# CHAPTER III

## LITERATURE REVIEW

### Systemic Lupus Erythematosus (SLE)

SLE is an autoimmune disease characterized by autoantibody production and immune complex formation in which self-reactive autoantibody cause disease either by directly binding to self-antigens or following the deposition of antibody-antigen immune complexes in blood vessels leading to vasculitis and tissue damage. Clinical manifestations of SLE could be diverse, including glomerulonephritis, dermatitis, thrombosis, vasculitis, seizures and arthritis. The primary cause of morbidity and mortality are glomerulonephritis which developes in about 60% of patients (Tsao 2003); (Kotzin 1996); (Gaffney, Kearns et al. 1998)

### Epidemiology

SLE is found worldwide with ranging from 25-250 per 100,000 individuals depending on racial and geographic background. The most commonly presents in women in their childbearing years. The gender difference in SLE prevalence is striking, with a female to mail ratio of 9:1. The prevalence of lupus in general US population is about 1 in 2000 but it varies among ethnic groups. The more prevalent in non-Caucasian than Caucasian populations. (Tsao 2003); (Hochberg 1997)

### Etiology

SLE demonstrates a complex pattern of inheritance that is consistent with the involvement of multiple susceptibility genes as well as environment risk factors (Nath, Kilpatrick et al. 2004). SLE is more prevalence among relatives of the affected patients but dose not follow simple Mendelian inheritance patterns. Strong evidence support the role of genetic component for susceptibility to SLE. Firstly, in twins who usually shared the same environment, the disease concordance rate is 2-5% for dizygotic twins and 24-58% for monozygotic twins. There are 10 – fold difference in the disease concordance rate between identical twins and fraternal twins. (Tsao 2003). Secondly, the degree of familial clustering, measured by comparing the risk of a sibling with the risk in the population as a whole(s), varies between 20-40 (Wandstrat and Wakeland 2001); (Wakeland, Liu et al. 2001).

Classification of SLE

The American Rheumatism Association (now the American College of Rheumatology, ACR) initially published classification criteria in 1971(Cohen, 1971), which were revise in 1982 (Tan, Cohen et al. 1982). A future revision has recently been proposed (Hochberg 1997). The criteria are for the classification of the disease

rather than for use as a diagnostic tool. The 1997 and 2004 updated criteria are outlined in Table 1. For the purpose of identifying patients in clinical studies, it is determined that a patient has SLE when at least four of eleven criteria are present, serially or simultaneously, during any interval of observation (Hochberg 1997).

**Table1**: Revised American Rheumatism Association criteria for classification of systemic lupus erythematosus (Hochberg 1997).

| Criterion | Description |
|---|---|
| 1. Malar rash | Fixed erythema, flat or raised over the malar eminences, tending to spare the nasolabial folds |
| 2. Discoid rash | Erythematosus raised patches with adhesion keratotic scaling and falicular plugging; atrophic scarring may occur in order lesions |
| 3. Photosensitivity | Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation |
| 4. Oral ulcers | Oral or nasopharyngeal ulceration, usually painless, observed by a physician observation |
| 5. Arthritis | Nonerosive arthritis, involving two or more peripheral joints, characterized by tenderness, swelling, or effusion |
| 6. Serositis | a) Pleuritis: convincing history of pleuritic pain of rub heard by a physician or evidence of pleural effusion<br>b) Pericarditis documented by ECG or rub or evidence of pericardial effusion |
| 7. Renal disorder | a) Persistent proteinuria greater than 0.5g/day or >3+ if quantitation not performed<br>b) Cellular casts (red cell, hemoglobin, granular, tubular, or mixed) |
| 8. Neurological disorder | a) Seizures in the absence of offending drugs or known metabolic derangements, e.g. uremia, ketoacidosis, or electrolyte imbalance<br>b) Psychosis in the absence of offending drugs or known metabolic derangements; e.g. uremia, ketoacidosis, or electrolyte imbalance |
| 9. Hematological disorder | a) Hemolytic anemia with reticulocytosis<br>b) Leukopenia: < 4000/µl total on two or more occasions<br>c) Lymphopenia: < 1500/µl on two or more occasions<br>d) Thombocytopenia: 100,000/µl in the absence of offending drugs |
| 10. Immunological disorder | a) Positive LE cell preparation<br>b) Anti-DNA: antibody to DNA in abnormal titer<br>c) Anti- Sm: presence of antibody to Sm nuclear antigen<br>d) False-positive serological test for syphilis known to be positive for at least 6 moths and confirmed by TPI or FTA-ABS |
| 11. Antinuclear antibody | An abnormal titer of ANA by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with 'drug-induced lupus' syndrome |

**Genetic studies in SLE**

The result from mouse models of SLE shown the first evidence for genetic linkage to an area of chromosome 1 in the mouse that is syntenic to human chromosome 1q23-1q42 (Tsao, Cantor et al. 1997). Several additional linkage studies in human have been performed using sib-pairs and extended family pedigrees. The parameter and test populations for each study as well as the genomic interval detected in six genome wide linkage analyses were summarize in table 2.

