I.INTRODUCTION

I.1 Background

Retinitis pigmentosa (RP) is a group of inherited retinal degeneration disorders characterized by night blindness, progressive loss of peripheral vision and characteristic pigmentary retinopathy. Retinitis pigmentosa can be divided into primary retinitis pigmentosa, in which there is no systemic abnormalities, and secondary retinitis pigmentosa where the degeneration of the retina associated with one or various other organs disorders.\textsuperscript{1-5} This disease is the most common inherited form of blindness and affecting more than 100.000 people in United State and 1.5 million people worldwide.\textsuperscript{6}

Indonesia has a population of 206 million, spread out over 25 provinces (Indonesian Center of Statistic Office: Survey of population, 2000) with prevalence of blindness was 1,5 % by year 2000 which is the highest among South East Asian countries. It can be break down as follow : prevalence of cataract was 0,78 %, glaucoma was 0,20 %, refraction was 0,14 and other that was age related diseases with 0,38 %. Mean while there was no data about blindness due to RP. There was no data also about prevalence of RP related to the race. Semarang is the capital city of Central Java Province with total residents of 1.389.416.\textsuperscript{7}

RP can be subdivided in syndromic (40 %) and non-syndromic (60 %) forms. Syndromic RP means that there are numerous systemic disease associated with RP. The most frequent forms of syndromic RP are Usher syndrome (prelingual hearing impairment followed by development of RP) and Bardet-Biedl syndrome which may caused not just only Retinitis but also mental retardation, obesity, polydactyl, mental retardation, hypogonadism, and renal failure. Non syndromic RP has a variations in phenotype in which genetically were heterogeneous which can be inherited by autosomal dominant (about 30 – 40 %)), autosomal recessive (50 – 60 %) or X
linked transmission (5 – 15 %) and it may also occur on a sporadic basis cases\(^6,8-10\). These proportions for inheritance pattern assume that isolated cases in which have no other affected relatives were autosomal recessive although a few cases may represent new dominant mutations such as uniparental isodisomy or X linked mutation\(^{11}\). Prevalence of non syndromic RP is approximately 1 in 4000 to 1 in 1000 in different parts of the world\(^8,11,12\).

Up to now, 39 genes and loci such as *EYS, RHO, CERKL*, and *RP1* have been implicated in non syndromic RP, yet the genetic bases of 50% of the cases, particularly of the recessive forms, remain unknown. An efficient strategy for mapping human genes that cause recessive traits has been devised that uses mapped restriction fragment length polymorphisms (RFLPs) and the DNA of affected children from consanguineous marriages. The method involves detection of the disease locus by virtue of the fact that the adjacent region will preferentially be homozygous by descent in such inbred children so this technique called homozygosity mapping. A single affected child of a first-cousin marriage is shown to contain the same total information about linkage as a nuclear family with three affected children. Calculations show that it should be practical to map a recessive disease gene by studying DNA from fewer than a dozen unrelated, affected inbred children, given a complete RFLP linkage map. The method should make it possible to map many recessive diseases especially RP for which it is impractical or impossible to collect adequate numbers of families with multiple affected offspring.

The high degree of genetic heterogeneity in arRP makes genetic screening and gene identification rather expensive and also time consuming. The use of high resolution of homozygosity mapping to detect disease gene loci for arRP enables a rapid screening of a large number of loci and is particularly very useful in analysis of consanguineous families in which regions of several centimorgans adjacent to the disease gene are expected to be homozygous by
descent. This approach is well suited to screening consanguineous arRP (autosomal recessive RP) families. Gene identification in families with arRP has been performed by homozygosity screening both in screenings of preexisting/candidate gene loci and genome-wide screening.

On the past era to find the mutation was directly use the sequencing of DNA but is fraught with excessive costs, time, manpower issues and finding nonpathogenic variants. Therefore, no centre offers testing of all currently 132 known genes.

The knowledge of genetic factors of Retinitis pigmentosa cases by molecular and clinical assessment is an advantage in giving prompt diagnosis and prevention through genetic counseling to the patient and their family. These serve as diagnostics tool in determining genetic factors that may play role as etiological cause of RP. In Indonesia due to lack of facilities molecular assessments have to be performed in other centre abroad.

