

**DETECTION OF COPY NUMBER VARIATIONS IN  
INTELLECTUALLY DISABLED PATIENTS IN  
INDONESIA USING HIGH RESOLUTION GENOME  
WIDE ARRAY ANALYSIS**

**DETEKSI *COPY NUMBER VARIATIONS* PADA PASIEN  
DISABILITAS INTELEKTUAL DI INDONESIA  
MENGUNAKAN ANALISIS *GENOME WIDE ARRAY*  
RESOLUSI TINGGI**



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**THESIS**

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## THESIS

### DETECTION OF COPY NUMBER VARIATIONS IN INTELLECTUALLY DISABLED PATIENTS IN INDONESIA USING HIGH RESOLUTION GENOME WIDE ARRAY ANALYSIS

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I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which to a substantial extent has been accepted for the award of any other degree or diploma of the university or other institute of higher learning, except where due acknowledgement is made in the text

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## CONTENTS

<b>TITLE</b> .....	i
<b>APPROVAL SHEET</b> .....	ii
<b>DECLARATION</b> .....	iii
<b>ACKNOWLEDGEMENT</b> .....	iv
<b>CURRICULUM VITAE</b> .....	vii
<b>CONTENTS</b> .....	xii
<b>ABBREVIATIONS</b> .....	xvi
<b>LIST OF TABLES</b> .....	xix
<b>LIST OF FIGURES</b> .....	xx
<b>LIST OF APPENDICES</b> .....	xxii
<b>GLOSSARY</b> .....	xxiii
<b>ABSTRACT (ENGLISH)</b> .....	xxv
<b>ABSTRACT (BAHASA INDONESIA)</b> .....	xxvi
<b>CHAPTER 1 INTRODUCTION</b> .....	1
1.1 Background.....	1
1.2 Research Question.....	4
1.3 Research Purposes .....	4
1.3.1 General Research Purposes.....	4
1.3.2 Specific Research Purpose.....	5
1.4 Research Benefits.....	5
1.5 Research Originality.....	5
<b>CHAPTER 2 LITERATUR REVIEW</b> .....	6

2.1	Intellectual Disability (ID).....	6
2.1.1	Definition of ID.....	6
2.1.2	Inheritance and Etiology of ID.....	8
2.2	Copy Number Variation (CNV).....	9
2.2.1	Classification of CNV.....	10
2.2.2	Databases for CNVs.....	12
2.2.3	Mechanisms Underlying the Formation of CNV.....	14
2.2.3.1	Homologous Recombination (HR).....	15
2.2.3.2	Non Homologous Recombination.....	16
2.2.4	Methods to Detect CNVs.....	20
2.2.4.1	Genome Wide Microarrays.....	20
2.2.4.2	Fluorescence In Situ Hybridization.....	22
2.2.4.3	Quantitative Polymerase Chain Reaction.....	23
2.2.4.4	Multiplex Ligation-Dependent Probe Amplification.....	24
2.2	Theoretical Framework.....	26
2.3	Conceptual Framework.....	27
	<b>CHAPTER 3 RESEARCH METHODS.....</b>	<b>28</b>
3.1	Research Field.....	28
3.2	Research Location.....	28
3.3	Research Period.....	29
3.4	Research Design.....	29
3.5	Population and Sample.....	29
3.5.1	Population.....	29

3.5.2 Sample.....	30
3.5.2.1 Inclusion Criteria.....	30
3.5.2.2 Exclusion Criteria.....	31
3.6 Research Variable.....	32
3.7 Detection of Copy Number Variations.....	32
3.7.1 Preparation.....	32
3.7.2 Detection of CNVs using high resolution genome wide array..	32
3.7.2.1 Array Laboratory Flow.....	32
3.7.2.2 Processing of Array Data .....	36
3.7.2.3 Filtering Relevant CNVs and Interpretation.....	36
3.7 Research Flow.....	39
3.8 Data Analysis.....	40
3.9 Research Ethics.....	40
<b>CHAPTER 4 RESULTS.....</b>	<b>41</b>
4.1 Genome Wide Array Analysis.....	41
4.2 FISH Study.....	47
4.3 Clinical Findings.....	50
<b>CHAPTER 5 DISCUSSION.....</b>	<b>53</b>
<b>CHAPTER 6 CONCLUSION AND FUTURE DIRECTIONS .....</b>	<b>67</b>
6.1 Conclusion.....	67
6.2 Future Directions.....	68
<b>CHAPTER 7 SUMMARY .....</b>	<b>69</b>

