattle, WA, USA

*- Voor papa -*

## Table of Contents


| | | |
|---|---|---|
| Chapter 1: | General introduction | 9 |
| Chapter 2: | Correlation analysis of clinical parameters with epigenetic modifications in the *DUX4* promoter in FSHD. | 35 |
| Chapter 3: | Chromatin remodeling of human subtelomeres and TERRA promoters upon cellular senescence: commonalities and differences between chromosomes. | 47 |
| Chapter 4: | Increased DUX4 expression during muscle differentiation correlates with decreased SMCHD1 protein levels at D4Z4. | 67 |
| Chapter 5: | DUX4 promotes transcription of *FRG2* by directly activating its promoter in Facioscapulohumeral muscular dystrophy. | 89 |
| Chapter 6: | Intrinsic epigenetic regulation of the D4Z4 macrosatellite repeat in a transgenic mouse model for FSHD. | 105 |
| Chapter 7: | Mutations in *CDCA7* and *HELLS* cause immunodeficiency, centromeric instability and facial anomalies syndrome. | 135 |
| Chapter 8: | General discussion | 149 |
| Chapter 9: | Appendices<br>Summary<br>Samenvatting<br>Curriculum vitae<br>List of publications<br>Dankwoord | 171 |