V. CONCLUSION AND RECOMMENDATION

V.1 Conclusion.

Thirty-six patients with diagnosed RP were recruited. Homozygosity mapping led to the identification of new mutations in consanguineous and non-consanguineous

patients with RP. Detailed clinical characterization revealed a variety of retinal appearances, ranging from nearly normal to extensive retinal remodeling, retinal thinning, and debris accumulation (bone spicules) depends on the staging of the disease. The molecular findings led to a reappraisal of the diagnosis in patients carrying mutations in several genes.

On conclusion in current study:

1. Type of inheritance   arRP   : 87.5 %

    adRP : 12.5 %

2. The genetic determinant /causative gene that played role in etiology of non syndromic RP patients mostly were arRP with monogenic mutations such as : *RHO* (c.403C>T; p.R135W), *CRB1* (c.3914C>T; p.P1305L), *ABCA4* (c.302+4A>C; altered splicing), *NR2E3 (*c.1025T>G; p.V342G), *EYS* (c.9082G>T; p.D3028Y), *MERTK* (c.2487-2A>G) altered splicing and *complex rearrangement*; p.G654AfsX41) with deletion of a genomic region containing exon 15 and accompanied by a duplication and inversion event and also stop mutation in *PDE6A*(c.1675C>A; p.Y558X)

3. The common mutation that played role in non syndromic RP in Indonesia so far was on *MERTK* gene with altered splice (c.2487-2A>G) and complex rearrangement p.G654AfsX41)

4. Most of the mutations that have been founding in this study were the novel mutations and only one mutation on *RHO* gene had been published already.

5. Compared to other population, the same genes appear to be involved in the aetiology of RP, although the majority of mutations are novel, and such may be unique for the Indonesian population

6. The mutations found is exclusively present in largest or 2nd largest homozygous region

7. Homozgosity mapping also has a limitation as for linkage studies of small families that may detect large intervals and may house hundreds of genes. Although fine mapping or previous linkage reported in other families may reduced the size of the putative interval, the overall aim of such studies, gene identification is dependent on examining functional candidate gene in the region

8. Combining the homozygosity region data in unrelated patients with the same phenotype also helpful to find the causative gene.

V.2. Recommendation

1. Homozygosity mapping with high resolution could be used for searching the genetic cause of recessive disorders especially on the Indonesian population proven by the high rate of solved families.

2. This technique also gives benefit for identifying the genetic defects underlying RP in the Indonesian population.

3. It was very important for the other relatives (non affected person) from the family to participate for narrowing the region of homozygous region and hopefully can find the

candidate gene for sequencing. So probably it was very helpful to add the DNA from other family members in family that has not been solved yet.

4. Functional studies are required to prove pathogeneicity of the mutated gene. It may be done if the mRNA of the patients and other relatives are ready.

5. Until now there is no data about the prevalence of RP in Indonesian population especially based on the causative gene mainly on the nonsydromic RP groups. Therefore, further study is needed to find out the prevalence rate of Indonesian RP. This finding may benefit for further investigation such as gene therapy. Hopefully in the future there will be a collaboration between University of Diponegoro with all University in Indonesia for managing the RP with the holistic treatment not just for the patients but also their siblings and their family.

6. The candidate gene for screening that might be the causative genes for RP were *FAM161A, RPE65, USH2A, PRCD*

7. On genetic counseling issue, this study may provide prognostic information and provide prenatal screening as well and eventually help the counselor to calculate the probability of their offspring for having the faulty gene. Especially for monogenic/ single gene disorder like RP it is useful for predicting the risks to the individuals of developing or transmitting particular conditions in absolute terms.

8. To prevent the disease to become more severe it is wise to educate the patient about their life style especially how to eliminate the radiation of the UV light through their eyes and also consume more vegetables and fruits on their daily menu. And for the carrier persons who bring one copy of faulty gene, it may suggested to marry the person that not have the family history of RP to prevent the manifestation of the disease.

SUMMARY

High resolution homozygosity mapping is an efficient gene mapping method applicable to rare recessive disorders. The basic idea of this method is to locate genes related to recessive traits. Using this technique, some mutations causative for RP have been identified in several Indonesian families.

Significant homozygous regions which did not have any known gene can be used for identifying novel genes causative for RP. To narrow down the homozygous regions it was necessary to have the DNA from all relatives. Most of the mutation that was founded is takes place on 1st to 3rd biggest homozygous region that harbors the causative genes of RP.

The high rate of solved families thus far indicates that the Indonesian population is extremely suitable to apply homozygosity mapping in a search for the genetic causes of recessive disorders.

Adequate diagnostic assessment, the initial pace in the counselling method, is not always obtained.   And of course the prognosis itself is difficult to predict, and genetic type may be impossible to ascertain in pedigrees. This study also emphasizes the clinical variability of RP and summarizes discrepancies in age of onset of the different genetic types.   Clearly, RP patients have to be evaluated extensively and carefully to make a diagnosis retinitis pigmentosa accurately.

The level and limitations of the diagnostic evaluation should be clearly understood by the clinician and of course the counsellor because some patients have a sporadic type of RP. The Counselling about the prognosis should consist of information regarding the great disparity among and within inheritance groups, families and patients with respect to period of onset and likely history of the RP.