CHAPTER I

INTRODUCTION

I.1. Background

Monosomy X is the absence of the second sex chromosome, results in a 45,X karyotype.[1,2] Monosomy X is the chromosomal characteristic for Turner Syndrome (TS), the most common sex chromosome abnormality in female, characterized by particular phenotypic features. It caused by loss of all or significant part of one of the sex chromosome.[3,4] TS affects approximately one in 2500-3000 female birth.[5] Monosomy X was also found in patients with mixed gonadal dysgenesis (MGD) which present a defective embryonic development of the testis.[6,7]

Clinical manifestation in patients with monosomy X varies and may be subtle. In TS, major clinical features are short stature and gonadal dysgenesis. Gonadal dysgenesis leads to ovarian failure in female. Other physical findings include webbing of the neck, lymphedema, congenital heart disease, and renal abnormality. Some patients show learning disabilities and mentally retarded in different degree.[8,9] The histological picture of a dysgenetic testis in MGD ranges from a streak gonad to only a reduction in tubular size and reduced number of germ cells. As a consequence, the external genitalia of patients with MGD ranges from predominantly male to predominantly female, including cases of striking genital ambiguity.[6,7]

Sex chromosome non-disjunction in meiosis I or II is the most common underlying cause of monosomy X. TS and MGD could also be caused by chromosome non-disjunction in mitosis, called mosaicism, or abnormality of the second sex chromosome.[1] Its various chromosomal re-arrangement mechanism results in variation of cytogenetic profile (monosomy X and its variants) and wide spectrum of the physical characteristic.[10]

Abnormal chromosome segregation in monosomy X cases was thought correlate with the presence of polymorphism in Methylenetetrahydrofolate reductase (MTHFR) gene. MTHFR is a gene that involve in folate metabolism. The C677T polymorphism (result in CC, CT, or TT genotype) in this gene may reduce the activity of MTHFR and interfere the methylation reactions of DNA. DNA hypomethylation of centromic and pericentromic regions may be the cause of sex chromosomal non-disjunction.[11,12]

A number of studies have reported the prevalence of C677T MTHFR gene polymorphism of TS in various populations and correlating the findings to chromosomal aneuploidy, but only few studies concerning Indonesian population.[11,12,18,19] Study of MTHFR gene polymorphism in TS diagnosed in Brazilian, show the conflicting result. Frequency of genotype CC, CT, and TT in the MTHFR gene in Javanese population has been learned, but the presence of this polymorphism in subject with monosomy X and its cytogenetic variants has not been ruled out.[12]

This study aims to describe the distribution of C677T MTHFR gene polymorphism of patients with monosomy X and its cytogenetic variants in Indonesian population.

I.2. Research Question

I.2.1. General Question

How is the distribution of C677T MTHFR gene polymorphism in patients with monosomy X and its cytogenetic variants?

I.2.2. Specific Questions

1. What is the frequency of CC genotype ?
2. What is the frequency of CT genotype ?
3. What is the frequency of TT genotype ?
4. What is the C allele frequency ?
5. What is the T allele frequency ?

I.3. Research Objective

I.3.1. General objective

To describe the distribution of C677T MTHFR gene polymorphism in patients with monosomy X and its cytogenetic variants

I.3.2. Specific objective

1. To find the frequency of CC genotype
2. To find the frequency of CT genotype
3. To find the frequency of TT genotype
4. To find the C allele frequency
5. To find the T allele frequency

I.4. Research Benefit

1. Provide information about monosomy X disease and its variants so may improve public awareness of this genetic disorder
2. Provide information about the possibility of involvement of folate metabolism in chromosomal non-disjunction in monosomy X cases
3. Provide information for subjects of this research and their doctors about their genetic polymorphism and its possible correlation with folat metabolism
4. Provide genetic counseling for subjects of this study about their genetic polymorphism, its possible correlation and prevention of Neural Tube Defect (NTD) and cardiovascular disease

I.5. Research Originality

1. The previous study described the frequency of the mutation of C677T MTHFR gene in Indonesian Javanese population. This study analyze polymorphism of the gene in patients with monosomy X and its variants in Indonesian population
2. The present study is the first study that perform analysis for MTHFR gene in patients with monosomy X and its variants in Indonesian population

Table 1. List of previous associated studies

No.	Title, author, journal	Research Method	Result
1.	Frequency of C677T and A1298C polymorphisms in the 5,10 methylenetetrahydrofolate reductase (MTHFR) gene in TS individuals. Santos K, Sofia H V, Marini L, Maria T M, Baptosta, Bonadia L C, et al . Genet Mol Bio. 2006;29(1)41-4	Case control study to compare MTHFR gene polymorphism in TS individuals and control	Higher frequency of C677T MTHFR gene polymorphism among TS individuals
2.	Prevalence of the Polymorphism *MTHFR* A1298C and not *MTHFR* C677T Is Related to Chromosomal Aneuploidy in Brazilian TS Patients. Oliveira K C, Boanco B, Verreschi I T N, Guedes A D, Galera B B, Galera M F, et al. Arq bras endocrinol metab. 2008;52(8):1374-81	Case control study to investigate the association between MTHFR gene polymorphism and TS	No correlation was observed between MTHFR gene polymorphism 677 and chromosomal aneuploidy in TS
3.	The C677T Mutation in the Methylenetetrahydrofolate Reductase Gene among the Indonesian Javanese Population. Sadewa AH, Sunarti, Sutomo R, Hayashi C, Lee MJ, Ayaki H, et al. Kobe J. Med. Sci. 2002; 48(4):137-44	Case control study to compare the frequency of mutation in Indonesian and Japanese population	Very low T allele frequency in Indonesian Javanese population and