

CHAPTER I

INTRODUCTION

1.1 Background

Over the past decades, genetic knowledge of many disorders especially Mental Retardation (MR), also known as Learning Disability or Intellectual Disability and epilepsy has been upgraded gradually.¹ Numbers of genetic factors revealed gradually as the main causative agent for some cases, which are monogenic, syndromic, Mendelian CNVs (Copy Number Variations) or chromosomal rearrangements.²

The reason why molecular screening becomes very important nowadays is actually quite simple. It is indeed one of the powerful methods to answer the big question from the clinician point of view, for researchers and most importantly for parents.³ By knowing the deficitst, clinicians and researchers coulddevelop new strategiesto prevent the diseases. Parents could also deal with theirpsychological issues. Family members of the patients have more concerns about how to manage the condition. By doing molecular screening, conclusion of Mental retardation and epilepsy genetic defect become clearer.²

Mental retardation with epilepsy is two diseases that are sometimes found in one patient. Those two conditions basically have different pathogenesis, but also have connection.^{4, 5} About 1-3% of the general population has MR, 25.5% of them having epilepsy.^{4, 6} This study focuses on patients with both MR and epilepsy.

MR is a neuro developmental disorder. According to American Association of Intellectual and Developmental Disabilities (AAIDD), MR or Intellectual disability is defined as a condition that is characterized by significant limitations both in intellectual functioning and adaptive behavior as expressed in conceptual, social, and practical skills, which acquired before the age of 18.¹ Disruption of cognitive and adaptive performance is present in two to three percent of the human population.^{1,2,7}

Epilepsy by definition is a brain disorder characterized predominantly by recurrent and unpredictable interruptions of normal brain function omitted called epileptic seizures. Epilepsy affects almost 1% of the whole population world wide⁸⁻¹⁰ and it is a condition that reflects dysfunction in the brain by some conditions. There are three main characteristics pointed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) about diagnosing epilepsy.¹¹ They are 1) history of at least one seizure, 2) enduring alteration in the brain that increases the likelihood of future seizures, and 3) association with neurobiology, cognitive, psychological, and social disturbances.¹²

With thenon-genetic causes during pre-natal, birth or post-natal period could also be the main causative that underly the defect. When those non genetic causes could not be found, the next step is going to start thinking about genetic factors. Several genes are known to be involved in MR with epilepsy. A few of these genes have been analyzed, such as *SCN1A*, *ARX*, *STXBPI* and *LGII*.^{13,14}

Starting few years ago, molecular screening studies has been done in Indonesia.^{15, 16} However, the lack of facilities in Indonesia, advanced molecular assessments have to be carried out in other centers abroad. Up until now there are only few studies on MR among Indonesian population carried out by Indonesian researchers or in collaboration with excellent centers. This is the first genetic study performed as MR with epilepsy comorbid condition in the Indonesian population. A previous study mostly focused on epilepsy in Indonesia, without mental retardation.¹⁷ More over genetic assessments as an etiological diagnostic method for MR and epilepsy have not been recognized yet as a routine diagnostic procedures.

1.2 Research Question

1.2.1 General Research Question

What are there genetic factors that playroles in the etiology of mental retardation with epilepsy in Indonesian population?

1.2.2 Research question in detail

1. Are there *SCN1A* mutations in Indonesian MRwith epilepsy population?
2. Is there *ARX* mutation in Indonesian MRwith epilepsy population?
3. Is there *STXBPI* mutation in Indonesian MRwith epilepsy population?
4. Is there *LGII* mutation in Indonesian MRwith epilepsy population?

1.3 Research objectives

1.3.1 General objective

To search for the underlying genetic defect of mental retardation patients with epilepsy in Indonesia.

1.3.2 Specific objectives

1. To search for *SCN1A* mutations and the inheritance pattern in Indonesian mental retardation with epilepsy population.
2. To search for *ARX* mutations and the inheritance pattern in Indonesian mental retardation with epilepsy population.
3. To search for *STXBPI* mutations and the inheritance pattern in Indonesian mental retardation with epilepsy population.
4. To search for *LGII* mutations and the inheritance pattern in Indonesian mental retardation with epilepsy population.

1.4 Research advantages

1. To know the underlying genetic defect, in order to search for inheritance pattern of Indonesian mental retardation with epilepsy population.
2. To encourage public awareness of genetic diseases, especially for the parents of patients with mental retardation with epilepsy in Indonesia.
3. To give more attentions of the importance of genetic counseling to mental retardation patients with epilepsy, especially for parents and relatives, also for Indonesian society.

1.5 Research originality

The table below illustrates the previous study associated with this study. What makes this research original is the fact that this is a systematic search of the genetic causes of MR and epilepsy in the population. Studies of Faradz SMH (1999), about the incidence of FRAX in large cohort is referred, also master thesis from Mundhofir FEP (2008), mentioned the incidence of chromosomal aberrations, FRAX and STD, and cytogenetic study from Soepalarto SA (2008)¹⁸ become the basic fundamental of this research. This study is an extension of the study of Mundhofir FEP (2008) study.

Table 1. Research Originality

No	Publications	Contents
1	Faradz, S. M. H., Lam-Po-Tang, P. R. L., Leigh, D. et al. Molecular screening for fragile-X syndrome in Indonesian children with developmental disability. Am J Med Genet 1999; 83, 350±351. ¹⁵	This is the first huge molecular screening program to determine the prevalence of fragile X syndrome among school children with developmental disability (DD) in Indonesia. The result of overall prevalence fragile-X in males with mild DD in special schools was 5/262 (1.9%).
2	Mundhofir, FEP. Cytogenetics, Molecular and Clinical Studies Among Mentally Retarded Individuals in Semarang [Master Thesis]. Semarang Indonesia: Diponegoro Univ.; 2008. ¹⁶	The prevalence of FXS in this study was 1,65 % (2/121) in the whole population and 2,15 % (2/93) in the male population. And the prevalence of STDs in the population was calculated to be 4,3% (5/117).
3.	Hirose S, Mitsudome A. X-linked mental retardation and epilepsy: pathogenetic significance of ARX mutations. ⁴	The findings provide solid evidence for the relationship between MR and epilepsy at a molecular level, opening a new avenue for understanding the pathogenesis of MR associated

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16. Mundhofir F. Cytogenetics, Molecular and Clinical Studies Among Mentally Retarded Individuals in Semarang. Thesis. Semarang: Universitas Diponegoro; 2008.
17. Gunadharna S. Psycho-Social Issues: Public awareness, understanding and attitude towards epilepsy in Bandung, Indonesia. *Neurology Asia [Supplement].* 2004;9:133 - 4.
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