<b>RINGKASAN</b> .....	73
<b>REFERENCES</b> .....	77
<b>APPENDIX</b> .....	86
<b>ARTICLE</b> .....	96

## ABBREVIATIONS

AAIDD	American Association on Intellectual and Developmental Disabilities
AGCC	Affymetrix GeneChip Command Console
ASHG	American Society of Human Genetics
BAC	Bacterial artificial Chromosome
BAZ1B	Bromodomain Adjacent to the Zinc finger domain 1 B
BEGAIN	Brain Enriched Guanylate Kinase Associated Protein
CLIP2	CAP-Gly domain containing Linker Protein 2
CGH	Comparative Genomic Hybridization
ChAS	Chromosome Analysis Suite
CNV	Copy Number Variation
DAEMON	Disk And Execution Monitor
DECIPHER	Database of Chromosomal Imbalance and Phenotype in Human Using Ensembl Resources
DEGS2	Delta(4)-desaturase, sphingolipid 2
DGV	Database of Genomic Variants
DLK1	Delta Like 1
DNA	Deoxyribo Nucleic Acid
ECARUCA	European Cytogeneticists Association Register of Unbalanced Chromosome Abberations



ELN	Elastin
EML1	Echinoderm Microtubule associated protein like 1
ESHG	European Society of Human Genetics
EVL	Enah/Vasp-like
FBS	Fetal Bovine Serum
FCN3	Ficolin 3
FISH	Fluorescent in situ Hybridization
FMR1	Fragile X Mental Retardation 1
FoSTeS	Fork Stalling and Template Switching
GECCO	Genomic CNV Classification Object
HR	Homologous Recombination
ID	Intellectual Disability
LCR	Low Copy Repeat
LOH	Loss of Heterozygosity
LIMK1	LIM domain Kinase 1
MAPD	Median of the Absolute values of all Pairwise Differences
MEG	Maternally Expressed Gene
MEM	Minimum Essential Medium
MLPA	Multiplex Ligation-dependent Probe Amplification
MMBIR	Microhomology Mediated Break Induce Replication
NAHR	Non-Allelic Homologous Recombination
NHEJ	Non-Homologous End Joining
NROB2	Nuclear Receptor Subfamily O, grup B, member 2

OMIM	Online Mendelian Inheritance in Man
PCR	Polymerase Chain Reaction
PEG	Paternally Expressed Gene
ROH	Region Of Homozigosity
RTL1	Retrotransposon- Like 1
RTL1as	Retrotransposon- Like 1 anti sense
RUMC	Radboud University Medical Centre
SNP	Single Nucleotide Polymorphism
UCSC	University of California Santa Cruz
UPD	Uni Parental Disomy
VOUS	Variation of Unknown Significance
WARS	Tryptophanyl-tRNA synthethase
WBS	Williams- Beuren Syndrome
WDR25	WD repeat domain 25
WSTF	William Syndrome Transcription Factor
WINAC	WSTF Including Nucleosome Assembly Complex
YY1	Yin Yang 1

## LIST OF TABLES

<b>Table 1</b>	Classification of ID based on IQ measurement.....	8
<b>Table 2</b>	CNV Classification in the human genome.....	11
<b>Table 3</b>	Public internet databases for array data interpretation.....	14
<b>Table 4</b>	Overview of the latest generation of commercially available microarrays for CNV detection.....	22
<b>Table 5</b>	Summary of some molecular methods to detect CNVs.....	25
<b>Table 6</b>	Total amount samples obtained from special schools in Indonesia.....	30
<b>Table 7</b>	Checklist of de Vries score for patient with chromosomal aberration.....	31
<b>Table 8</b>	CNVs found in subjects by genome wide array analysis using CytoScan HD Affymetrix platform.....	42
<b>Table 9</b>	Distribution of significant LOH region in Patient 5 .....	42
<b>Table 10</b>	Clinical features of patients with Copy Number Variants .....	51
<b>Table 11</b>	Patient 2 and 3 phenotypes compared to WBS typical phenotype .....	57