There were only one study about RP in Indonesian population carried out by Indonesian researchers or in collaboration with foreign researchers especially there are no report has been published for mutation among RP patients in Indonesia. In that study shown that peripherin/RDS gene polymorphisms were found in Indonesian patients with retinitis pigmentosa\(^\text{13}\)

The aim of this study is to establish a definite diagnosis and to looking for mutations that present in Indonesian RP patients by high resolution homozygosity mapping, linkage analysis and DNA sequencing. This study also focusing only on non-syndromic RP for the reason that RP is a monogenic disorder and also these cases are much more comparing to syndromic RP. And so far the RP cases that came to the hospital are non syndromic RP.

The type of inheritance and causative gene of the RP will be used by genetic counselor to give the counseling to the patients and their relatives as well.
I.2. Research Questions

1.2.1 General Research Question

1. What is the genetic determinant that may have played role in the etiology of non-syndromic retinitis pigmentosa patients in Semarang Indonesia?

1.2.2 Specific Research Question

1. What are the gene mutations or loci found in the non-syndromic RP patients?
2. By using high resolution homozygosity mapping is it possible to find out the causative genes or loci on the non-syndromic RP?
3. What are the most common of causative gene found that might cause retinitis pigmentosa in Semarang, Indonesia?

1.3. Research objective

1.3.1 General research objective

To identify the causative gene / loci of non-syndromic RP in Indonesia.

1.3.2 Specific research objectives

1. To find out the common mutation that may played role in non- syndromic retinitis pigmentosa patients in Indonesia
2. To determine the type of inheritance among non-syndromic retinitis pigmentosa patients in Indonesia
3. To find out the novel mutation for better understanding of RP.

1.4. Research advantages:

1. To find out more precisely the type of inheritance to the subsequent descent.
2. To provide genes mutations found and type of inheritance RP that can be used by genetic counselors when giving counseling to the patients and their family.
3. To provide the information for pre implantation diagnosis and pre natal diagnosis

4. To encourage other researcher for further study in ophthalmogenetics especially on RP patients from Indonesia population.

5. To encourage public awareness of RP as genetic disease in Indonesia.

1.5. Research Originality

1. Screening candidate gene that might cause RP in Semarang is the first study in Indonesia.

2. Screening candidate genes on RP patients from Semarang using the homozygosity mapping is the first study in Indonesia.

3. Mutation on several genes such as $RHO$, $PDE6A$, $ABCA4$, $EYS$, $CRB1$, $NR2E3$ and $MERTK$ that might be causes of non-syndromic RP in Indonesia is the first study.
### Table 1. Previous research related to the study about RP genes.

<table>
<thead>
<tr>
<th>No</th>
<th>Author, Publication, Year</th>
<th>Title of publication</th>
<th>Results</th>
<th>Similarities / Differences</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Irena T 2008</td>
<td>Phenotype-Genotype Correlations in Autosomal Dominant Retinitis Pigmentosa Caused by RHO, D190NRPE65</td>
<td>Patients with RHO (D190N) adRP show classic signs of RP on funduscopy</td>
<td>The same gene but different site of mutation</td>
</tr>
<tr>
<td>2</td>
<td>Mamatha G 2007</td>
<td>Retinitis pigmentosa: mutation analysis of RHO, PRPF31, RP1, and IMPDH1 genes in patients from India</td>
<td>RHO, PRPF31, RP1, and IMPDH1 and identified causative mutations in 4% of isolated and 2% of adRP patients from India</td>
<td>The same gene but different site of mutation</td>
</tr>
<tr>
<td>3</td>
<td>Frauke C 2007</td>
<td>Recurrent Mutation in the First Zinc Finger of the Orphan Nuclear Receptor NR2E3 Causes Autosomal Dominant RP</td>
<td>Identification of the photoreceptor cell-specific nuclear receptor gene NR2E3 as a novel disease locus and gene for adRP</td>
<td>The same gene but different site of mutation</td>
</tr>
<tr>
<td>4</td>
<td>Collin R 2008</td>
<td>Identification of a 2 Mb Human Ortholog of Drosophila eyes shut/spacemaker that Is Mutated in Patients with RP</td>
<td>One of the largest human genes, and it is by far the largest retinal dystrophy gene</td>
<td>The same gene but different site of mutation</td>
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<tr>
<td>5</td>
<td>Budu 2005</td>
<td>Peripherin / RDS gene in Indonesian patients with RP: geographic comparison of pleomorphic variations</td>
<td>The prevalence of alteration in Indonesian patients was similar to that in Japanese patients</td>
<td>Peripherin/RDS gene polymorphism</td>
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