MUTATION ANALYSIS OF MENTAL RETARDATION PATIENTS WITH EPILEPSY IN INDONESIA

ANALISIS MUTASI PADA PASIEN MENTAL RETARDASI DENGAN EPILEPSI DI INDONESIA

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Research Thesis

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ABSTRAK

Analisis Mutasi Pasien Mental Retardasi dengan Epilepsi di Indonesia

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Latar Belakang: Sebanyak 1-3% populasi umum menderita retardasi mental, 25.5% diantaranya mengalami epilepsi. Fokus penelitian ini adalah pada pasien MR dengan epilepsi. Beberapa gen diketahui menjadi penyebab keduanya. Gen yang menjadi fokus pada penelitian ini adalah: *SCN1A*, *ARX*, *STXBP1* dan *LGI1*. Ini adalah studi genetik pertama yang menyelidiki tentang MR dengan epilepsi pada populasi Indonesia.

Tujuan: Mencari faktor genetik pada kasus MR dengan epilepsi di Indonesia.

Material dan Metode: Sebanyak 32 kasus epilepsi didapat dari 527 pasien MR di SLB Semarang dan Bandung. Seluruh pasien MR telah diperiksa abnormalitas sitogenetiknya dan melalui skrining *CGG repeats* gen *FMR1*. Juga telah melewati skrining delesi/ duplikasi subtelomerik menggunakan MLPA. Satu kasus yang positif terdeteksi dieksklusi. Sebanyak empat kasus curiga sindromik diskrining gen-gen berikut: *PTEN*, *UPF3B, MED12*, *UBE3A*, dan *TCF4.* Kemudian seluruh kasus diperiksa mutasi gen *SCN1A, LGI1* dan *STXBP1*. Skrining gen *ARX* dilakukan pada 19 pasien laki-laki.

Hasil dan Diskusi: Tidak ditemukan mutasi pada skrining gen *PTEN*, *MED12*, *UBE3A*, maupun *TCF4*. Bbegitu juga pada gen *ARX*. Pada skrining gen *SCN1A* teridentifikasi 18 *SNPs* dan 2 *UVs* (c.2143+44C>T) dan c.2808G>A (p.Val936Val). Satu *UV* ditemukan pada gen *STXBP1*: c.730C>G (p.Leu244Val) namun tidak patogenik. Hasil tersebut mengindikasi bahwa variasi genomik pada gen terpilih untuk skrining bukan jenis yang umum ditemukan pada populasi MR dengan epilepsi di Indonesia.

Kesimpulan: Tidak ditemukan mutasi patogenik pada pasien MR dengan epilepsi di Indonesia. Pentingnya konseling genetik utamanya untuk kalkulasi resiko penurunan, model penurunan dan manajemen pasien lebih lanjut.

Kata kunci: retardasi mental, epilepsi, mutasi.

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ABSTRACT

Mutation Analysis of Mental Retardation Patients with Epilepsy in Indonesia

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Background: About 1-3% of the general population has Mental Retardation, 25.5% of them have epilepsy. This study focuses on patients with both MR and epilepsy. Several genes are known to be involved in MR with epilepsy. Only few of these genes have been analyzed for mutations in the Indonesian patient cohort: *SCN1A*, *ARX*, *STXBP1* and *LGI1*. This is first genetic study for MR with epilepsy in Indonesian population.

Aim: To seek underlying genetic defect in Indonesian MR patients with epilepsy.

Materials and methods: Epilepsy cases were found in 32 out of 527 mentally retarded pupils at special-ed-schools in Semarang and Bandung. All 527 MR patients were previously screened for cytogenetic abnormalities and CGG repeats in the *FMR1* gene. They were subsequently screened for subtelomeric deletions/duplications using MLPA analysis. From those 32 cases, one case with positive result was excluded. In four suspected syndromic patients specific genes (*PTEN*, *UPF3B, MED12*, *UBE3A*, and *TCF4*) were analyzed. Patients were screened for mutations in the *SCN1A, ARX, LGI1* and *STXBP1* genes.

Results and Discussion: No mutation was found in the *PTEN*, *MED12*, *UBE3A*, or *TCF4* genes. So did testing of 19 patients for *ARX* gene mutations. In the *SCN1A* gene, 18 SNPs and 2 UVs have been identified [(c.2143+44C>T) and (c.2808G>A) (p.Val936Val)]. One UV has been identified in the *STXBP1* gene: (c.730C>G) (p.Leu244Val) but proven to be non pathogenic. These results suggest that genomic variations in screened genes are rarely found among MR with epilepsy population in Indonesia.

Conclusions: No pathogenic mutation has been identified in Indonesian MR with epilepsy patients. Genetic councelling aspect is also very important to calculate the risk of inheritance, mode of inheritance and further management of the patients.

Key words: mental retardation, epilepsy, mutation.

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List of Abbreviations and Glossary

AAIDD : American Association of Intellectual and Developmental Disabilities

ARX : The Aristaless Related Homeobox gene

CGH : Comparative Genomic Hybridization

CNVs : Copy Number Variations

DD : Development Delay

DNA : Deoxyribonucleic acid

DSM : Diagnostic and Statistical Manual of Mental Disorders

EDTA : Ethylenediaminetetraacetic acid

EEG : Electro encephalogram

FISH : Fluoresence In Situ Hibridization

FMR1 : Fragile X Mental Retardation 1

GABA : *g*-aminobutyric acid

IBE : International Bureau for Epilepsy

ICD-10 : International Classification of Disease 10

ILAE : International League Against Epilepsy

IQ : Intelligence Quotients

LGI1 : Leucine-rich, glioma inactivated 1 gene

MCD : Malformation of Cortical Development

MED12 : Mediator of RNA polymerase II transcription, subunit 12 gene

MLPA : Multiplex Ligation Probe Amplification

MTA : Material Transfer Agreement

MQ	: MilliQ
MR	: Mental retardation
NCBI	: National Center for Biotechnology Information
OMIM	: Online Mendelian Inheritance in Man
PAR	: Pseudo Autosomal Regions
PCR	: Polymerase Chain Reaction
PTEN	: Phosphatase and tensin homolog gene
RefSeq	: Reference Sequence
RUNMC	: Radboud Universiteit Nijmegen Medical Centre
SCN1A	: Gene that encode sodium channel, voltage-gated, type I, alpha subunit
STXBP1	: Syntaxin-binding protein 1 gene
SMEI	: Severe myoclonic epilepsy of infancy
SNP	: Single Nucleotide Polymorphism
STDS	: Sub-telomeric duplications and deletions
TCF4	: Transcription factor 4 gene
TE	: Tris EDTA, buffer
UBE3A	: Ubiquitin-protein ligase E3A gene
UCSC	: University of California Santa Cruz
WHO	: World Health Organization
WISC-IV	: Wechsler Intelligence Scale for Children IV
WPPSI	: Wechsler Preschool and Primary Scale of Intelligence
WS	: West Syndrome

Declaration

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.

Semarang, July 2011

Alfi Afadiyanti

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