## LIST OF FIGURES

<b>Figure 1</b>	NAHR mechanism .....	16
<b>Figure 2</b>	Fork Stalling and Template Switching mechanism .....	17
<b>Figure 3</b>	MMBIR mechanism.....	19
<b>Figure 4</b>	Schematic of array CGH technology.....	20
<b>Figure 5</b>	The automated data filtering “pipeline”.....	37
<b>Figure 6(a)</b>	A 1.1 Mb loss in 14q32.2q32.31 was detected in Patient 1 (arr 14q32.2q32.31 (100,388,343-101,506,214)x 1 dn).....	43
<b>Figure 6(b)</b>	Trio analysis confirms that the deletion has occurred de novo in the patient.....	43
<b>Figure 7</b>	A 1.4 Mb loss in 7q11.23 (Williams Beuren Syndrome ) was detected in Patient 2 .....	44
<b>Figure 8</b>	A 1.4 Mb loss in 7q11.23 (Williams Beuren Syndrome ) was detected in Patient 3 .....	44
<b>Figure 9(a)</b>	A 1.7 Mb gain in 1p36.11p35.3 was detected in Patient 4 (arr1p36.11p35.3(27,193,049-28,899,662)x3 dn).....	45
<b>Figure 9(b)</b>	Trio analysis confirms that the gain has occurred de novo in the patient.....	45
<b>Figure 9(c)</b>	A 240 kb gain in 6q11.1 was detected in Patient 4 (6q11.1(62,664,971-62,935,276)x3) .....	46
<b>Figure 9(d)</b>	Trio analysis revealed that this gain was inherited from the mother.....	46

<b>Figure 10</b>	FISH study in Patient 1 and her father. FISH study in 30 metaphases from cultured peripheral blood.....	48
<b>Figure 11</b>	FISH study in Patient 2 and his parents. FISH study in metaphases from cultured peripheral blood.....	49
<b>Figure 12(a)</b>	Metaphase FISH study in Patient 4 using RP4-633N17 (green) located on 1p36.11& RP11-290H1 (red) .....	50
<b>Figure 12(b)</b>	Interphase FISH study in Patient 4 showed one normal chromosome 1 and duplicated 1p36.11p35.3.....	50
<b>Figure 13</b>	Clinical photographs of patients 1,2,3,4 and 5.....	52
<b>Figure 14</b>	Screenshot of the UCSC genome browser showing the RefSeq genes and a micro RNA cluster.....	53
<b>Figure 15</b>	RefSeq genes in the deleted 7q11.23 region, flanked by segmental duplication, in Patient 2 and 3.....	60
<b>Figure 16</b>	Screenshot of the UCSC Genome Browser showing the DECIPHER patients and RefSeq.....	62
<b>Figure 17</b>	Diagnostic algorithm for patients with suspect chromosomal aberration in Indonesia.....	66

## LIST OF APPENDICES

<b>Appendix 1</b>	Clinical Examination Form.....	92
<b>Appendix 2</b>	Informed Consent Form.....	101

## GLOSSARY

Copy number variation	A genomic structural variation ranging from kilobases (kb) to megabases (Mb) that are not identifiable by conventional chromosomal banding
Intellectual disability	Neurodevelopmental disorder that is characterized by an intelligence quotient (IQ) of 70 or below, and deficits in at least two behaviors related to adaptive functioning diagnosed by 18 years of age
Array	A collection of microscopic DNA spots attached to a solid surface. Each spot contains picomoles ( $10^{-12}$ moles) of a specific DNA sequence known as probes.
FISH	Fluorescent in situ hybridization. A cytogenetic technique that is used to detect and localize the presence or absence of specific DNA sequence on chromosomes by using fluorescent probes
MLPA	Multiplex Ligation-dependent Probe Amplification. A variation of the multiplex polymerase chain reaction that permits multiple targets to be amplified with only a single primer pair. Only those primers that hybridize to the target sequences are amplified, and the resulting products can be analyzed by capillary electrophoresis
qPCR	Quantitative Polymerase Chain Reaction. A

quantitative measurement of DNA based polymerase chain reaction

ROH Region Of Homozigosity. When the genomics copies derived from each parent have the same base for the polymorphic region

SNP Single Nucleotide Polymorphism. a DNA sequence variation occurring when a single nucleotide (A,T,C or G) in the genome differs between paired chromosomes

Trio A group consists of child, father, and mother



## ABSTRACT

**Background:** Intellectual disability (ID) is a neurodevelopmental disorder that is characterized by an intelligence quotient (IQ) of 70 or below, and deficits in at least two behaviors related to adaptive functioning diagnosed by 18 years of age. The etiology of ID can be classified as genetic and non-genetic factors. Chromosomal abnormality is a frequent genetic cause of ID. Routine cytogenetic analysis remained the major diagnostic test for ID patients in Indonesia. However, it cannot detect the submicroscopic chromosomal rearrangement termed copy number variation (CNV). The use of genome wide array analysis to detect CNVs might increase the rate of diagnostic yield in ID patients in Indonesia.

