CHAPTER VI

CONCLUSION AND FUTURE DIRECTIONS

6.1. Conclusion

The conclusions of this study are as follows:

1. This study did not find any pathogenic causative missense, nonsense, splicing, small deletions, and small insertions mutations of *ASPM, WDR62, CENPJ, CDK5RAP2, MCPH1* and *STIL* genes in MR individuals with microcephaly, which made up 9.1% of all 527 MR individuals. This may be because the microcephaly and mental retardation in the affected individuals were not caused by genetic defects (such as due to prenatal infections), the causes were genetic mutations but not in the genes investigated in this study, or the causes were genetic mutations, but in the gene that had not yet been discovered.
2. This study found a total of 25 unclassified variants in 15 individuals in *ASPM* and *WDR62* genes, which are categorized as either "unlikely to be pathogenic" or "likely to be pathogenic" based on protein prediction results. Based on the variants found on the *ASPM* gene, twins discordance is found in this study, where two monozygotic twin sisters with similar variants have different phenotypes (only one sister is affected with mental retardation and microcphaly).
3. This study did not find any pathogenic causative missense, nonsense, splicing, small deletions, small insertions, and large deletions mutations of the *PTEN* gene in the Indonesian mentally retarded individuals with macrocephaly, which made up 1.9% of all 527 MR individuals. This finding may be due to mutations that were not in the genes investigated in

this study, or the causes were genetic mutations, but in the gene that had not yet been discovered.

4. This study did not find unclassified variants in the *PTEN* gene which were categorized as either “unlikely to be pathogenic” or “likely to be pathogenic” based on protein prediction results.

6.2. Future Directions

The recommendations regarding possible future studies based on the findings of the current study are:

1. Testing the presence of causative mutations using MLPA to detect not just point mutations but also large deletions or duplications in the genes which had not yet been done in this research.
2. Performing whole exome sequencing on the discordant twins found in this study in order to find new gene that may explain the cause of the microcephaly and mental retardation. In addition, further follow up study on other family members that include 3 generations and epigenetic studies on the twins can be done.
3. Early detection of microcephaly or macrocephaly should be done by measurement of birth OFC and monitoring using consistent head chart suitable for the Indonesian population. Furthermore, an Indonesian reference head chart should be established for use in the Indonesian population.