



Universiteit
Leiden

The Netherlands

The human genome; you gain some, you lose some

Kriek, M.

Citation

Kriek, M. (2007, December 6). *The human genome; you gain some, you lose some*. Retrieved from <https://hdl.handle.net/1887/12479>

Version: Corrected 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/1887/12479>

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

The human genome; you gain some, you lose some

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit van Leiden,
op gezag van de Rector Magnificus prof.mr. P.F. van der Heijden,
volgens besluit van het Collega van Promoties
te verdedigen op donderdag 6 december 2007
klokke 15.00 uur

door

Marjolein Kriek
geboren te Leiden, in 1973

PROMOTIECOMMISSIE

Promotoren: Prof. dr. M.H. Breuning
Prof. dr. G-J. B. van Ommen

Co-promotor: Dr. J.T. den Dunnen

Referent: Prof. dr. H.H. Ropers (Max Planck Instituut te Berlijn)

Overige leden: Dr. K. Szuhai

Voor Bram

ISBN 978-90-9022286-8

Designed by: Grafisch Bureau Christine van der Ven, Voorschoten

Cover design: Ik heb tijdens mijn promotieonderzoek gezocht naar veranderingen in het erfelijk materiaal, die het voorkomen van een verstandelijke beperking bij de mens zouden kunnen verklaren. De voorkant van dit proefschrift laat de vormgeving van een mens zien, vertaald door Petra Kaak, kunstenares bij Kunst en Vliegwerk.

Kunst & Vliegwerk verzorgt een bijzondere vorm van dagbesteding voor kunstzinnig getalenteerde mensen met een verstandelijke handicap.

Printed by: Grafische Producties, Universitair Facilitair Bedrijf, Leiden

The author of this thesis was financially supported by the Netherlands Organisation for Health Research and Development (ZON-Mw), registration number 940-37-032.

© 2007 M. Kriek, Leiden, The Netherlands

All rights reserved. No part of this thesis may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system, without permission from the copyright owner.

CONTENT

List of definitions	8
List of abbreviations	10

CHAPTER I INTRODUCTION 11

1. The plasticity of human genome	12
2. CNVs with no obvious phenotypic trait	13
2.1 Neutral CNVs	13
2.2 Segmental duplications	15
2.2.1 Characteristics of segmental duplicons	15
2.2.2 Intra- and interchromosomal duplicons	16
3. CNVs with phenotypic trait: genomic disorders	17
3.1 Genomic disorders	17
3.2 Mental retardation	17
3.3 Congenital Malformation	18
4. Different types of variations	19
4.1 Whole chromosome alterations	19
4.2 Partial chromosome alterations	19
4.2.1 Subtelomeric CNVs	19
4.2.2 CNVs in microdeletion syndromes regions	21
4.2.3. Other interstitial CNVs	23
4.3 Other variations	24
5. Consideration regarding pathogenicity of CNVs	24
6. Detection of CNVs	26
6.1 Standard cytogenetic tools	26
6.1.1 Karyotyping	26
6.1.2 Fluorescent <i>in situ</i> Hybridisation (FISH) analysis	27
6.1.3 Fiber FISH	28
6.1.4 Multiprobe FISH and Spectral Karyotyping	28
6.2 High resolution tools (not genome-wide)	29
6.2.1 History	29
6.2.2 Restriction Fragment Length Polymorphisms	29

6.2.3	Southern Blotting	30
6.2.4	Pulse Field Gel Electrophoresis (PFGE)	30
6.2.5	Microsatellites for detecting CNVs	30
6.2.6	Quantitative real-time PCR	32
6.2.7	Towards MAPH and MLPA	32
6.2.8	MAPH	32
6.2.9	MLPA	33
6.2.10	Data analysis of MLPA and MAPH	34
6.3	Whole genome (high resolution) tools: recent genomic approaches	34
6.3.1	Overview	34
6.3.2	Array-CGH using BAC clones	35
6.3.3	Array-CGH using long oligos	36
6.3.4	SNP based arrays	36
6.3.5	Comparing cross platform	36
7.	Scope of this thesis	37
8.	In summary	39

CHAPTER II SCREENING ‘LARGE’ PATIENT GROUPS 41

1.	Genetic imbalances in mental retardation <i>J Med Genet. 2004 Apr;41(4):249-55</i>	43
2.	Copy number variation in regions flanked (or unflanked) by duplicons among patients with developmental delay and / or congenital malformations; detection of reciprocal and partial Williams Beuren duplications <i>Eur J Hum Genet. 2006 Feb;14(2):180-9</i>	63
3.	Diagnosis of genetic abnormalities in developmentally delayed patients: a new strategy combining MLPA and array-CGH <i>Am J Med Genet A. 2007 Mar 15;143(6):610-4</i>	83