**Methods:** Eighteen patients with ID who had normal results after karyotyping, CGG repeat analysis in the *FMR1* gene and subtelomeric MLPA testing were included. Detection of CNVs were done by using high resolution genome wide array analysis (Affymetrix CytoScan HD Array platform) with an average test resolution of approximately 20 kb then analyzed by using Chromosome Analysis Suite (ChAS) Software V.2.0. The various CNV detected were classified by comparing in house and international normal and affected individual datasets, gene contents and literature studies. FISH studies were performed for carrier testing and the possible presence of a balanced chromosome rearrangement in the parents and/or mosaic imbalance.

**Results:** Three out of 18 patient with ID were found to carry pathogenic CNV i.e one patient with 14q32.2q32.31 microdeletion of 1.1 Mb and 2 patients with 7q11.23 microdeletion of 1.4 Mb (Williams-Beuren Syndrome). One patient with 1p36.11p35.3 microduplication of 1.7 Mb were found to carry likely pathogenic CNV. In addition, there is one patient carried large homozygous regions totaling ~7% of the autosomal genome which one of these homozygous stretches harbours a mutated recessive disease gene.

**Conclusion:** The genome wide array analysis in this study has an additional detection rate of 16.7% (3 out of 18 patients) causative CNVs in selected ID patients after routine karyotyping combined with subtelomeric MLPA and CGG(n) repeat analysis in the *FMR1* gene.

**Keywords:** Intellectual disability, copy number variation, genome wide array analysis

## ABSTRAK

**Latar belakang:** Disabilitas intelektual adalah kelainan perkembangan syaraf yang ditandai dengan  $IQ \leq 70$  dan deficit sekurangnya dua perilaku terkait fungsi adaptif yang terdiagnosis sebelum usia 18 tahun. Penyebabnya dapat diklasifikasikan sebagai factor genetic dan non-genetik. Kelainan kromosom adalah penyebab genetik tersering pada disabilitas intelektual. Analisis sitogenetik rutin masih menjadi tes diagnosis utama pada pasien disabilitas intelektual di Indonesia. Meskipun demikian, tes tersebut tidak dapat mendeteksi kelainan kromosom submikroskopik yang disebut *copy number variation* (CNV). Analisis menggunakan *genome wide array* kemungkinan menaikkan tingkat penegakan diagnosis pada pasien disabilitas intelektual di Indonesia.

**Metode:** Sampel DNA diambil dari delapan belas pasien dengan disabilitas intelektual yang mempunyai hasil normal setelah analisis karyotyping, CGG *repeat* pada gen *FMRI* dan subtelomerik MLPA. Deteksi CNV dilakukan dengan menggunakan teknik *genome wide array* (Affymetrix CytoScan HD Array platform) dengan resolusi rata-rata 20 Kb yang selanjutnya dianalisis menggunakan *Chromosome Analysis Suite (ChAS) Software V.2.0*. Variasi CNV yang terdeteksi diklasifikasikan dengan cara membandingkan dataset *in house* dan internasional dari individu normal dan penderita, isi gen, dan studi literatur. Uji FISH dilakukan dalam rangka validasi rutin untuk mengetahui adanya *balance rearrangement* atau mozaik tingkat rendah pada orang tua.

**Hasil:** CNV patogenik ditemukan pada 3 dari 18 pasien dengan disabilitas intelektual yaitu satu pasien dengan mikrolelesi 1.1 Mb pada kromosom 14q32.2q32.31 dan 2 pasien dengan mikrolelesi 1.4 Mb pada kromosom 7q11.23 (Williams-Beuren Syndrome). *Likely pathogenic CNV* ditemukan pada satu pasien dengan mikroduplikasi 1.7 Mb pada kromosom 1p36.11p35.3. Terdapat pula satu pasien dengan regio homozigot luas (7% dari total autosom) dimana salah satu daerah homozigot ini mengandung gen penyakit resesif yang termutasi.

**Kesimpulan:** Analisis dengan *genome wide array* pada studi ini memiliki tambahan tingkat deteksi CNV penyebab disabilitas intelektual sebesar 16.7% (3 dari 18 pasien) setelah analisis karyotype rutin dikombinasi dengan subtelomerik MLPA dan CGG *repeat* pada gen *FMRI*.

Kata kunci: Disabilitas intelektual, *copy number variation*, *genome wide array*