**Genetic study using lupus murine models: Congenic Mice**

Numerous initial linkage analyses to identify the SLE-susceptible genes are actually derived from the New Zealand inbred lupus mice or their relatives (NZB×NZW or BWF1, NZM2410). I would like to mention on linkage analysis from the NZM2410, which are the most studies lupus murine model by using microsatellite polymorphic markers, Morel L, *et al.* have initially identified at least 4 SLE-susceptible genomic intervals and called them *Sle1* (on chromosome 1), *Sle2* (on chromosome 4), *S1e3* (on chromosome 7) and *S1e4* (on chromosome 17) (Morel, Rudofsky et al. 1994); (Morel, Mohan et al. 1999). They subsequently developed multiple mouse strains of C57BL/6 (B6) mice *congenic* for these SLE-susceptible genomic intervals (by introducing these SLE-susceptible genomic into the nonautoimmune C57BL/6). These SLE-susceptible genomic strains allowed them to differentially evaluate the roles of these intervals to the clinical manifestation of lupus in these mice, suggesting a similar role in human disease. *Congenic* B6 *Sle1* mice develop a selective loss of B cell tolerance to chromatin and with a preferential targeting of H2A/H2B/DNA subnucleosome, reminiscent of drug-induced lupus. However, these mice develop no or late-onset minimal nephritis and have normal survival. *Congenic* B6 *Sle2* mice develop a distinctly significant B cell hyperactivity. There are increased number of CD5-expressing peritoneal B-1 cells and elevated levels of polyreactive or polyclonal IgM. However, *Sle2* insufficiant for generating IgG autoantibody or lupus nephritis. In contrast, in *Congenic* B6 *Sle4* mice have normal immunophenotypes with normal survival.

It was not surprising that none of the monocongenic mice develop fully penetrant lethal glomerulonephritis like their original parents. The differential dissection of the roles of these genomic intervals using monocongenic emphasized the polygenic complexity of SLE. Interestingly, the presence of bi-or tri-congenic SLE susceptible genomic internals can reproduce the lethal glomerulonephritis similar to their parents (Bowness, Davies et al. 1994); (Morel, Rudofsky et al. 1994); (Morel, Mohan et al. 1999). For example, the bicongenic B6 *Sle1/Sle3* or tricongenic B6 *Sle1/Sle2/Sle3* contain the minimal set of genes sufficient to reconstitute a fully penetrant SLE lethal glomerulonephritis. Although the role of *Sle1* and *Sle3* are clearly demonstrated, the presence of *Sle1* is necessary for the production of nephritogenic antibodies and clinical

glomerulonephitis in the bi/tricongenic recombinations. mapping of *Sle1* revealed the presence of a cluster functionally related loci (Sle1a /Sle1b and Sle1c) that independently mediate the losss of tolerance to nuclear antigen. The fourth locus (Sle1d) affected end-organ susceptibility to autoimmune damage. Interestingly, this region is syntenic to *sle1d* in NZM2410 gene mapped to chromosome1(1q41-42). Candidate genes within this region in human include poly-ADP-ribosyl transferase (PARP) gene, HLXI gene (Tsao, Cantor et al. 1999). Less study was done with TGFß2 gene.