CHAPTER III CASE REPORT BASED FINDINGS	93
1. A complex rearrangement on chromosome 22 affecting both homologues; haplo-insufficiency of the Cat eye syndrome region may have no clinical relevance	95
<i>Hum Genet. 2006 Aug;120(1):77-84.</i>	
2. Peters Plus Syndrome Is Caused by Mutations in B3GALT1, a Putative Glycosyltransferase	111
<i>Am J Hum Genet. 2006 Aug; 79(3):562-6.</i>	
3. Telomeric deletions of 16p causing alpha-thalassemia and mental retardation characterized by multiplex ligation-dependent probe amplification	121
<i>Human Genet. 2007 Jun 28 [Epub ahead of print]</i>	
4. Comparison of four genome-wide platforms using overlapping interstitial 2p alterations	141
<i>Submitted</i>	
CHAPTER IV	159
1. Discussion	161
2. Summary	165
3. Nederlandse Samenvatting	169
CURRICULUM VITAE	175
LIST OF PUBLICATIONS	177
REFERENCES	181
APPENDIX 1. MAPH/array-CGH request form	196
2. Colour pictures	197

LIST OF DEFINITIONS

Acrocentric chromosomes:	Chromosomes lacking the short arm. The human acrocentric chromosomes are 13, 14, 15, 21, and 22.
Congenital malformation:	A physical defect present in the newborn.
Copy number:	The number of copies of a given chromosomal locus.
Copy number variation:	Alteration of a copy number of a certain DNA sequence in relation to the normal situation.
with phenotypic trait:	variation with clinical consequences.
without phenotypic trait:	variation without obvious clinical consequences (also called Polymorphic CNVs).
Deletion:	Loss of a DNA sequence.
Duplication:	An extra copy of a DNA sequence.
Duplicon:	Duplicon or segmental duplication has been defined as sequences of DNA greater than 1 Kb in size sharing a homology of at least 90 %.
False positive result:	An incorrect positive result of a test.
False negative result:	A result that appears negative but fails to reveal an alteration.
Gene:	Coding sequence.
Gene desert:	Region in the human genome that does not contain genes.
Genomic disorders:	The clinical condition that results from a dosage alteration of gene(s) located within a rearranged segment of the genome.
Mendelian inheritance:	Several inheritable traits or congenital conditions in humans are classical examples of Mendelian inheritance: Their presence is controlled by a single gene that can either be of the autosomal-dominant or -recessive type. People that inherited at least one dominant gene from either parent usually present with the dominant form of the trait. Only those that received the recessive gene from both parents present with the recessive phenotype (Wikipedia).

Mental retardation (MR) classification:	Mild MR (intelligent quotient (IQ) between 50 and 70), moderate MR (IQ between 35 and 50), severe MR (IQ between 20 and 35) and profound MR (IQ below 20).
Polymorphic CNVs:	CNVs (deletions as well as duplications) that are not related to a clinical phenotype (also called CNVs without phenotypic trait).
Phenotypic trait:	Any (abnormal) clinical feature, such as mental retardation, congenital malformations, dysmorphologies.
Translocations:	Exchange of genetic material between two different chromosomes.
Robertsonian translocations:	These translocations are produced by exchange in proximal short arms of the acrocentric chromosomes. Both centromeres are present, however, they function as one unit. This translocation is named after W.R.B. Robertson who described fusion of acrocentric chromosomes in insects.
Reciprocal translocations:	A translocation where part of one chromosome is exchanged with a part of a separate non-homologous chromosome.
Transposition:	Transfer of a segment of DNA to a new position on the same or another chromosome.
Uniparental disomy:	A euploid cell in which one of the chromosome pairs have been inherited exclusively from one parent. If two identical homologues are inherited this called isodisomy; if non-identical homologues are inherited the term heterodisomy is used. This occurs when non-disjunction during meiosis in one parent leads to formation of a disomic gamete. A trisomic zygote is formed and trisomic rescue with loss of the chromosome from the other parent occurs. UPD is of particular relevance in imprinted regions of the genome.

LIST OF ABBREVIATIONS

Bp	Base pair
BAC	Bacterial Artificial Chromosome
CGH	Comparitive Genome Hybridisation
CM	Congenital Malformation
CNVs	Copy Number Variation
COBRA	COmbined Binary RATio
DD	Development Delay
DNA	Deoxyribonucleic acid
DOP-PCR	Degenerate Oligonucleotide Primed Polymerase Chain Reaction
FISH	Fluorescent in Situ Hybridisation
I.Q.	Intelligence Quotient
K	Kilo
Kb	Kilo base (one thousand base pairs)
LCR	Low Copy Repeat
MAPH	Multiplex Amplifiable Probe Hybridisation
Mb	Mega base (one million base pairs)
M-FISH	Multi-colour FISH
MLPA	Multiplex Ligation-dependent Probe Amplification
MR	Mental Retardation
NAHR	Non Allelic Homologous Recombination
Nt	Nucleotide
PAC	P1 derived Artificial Chromosome (PAC)
PCR	Polymerase Chain Reaction
PFGE	PulseField Gel Electrophoresis
RFLP	Restriction Fragment Length Polymorphism
SKY	Spectral Karyotyping
SNP	Single Nucleotide Polymorphism
UPD	Uniparental Disomy
VNTR	Variable Number of Tandem Repeats