CHAPTER I

INTRODUCTION

The Human Complement system is one of the essential effector mechanism in humoral immune response. It consists of more than 20 components of regulatory plasma proteins and several cellular receptors for fragments C3 and C4. The genetic of this system has become a major field of research in the last 10 years because of the detection of many hereditary complement deficiencies often related to diseases (1,2,3,4) as well as the description of a structural genetic polymorphism of several complement components (5,6,7).

Studies of complement polymorphism has been undertaken for two main reasons. Firstly, since hereditary complement deficiency have been described for almost all the complement proteins including the presently described complement receptor, studies of structural polymorphism and their mode of inheritance provide insight into the genetic mechanism underlying these deficiencies (6,7). Hereditary complement deficiencies are either due to partial or complete absence of synthesis of a component or due to the synthesis of an incomplete or abnormal protein. Secondly, with the recognition that three complement components, Bf, C2, and C4 coded by genes within the major histocompatibility complex of man and several other species, polymorphism of these components would provide useful genetic marker for HLA association with disease susceptibility (8,9).

In genetic studies of complement, C4 is one of the component that has attracted most attentions. It is coded for by genes of the

major histocompatibility complex (MHC), linked between HLA-B and HLA-D/DR related to the immune response gene (8). In addition, the fourth complement component coded for by two closely linked loci, C4A and C4B, each of which have many alleles, showed structural polymorphism (10). The genetic complexity of C4 extends to the number of loci which may be deleted or unexpressed (null allele) and the duplication on the chromosome. Moreover, of great interest was the observation that the two forms of C4, C4A and C4B, differ in their structure and function with respect to their binding to antigens and antibodies (11,12,13). C4A more efficiently mediated the inhibition of immune complex precipitation (11,12,14). Thus, abnormal or defective C4 may result in inappropriate handling of immune complexes.

Special attention has been paid on certain autoimmune disorders,for instance, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and insulin depenpdent diabetes mellitus (IDDM). This gives rise to a series of investigation on major histocompatibility complex antigens, particularly C4, with autoimmune disease (15,16,17, 18,). According to Fielder and others, the incidence of C4 null alleles was significantly higher in SLE patients, with concordant results in the Caucasians,Black and Japanese ethnic groups (15,19,20). In addition, linkage disequilibrium between C4 alleles and certain haplotypes have been reported (21). Thus, combination of alleles of MHC Class I,II and III (called supratypes), or alleles within MHC class III alone (Bf,C2,C4A,C4B ; called complotypes) have been found to associate with diseases and may be attributable to increase susceptibility to autoimmune disorders. Nevertheless, it should be

noted that racial variations in MHC antigen frequency might have significant effect on the strength of diseases association. For example, Kay and Dawkins demonstrated that a special supratype : HLA - Bw62,- Cw3,- BfS,- C4A3, - C4B2.9,- DR4 occurs in approximately 10% of patients with RA but only 1% in normal population of Western Australians (17,21). On the other hand, Tokunaga (22) described a strong association between rheumatoid arthritis and HLA-DR4, C4A*QO and C4B*5 in Japanese.

Consequently, this study was undertaken to examine the C4 allotypes in systemic lupus erythematosus (SLE) and rheumatoid arthritis in Thai patients.