**Table2.** Summary of human linkage studies in SLE

| Study parameter | UMN1 | UMN2 | UMN1+2 | OMRF | OMRF | USC | Uppsala |
|---|---|---|---|---|---|---|---|
| No. of Fammilies | 105 | 82 | 187 | 94 | 126 | 80 | 17 |
| Type of study | sibpairs | sibpairs | sibpairs | pedigree | pedigree | pedigree | pedigree |
| No. of SLE patients | 220 | 179 | 399 | 220 | 295 | 188 | 44 |
| No. of unaffectrd | 155 | 101 | 256 | 313 | 449 | 246 | 106 |
| No. of ethnic gr. | 5 | 4 | 5 | 3 | 3 | 2 | 1 |
| *Ethnicity (%)* | | | | | | | |
| - Caucasian | 80 | 78 | 79 | 58 | 61 | 46 | 100 |
| - African | 5 | 15 | 10 | 33 | 32 | 0 | 0 |
| - Hispanic | 8 | 6 | 7 | 0 | 0 | 54 | 0 |
| - Asia | 3 | 0 | 2 | 0 | 0 | 0 | 0 |
| - Mixed | 4 | 1 | 2 | 9 | 7 | 0 | 0 |
| Major loci[a] | 6p11-21 | 7p22 | 10p13 | 2p15 | 4p16-15 | 1q43 | 2q37 |
| | 16q12 | 7q21 | 7q36 | 1q23 | 1q22-24 | | 4p15-13 |
| | 14q21 | | 6p11-12 | 1q25 | | | 19p13 |
| | 20p12 | | 16q12 | 13q32 | | | 19q13 |
| | | | | 20q13 | | | |
| Reference | (Gaffney, Kearns et al. 1998) | (Gaffney, Ortmann et al. 2000) | (Gaffney, Ortmann et al. 2000) | (Moser, Neas et al. 1998) | (Gray-McGuire, Moser et al. 2000) | (Shai, Quismorio et al. 1999) | (Lindqvist, Steinsson et al. 2000) |

UMN = A study conducted at University of Minnesota

OMRF = A study conducted at Oklahoma Medical Research Foundation

USC = A study conducted at University of Southern California

Uppsala = A study conducted at University of Uppsala

[a] = Only loci with a lod score > 2 using the complete cohort are listed here

**Role of TGF-ß in SLE pathogenesis**

Result of the studies in lupus murine model have demonstrated an important of susceptible loci on chromosome 1 and polygenic complexity of SLE (Morel, Mohan et al. 1999). Similarly, evidence for linkage to SLE of 1q41-42 was shown in a targeted genome screen of the human chromosome1 region corresponding to the identified murine SLE susceptibility loci (Tsao 2003). These result emphasize the important gene on 1q41-42 position. TGF-ß2 is one of the important candidated gene in human located on chromosome1 position 1q41.

Loss of immune tolerance to self-components is the basis of SLE. SLE is a disorder of generalized autoimmunity characterized by B cell hyperactivity with numerous auto-antibodies againt nuclear antigen. Moreover, SLE is a T cell-dependent disease with T cell dysfunction. Strict control of T cell homeostasis is required to permit normal immune responses and prevent undesirable self-targeted responses. Transforming growth factor- ß (TGF-ß) has been shown to have an essential role in that regulation. Owing to its broad expression, and inhibitory effects on multiple cell types of the immune system, TGF-ß regulation is complex. Recent studies about TGF-ß in T cell regulation has become clearer. TGF-ß inhibits the differentiation of both $CD4^+$ and $CD8^+$ naive T cells into effectors. This effect is not dependent on inhibition of proliferation. Furthermore, TGF-ß blocks T helper ($T_H$)2 development by inhibiting expression of a Gata-3 (a master $T_H2$ transcriptional activator). Similarity, TGF-ß might blocks $T_H1$ development through the inhibition of a master $T_H1$ transcriptional activator. Blocking TGF-ß signaling in T cells by using transgenic approach leads to spontaneous T cell activation and inflammation, indicating that TGF-ß signaling in T cells is essential for cell homeostasis (Gorelik and Flavell 2002).

Besides their role in immune regulation, TGF-ßs are considered pleiotropic factors because they have been shown to play a regulatory role in most processes linked to the control of somatic tissue development and renewal (Sporn, Roberts et al. 1986); (Roberts 1998). TGF-ßs may be considerated as prototypic multifunctional signaling molecules. Indeed, these factors can exert either a positive or a negative effect on proliferation, differentiation, or cell death, depending on the stage of the target cell. In general, TGF-ßs has a stimulatory effect on cells of mesenchymal origin and an inhibitory effect on cells of epithelial or neuroectodermal origin. Various studies have shown that TGF-ßs play an important role in a number of diseases, including osteoporosis, spinal osteophytosis, myocardial infarction, Alzheimer 's disease, proliferative diabetic retinopathy and breast cancer (Yamada, Okuizumi et al. 2000); (Cambien, Ricard et al. 1996); (Luedecking, DeKosky et al. 2000); (Beranek, Kankova et al. 2002); (Ziv, Cauley et al. 2001). The study expression of TGF-ß1, ß2 and ß3 genes during mouse embryogenesis found that TGF-ß1 was expressed predominantly in the mesodermal components of the embryo

