CHAPTER I

INTRODUCTION

I. 1. Background

The term "retinitis pigmentosa" (RP) refers to a large, clinically and genetically diverse group of retinal dystrophies which primarily affect rods, followed by cone photoreceptor cell degeneration(1-3). The disease is characterized by night blindness (nyctalopia), loss of peripheral vision and subsequent severe central visual impairment due to progressive photoreceptor cell degeneration (4). The funduscopy typically reveals classical triad of symptoms: bone spicule-like pigmentation, attenuated arterioles and waxy pallor of the optic disc.

The disease can be subdivided into non syndromic RP in which there is no systemic abnormalities, and syndromic retinitis pigmentosa where the retinal degeneration is associated with other disorders, such as hearing impairment and intelectual disability. The most frequent syndromic form of RP is Usher Syndrome, followed by Bardet Biedl syndrome (BBS) and other syndromes. Worldwide prevalence of non syndromic RP is approximately between 1 case per 4000 persons to 1 case per 1000 persons (4,5). In this study we are mainly focus on the non syndromic RP since the majority of RP cases, particularly in Indonesian population occur in the non syndromic form. Furthermore, most of the genes responsible for syndromic RP have already been known, whereas

50% of non syndromic genes still remain to be identified. Therefore, search for these genes are important to unravel the genetic defects responsible for non syndromic RP.

Retinitis pigmentosa is a genetically heterogeneous disorder which has been associated with mutations in over than 50 different genes. The disease causing mutations can be inherited in an autosomal dominant (adRP, 30 - 40%), autosomal recessive or sporadic (arRP, 50 - 60%) X-linked (xlRP, 5 - 20%)and digenic manner (1;3;5). This genetic diversity has hampered the identification of the retinal dystrophy genes, as most of the genes affect only a small number of cases. To date, mutations in more than 165 genes have been identified in patients with inherited nonsyndromic and syndromic retinal diseases, and it is estimated that approximately one-third of the causative genes remains to be identified (6).

The molecular genetic analysis approach available for gene identification studies have evolved dramatically during the last two decades. In 1990, linkage analysis had succesfully identified rhodopsin (*RHO*) gene and the chorodemia (*CHM*) gene was found using positional cloning approach (7, 8). Recently, with the development of microarray technology allowing rapid genotyping of thousands of single nucleotide polymorphisms (SNPs) spread across the genome. SNP microarray has also proven to be very effective in mapping homozygous regions of

recessive disease genes. Furthermore, this approach is less time consuming and cost-effective compared to the previous methods.

For the past 4 years, the gene augmentation therapy in *RPE65* gene has been shown as a very promising treatment for RP which was known previously as an incurable disease (6). Conversely, the developing countries have hitherto not benefited from these trends. Due to some socio-economical and cultural factors, the diagnosis of RP is frequently made at later stages of the disease which causes worse prognosis in comparison to the developed countries. Furthermore, the knowledge of molecular genetics of the disease, as well as the management of the patients, is still falling behind.

According to the World Health Organization, 90% of the people suffering from blindness live in the developing countries (9). In Indonesia, blindness of various causes is estimated to affect about 1.3 million people, with a prevalence of 1.5% which is the highest among South East Asian countries. Previous study by Sitorus R. et al. stated that hereditary causes including RP were the second most common cause of blindness (10). To date, only few studies have described RP in Indonesian population. From these studies, mutations in several genes has been identified, such as *RHO, ABCA4, NR2E3, EYS* and *MERTK* (11-13).

This study aim to elucidate the underlying genetic defects causing non syndromic RP in Indonesian families by means of

homozygosity mapping. The present study will mainly focusing in non syndromic RP due to the larger proportion of non syndromic compared to syndromic RP in general. Furthermore, to date, the majority of RP cases that are recorded in the hospitals which are involved in this study are in the non syndromic form of RP. The understanding of genetic etiology of RP in Indonesian population is essential for providing early diagnosis and proper management to the patients and their family.

I. 2.   Research questions

1. 2. 1   General research question

What are the genetic defects responsible for non syndromic RP in Indonesia using high resolution homozygosity mapping?

I. 2.1   Specific research questions

1. What are the genetic defects responsible for non syndromic RP patients in Indonesia using high resolution homozygosity mapping?
2. What is the inheritance manner of non syndromic RP in Indonesia?

I. 3.   Research objectives

I. 3.1.   General objective

To describe the genetic defects responsible for non syndromic RP in Indonesia using high resolution homozygosity mapping

I. 3. 2. Specific objectives

1. To identify the genetic defects responsible for non syndromic RP in Indonesia using high resolution homozygosity mapping

2. To describe the inheritance manner of non syndromic RP patients in Indonesia

I. 4.   Research benefits

1. Improvement of the public awareness of genetic diseases like RP, which is especially important in developing countries like Indonesia

2. Knowing the causative mutation will ultimately lead to a precise diagnosis and a better prognosis prediction

3. Providing more accurate information for RP will enable genetic counselors to recognize the disease and the type of inheritance of the disease

4. Encouragement of other researchers for further studies in ophthalmogenetics, especially on RP patients from Indonesian population

5. Contribution to the development of the new treatments for RP, such as gene therapy

I. 5.   Research originality

1. Previous study about identification of genetic defects in retinitis pigmentosa in Indonesian with an emphasize in familial cases using

homozygosity mapping has been performed (Siemiatkowska, et al, in press) with 16 families from several regions in Indonesia. Seven novel mutations were found. The present study is an extension of the previous study in Indonesian RP patients.

2. The present study is a study on RP with the largest number of samples in Indonesian population, with the majority of the cases are sporadic/ simplex RP. Thus, it is suitable to measure the effectiveness of homozygosity mapping in the sporadic cases.

3. This study is the first study that performs a screening with all identified RP disease-causing mutations in the Indonesian population.

Table1. List of previous associated studies (13)

No.	Author	Title of Publications	Method	Result
1.	Siemiatkowska AM, Arimadyo K, Moruz LM, Astuti GDN, de Castro Miro M., Faradz SM, Zonneveld-Vrieling MN, et al.	Molecular genetic analysis of retinitis pigmentosa in Indonesia using genome-wide homozygosity mapping. Mol. Vis. 2011;17:3013-24.	SNP microarray followed by homozygosity mapping in Indonesian population	Seven novel mutations were found as a mutations responsible for RP
2.	Collin RW, van den Born LI, Klevering BJ, de Castro-Miró M, Littink KW, Arimadyo K, et al.	High-resolution homozygosity mapping is a powerful tool to detect novel mutations causative of autosomal recessive RP in the Dutch population. Invest. Ophthalmol. Vis. Sci. 2011; 52(5): 2227-2239.	SNP microarray followed by homozygosity mapping in Indonesian population	Homozygosity mapping is an effective approach to detect mutations causing RP in the Dutch population