# CHAPTER V

DISCUSSION

In present study, four mutations were found in four different families, p.P1305L in *CRB1* gene, p.V99I and p.G244S in *RPE65* and p.R338X in *RP1* gene were found in Indonesian RP families. The p.P1305L variant in *CRB1* gene that was found in three different families which originated from different regions of Central Java suggests that this mutation can be considered a founder mutation in Javanese ethnicity. Further analysis of RP patients from Java may elucidate this mechanism.

To date, 11 mutations in 8 genes have been identified in two studies in Indonesian families. *CRB1* gene has the largest percentage of mutations in the cohort. Although many mutations have been identified, over than 60% cases still remain to be solved (Figure 44).
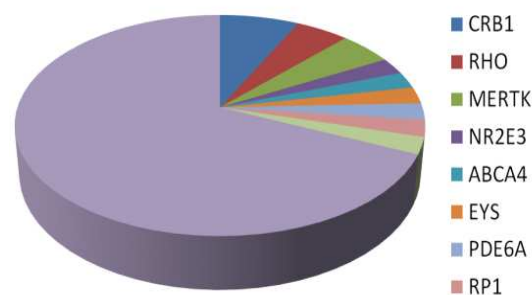
Figure 44. All identified mutations in Indonesian RP patients

CRB1 mutation has the largest percentage among other disease causing genes

The p.P1305L mutation in *CRB1* gene was found in two of the families in this cohort. Previous study by Siemiatkowska, et al in Indonesian families has demonstrated this mutation in one of Indonesian RP families (13). From the haplotype comparison, a 700 kb stretch of same haplotype were shared between two affected from this study. To date, this mutation has never been reported in any other populations. Therefore, we presumed this mutation as a founder mutation in Java population.

The R338X truncating mutation in exon 4 of *RP1* that was found in this study is suitable to confirm the disease mechanism modeling in arRP caused by *RP1* mutations. This mutation is expected to result in truncated protein production which lost the microtubule binding domain. Normal allele still retains their normal function to produce 50% of normal wild type Rp1 protein which is sufficient to maintain the photoreceptors function. Thus, mutation in this particular region in will only cause RP in homozygous state.

Candidate genes selection on the three largest IBD regions and regions larger than 3 Mb has been proven as an effective approach to identify the genetic alterations responsible for autosomal recessive disease in the previous studies. *RP1* mutation was found in the fourth largest homozygous regions with 1.3 Mb in size. This finding suggests that it is important to also consider small IBD regions to find candidate genes.

Homozygosity mapping has proven its ability to detect the genetic defects responsible for RP either in consanguineous or non-consanguineous families. Previous study by Arimadyo K found seven disease-causing mutations for RP in Indonesia cohort. Most of the families in this study are multiplex families and consanguineous families. Conversely, the majority of the cases in this study are sporadic cases. These differences between two patient series implicate that although homozygosity mapping is able to identify genetic defects in sporadic cases, but this approach is mostly effective in consanguineous or multiplex RP families.

Until 4 years ago, no therapies were available for patients with inherited retinal dystrophies (IRDs). Gene replacement therapy was shown to be safe and moderately effective in LCA/early-onset RP patients with *RPE65* mutations (71). Molecular genetic analyses are crucial for the development of this new treatment. For *RPE*65 mutation that was found in this study, gene therapy by human retinal gene transfer with rAAV2-RPE65 vector may be suitable.

The result of this study will provide information about the causative mutations in RP in Indonesian population. Knowing the pathogenic mutation will enable genetic counselors to inform the probands and their families about the inheritance mode of the disease, as well as the prognosis. This study will also improve the public awareness about RP as a genetic disease and enhance the prevention of recurrence

of this disease in the next generation by knowing the disease inheritance mode. Furthermore, present study will motivate further research to provide more information about inherited retinal diseases in Indonesian population.