such as hematopoitic cells, the mesenchymal tissues. The strongest TGF-ß2 signals were found in early facial mesenchyme and in some endodermal and ectodermal epithelial cell layers such as lung and cochlea epithelia. TGF-ß3 was strongest in prevertebral tissue, in some mesothelia and in lung epithelia. All three isoforms were expressed in bone tissue. These results in regard to known regulatory elements of the TGF-ß genes and their receptors (Schmid, Cox et al. 1991).

TGF-ß1 is generally considered to be the major or predominant isoform involved in fibrosis, with the roles of TGF-ß2 and TGF-ß3 being less clear. But study about the actions of each isoform on production and degradation of extracellular matrix proteins by cultured rat mesangial cells, renal fibroblasts, and tubular epithelial cells shown that each isoform increased matrix protein synthesis and reduced matrix degradation by renal cells similarly. Combination of TGF-ßs isoform showed additive effects. So all 3 TGF-ßs isoforms have fibrogenic effects on renal cells (Yu, Border et al. 2003).

The past studies on the mechanisms of kidney damage in lupus show that lupus-prone MRL-lpr mice that develop marked renal inflammation have high levels of type 1 cytokines such as IFNg, whereas NZM2410 mice that develop severe glomerulosclerosis and rapidly progressive renal disease in early stages over-express type 2 cytokines such as IL4. Recently, found another mechanism of kidney damage in lupus-prone NZB/NZW F1 mice which display a typical progression of lupus nephritis from an early inflammatory to a late chronic fibrotic phase. As these mice begin to develop renal disease, they exhibit marked over-expression of TGF-ß protein and Tgfb1 and Tgfb2 mRNA levels in the kidneys, as determined by ELISA, Western blot, immunohistochemistry and in situ hybridization. Treatment of these mice with an anti-TGF-ß Ab inhibits the development of chronic kidney disease; chronic lesions, particularly glomerulosclerosis and tubular atrophy, and collagen IV mRNA levels are markedly reduced in the treated animals as compared to mice injected with isotype-matched control Ig or saline. It is noteworthy that anti-TGF-ß or anti-IL4 mAb treatments had no significant effects on anti-dsDNA Ab levels, renal Ig deposition and glomerular and interstitial inflammation. Thus, IL4 and TGF-ß may selectively contribute to the development of chronic kidney damage (Ram and Chisholm 1969).

**Structure of transforming growth factor (TGF-ß)**

Transforming growth factor type ß (TGF-ß) refer to a family of structurally highly conserved growth regulatory polypeptides that both stimulate and inhibit cell proliferation, depending largely on the cell type (Sporn, Roberts et al. 1986). The TGF-ßs are part of a larger superfamily of structurally homologous peptide growth (Kingsley 1994); (Hogan, Blessing et al. 1994). Member of this family share a characteristic protein domain structure consisting of a signal peptide and a large pre-pro peptide, from which a small mature peptide is

cleaved. The remainder of the pre-pro region of the TGF-ß precursor remains bound to the mature peptide after cleavage, keeping it in an inactive state. This portion of the pre-pro region is called the latency-associated peptide (LAP) (Sha, Yang et al. 1991); (Munger, Harpel et al. 1997); (Roberts 1998).

Three highly similar isoforms of TGF-ßs, called TGF-ß1, TGF-ß2 and TGF-ß3 were identified and cloned from mammals between 1985 and 1988 (Derynck, Jarrett et al. 1985); (de Martin, Haendler et al. 1987); (ten Dijke, Hansen et al. 1988). Although the regulatory role of these three isoforms may differ, it has been established that all three are involved in the regulation of hematopoiesis. Two other isoforms, called TGF-ß4 and TGF-ß5, have been cloned, in the chicken and in xenopus, respectively (Jakowlew, Moody et al. 1998); (Kondaiah, Sands et al. 1990).

