

CHAPTER V

DISCUSSION

Pathogenic mutations in Indonesian mental retardation and epilepsy list were unable to found, in whom had been sequenced the coding regions of *UBE3A*, *UPF3B* and or *MED12*, *PTEN*, and *TCF4* genes. After sequencing the different genes, no mutation found still. Also, any pathogenic mutation in *SCN1A*, *ARX*, *STXBPI* and *LGII* genes sequencing were not found.

Some of the patients with mental retardation and epilepsy in the patients list had additional clinical features which are compatible with some syndromes. One of the patients showed features of Angelman syndrome. Angelman syndrome is characterized by mental retardation, movement or balance disorder, characteristic abnormal behaviors, and severe limitations in speech and language. The patient has severe MR, speech impairment, seizures, and attention disorder.⁸² The most common cause of Angelman syndrome is a methylation defect due to a maternal deletion or parental UPD15, but this has been excluded in this patient. Another, less frequent, cause of Angelman syndrome is a point mutation in the *UBE3A* gene.⁸³ This gene has been sequenced for this patient, but no mutations have been identified.

Second, *UPF3B* gene. Its defect is the underlying cause of Lujan syndrome. According to Buggenhout et al. 2006, Lujan-Fryns syndrome is characterized by X-linked mental retardation and a marfanoid habitus.^{74, 84} The patient is a male, mentally retarded and tends to be marfanoid. No mutations have been identified in the *UPF3B* gene.

Third, *PTEN* gene. Its defect is the underlying cause of Cowden syndrome.⁸⁵ This patient has some of Cowden syndrome criterias such as: macrocephaly, hamartomas, and MR. The *PTEN* gene has been sequenced and checked by MLPA, but no mutations were found. Fourth case was

tested with *TCF4* gene. The Pitt-Hopkins syndrome is a form of severe epileptic encephalopathy with mental retardation and intermittent hyperventilation, as well as characteristic facial gestalt.^{86, 87} The patient has severe MR and similarity with PHS facial features, but no mutation in the *TCF4* gene.

SCN1A, *ARX*, *STXBPI*, and *LGII* genes were chosen based on supported journals and the mutation frequency of those genes. Although no pathogenic mutation on *SCN1A* found, two unclassified variants in the intron 12 and exon 15 were captured. None of them are proven pathogenic.

Genetic is only one of the factor that play roles on etiology of MR with epilepsy.² In genetic itself, there are many other possibilities that have not investigated yet. More sophisticated techniques to detect the cytogenetic abnormalities could be used. SNP arrays, despite of its high expenses, this techniques provided revelations around 11% of MR genetic causes.⁸⁸

In addition, splice site investigation, using prediction programs such as Alamut software (<http://www.interactive-biosoftware.com/alamut.html>) suggested that the intronic polymorphism and variants and exonic polymorphisms in *SCN1A* and *STXBPI* genes did not cause splice alterations.^{89, 90}

Although common genes that are associated with particular disease already investigated, there are also other factors called epigenetic.⁹¹ Several studies have examined the roles of these genes. Nakayama et al. 2003, mentioned that they were failed to find the causative mutation of febrile seizures patients.⁹² Wallace et al. 1998, screened for *SCN1B* mutations in 25 FS families and found no disease-causing mutations.⁶⁷ Malacarne et al. 2002, screened for *SCN1A* mutations

in 32 FS multiplex families and found one coding polymorphism (T1067A), but there was no evidence for an association of any of the alleles with FS.⁹³