TGF-ßs are synthesized as precursor proteins, which are biologically inactive. They consist of pre-pro-peptides, which require a 2 step process to give rise to active TGF-ßs (Gentry, Lioubin et al. 1988). A first proteolytic cleavage leads to the elimination of a hydrophobic signal peptide, in the N- terminal region of the precursor protein, yielding pro-TGF-ß. A second cleavage leads to the separation of the pro-region of the protein from the TGF-ß mature peptide. Once synthesized and processed, TGF-ßs are released by cells as latent complexes, which are biologically inactive. Two forms of latent complexes have been described, the small and large latent complexes. In the small latent complexes, one molecule of mature, active TGF-ß is noncovalently associated with one disulfide-bonded pro-peptide dimmer, called latency-associated protein or LAP. In the large latent complex, LAP is linked by disulfide bonds to one member of a family of high-molecular-weight proteins, called latent TGF-ß-binding proteins or LTBPs (Miyazono, Hellman et al. 1988); (Wakefield, Smith et al. 1988).

Complete amino acid sequence of human TGF-ßs shown a comparison of the amino acid sequences of TGF-ß2 and TGF-ß1 indicate that TGF-ß2 and TGF-ß1 differ from each other by 32 amino acid substitutions: 80 out of 112 residues, or 71.4%, are identical (Derynck, Jarrett et al. 1985). The proteins coded for by the human TGF-ß1 and TGF-ß2 cDNAs show an overall homology of 41%. The mature and amino-terminal precusor regions show 71% and 31% homology, respectively. Northern blot analysis identified TGF-beta 2 transcripts of 4.1, 5.1, and 6.5 kb using mRNA from several different sources. Analysis of polyadenylated RNA from tamoxifen-treated PC-3 cells showed that the clone was isolated from a tamoxifen-treated human prostatic adenocarcinoma cell line (PC-3) contain higher numbers of transcripts for TGF-beta 1 than for TGF-beta 2, although they produce more TGF-beta 2 protein than TGF-beta 1. This suggests that there is a post-transcriptional level of regulation for the production of these proteins (Madisen, Krumm et al. 1998).

The expression and structure of TGF-ß2 transcripts in rat muscles showed the biological importance of TGF-ß2 similars in human. An alternatively spliced TGF-ß2 transcript is present in human. TGF-ß2 has alternate splicing in 3 splice patterns, pattern 1 has 84 nucleotide inserted between exon1 and exon2. Pattern 2 has no 84 nucleotide inserted. Pattern 3 has splicing occurred between exon1 and exon 3. Analysis of cDNA clones coding for human and simian TGF-ß2 revealed the existence of two types of TGF-beta 2 precursor proteins of 414 amino acids (TGF-ß2,414) and 442 amino acids (TGF-ß2,442) in length. TGF-ß2,442 contains a 29-amino-acid insertion in the amino terminus of the precursor region that replaces an Asn residue located at position 116 in TGF-ß2,414. Of these 29 amino acids, three are cysteines, suggesting a more extensive disulfide-bond mediated secondary structure for TGF-ß2, 442 than for TGF-ß2,414. Northern blot analysis using probes specific for the insert in TGF-ß2, 442 indicated that this protein is encoded by a minor 5.1-kb mRNA species present in human and simian cells. Since the DNA sequences flanking the insert are identical between clones coding for the two precursor protein, we suggest mRNAs coding for these proteins arise via differential splicing. Evidence is also presented that additional TGF-β2 mRNA heterogeneity is due to alternate polyadenylation. Therefore the 414-amino-acid precursor be referred to as TGF-ß2a and the 442-amino-acid precursor be referred to as TGF-ß2b (Webb, Madisen et al. 1988). The function of each splicing form was not known at the present.

The TGF-ß isoforms initiate signal transduction via common receptors, although the full potency of TGF- ß2 is only achieved if betaglycan is also present (Massague 1998). Each isoform, however, has unique biological actions, as indicated by the distinct phenotypes of their knock-out mice (Shull, Ormsby et al. 1992); (Kulkarni and Karlsson 1993); (Sanford, Ormsby et al. 1997); (Proetzel, Pawlowski et al. 1995); (Kaartinen, Voncken et al. 1995); (Letterio and Bottinger 1998). The resulting form TGF-ß2 knockout mice play important role in multiple development processes. TGF-ß2 null mice exhibit perinatal mortality and a wide range of development defects for a single disruption. These include cardiac, lung, craniofacial, limb, spinal column, eye, inner ear and urogenital defects (Sanford, Ormsby et al. 1997). The primary determinant of the unique functions of each TGF-ß isoform in vivo appears to reflect their distinct patterns of transcription (Millan, Denhez et al. 1991); (Schmid, Cox et al. 1991). However, translational control and activation of the latent complex are also important (Munger, Harpel et al. 1997); (Roberts 1998); (Arrick, Grendell et al. 1994).

**Genetic study of TGF-ß1 polymorphism in SLE and other disease was shown in table 3**

**Table3.** Association of TGFß1 polymorphism with SLE and other diseases.

| Country/Ethnic | Cases/controls | Specificity | OR/ RR | References |
|---|---|---|---|---|
| France/ Caucasian | 563/629 | Significant association between TGFß1(-509CT ) allele and myocardial infarction | > 1 | (Cambien, Ricard et al. 1996) |
| Germany/ German | 45/107 | Significant association between TGFß1(-800GA, +72insC, codon10 and codon25) allele and lung fibrosis in transbronchial biopsies/(-800GA, +72insC and codon25) allele lung fibrosis and no allograft fibrosis | > 1 | (Awad, El-Gamel et al. 1998) |
| UK/ Caucasian | 171/107 | Significant association between TGFß1 codon10 TT geontype ,codon25 GG genotype and cystic fibrosis | > 1 | (Arkwright, Laurie et al. 2000) |
| Japan/ Japanese | 29/36 | Significant association between TGFß1 (+29CT) and spinal osteophytosis | _ | (Yamada, Okuizumi et al. 2000) |
| Pennsylvania/ Caucasian | 412/367 | No significant association between TGFß1 and Alzheimer's disease | > 1 | (Luedecking, DeKosky et al. 2000) |
| Crech/ Caucasian | 170/118 | No significant association between TGFß1(-800GA, -509CT, codon10 and codon25) allele and allergy and asthma | > 1 | (Buckova, Izakovicova Holla et al. 2001) |
| Japan/ Japanese | 155/110 | Significant differences in TGFß1(codon10) CT or TT genotype between healthy control and rheumatoid arthritis | > 1 | (Sugiura, Niimi et al. 2002) |
| Germany/ German | 48/97 | Significant association between TGFß1$^{25}$ArgPro allele(codon25) and liver fibrosis | > 1 | (Gewaltig, Mangasser-Stephan et al. 2002) |
| Japan/ Japanese | 110/59 | Significant association between TGFß1 (codon10)TT genotype and systemic sclerosis | > 1 | (Ohtsuka, Yamakage et al. 2002) |
| Germany/ German | 203/158 | No significant association between TGFß1 (codon25) and SLE | > 1 | (Schotte, Willeke et al. 2003) |
| Brazil/ Brazilian | 100/74 | Significant association between TGFß1(-509CT ) allele and chronic periodontitis | > 1 | (de Souza, Trevilatto et al. 2003) |
| Taiwan/ Chinese | 184/138 | No significant association between TGFß1(-988CA, -800GA, -509CT, codon10 and codon25) and SLE | > 1 | (Lu, Cheng et al. 2004) |
| US/ Mexican American | 46/64 | No significant association between TGFß1(-509CT ) allele and SLE | > 1 | (Caserta, Knisley et al. 2004) |
| US/ Mexican American | 50/64 | No significant association between TGFß1(-509TC ) and sjogren's syndrome | > 1 | (Caserta, Knisley et al. 2004) |
| South Iran | 110/110 | No significant association between TGFß1( -800GA, -509CT ) and recurrent spontaneous abortion | > 1 | (Amani, Zolghadri et al. 2004) |

TGF-ß2 has 99.27 kb, 465 SNPs. TGF-ß2 consist of 6 introns and 7 exons (-1000-+96054 related from transcription start site) (http://snpper.chip.org). Because of TGF-ß2 production found in mesangial, endothelial and epithelial cell. Various studies about the abnormality from glomerulonephritis indicated that the important role of TGF-ß2 gene due to renal fibrosis and chronic kidney disease (Grande 1998). Many studies of TGF-ß2 with other disease such as cleft palate in Philippines and carcinoembryonic antigen (CEA) not found associated with SLE. Moreover, study the 4 bp insertion polymorphism within the TGF-ß2 gene does not also appear to be associated with SLE. Data was shown in table 4 (Alansari, Hajeer et al. 2002).

**Table4.** Association studies between TGF-ß2 polymorphism and SLE

| Country/Ethnic | Cases/controls | Specificity | P value | References |
|---|---|---|---|---|
| UK, Span, Turkey<br>Caucasian, Spanish, Turkish | 187,84,90/<br>90,111,92 | No significant association between<br>TGF-ß2 and SLE | ><br>0.05 | (Alansari, Hajeer et al.<br>2002) |