Association between polymorphisms in the *FCGRT* gene and lupus nephritis in Chinese patients

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Abstract

Objective

Studies on mouse models have indicated that the neonatal Fc receptor (FcRn) plays important roles in a variety of autoimmune diseases. A variable number of tandem repeat (VNTR) polymorphisms within the FCGRT *gene have been detected, and were found to affect the expression and functioning of FcRn. This study investigated the possible association of* FCGRT *VNTR polymorphisms with susceptibility and clinical manifestations in patients with lupus nephritis (LN).*

Methods

A total of 404 Han Chinese subjects, comprising 200 patients with LN and 204 geographically-matched healthy controls, participated in the study. The FCGRT *VNTR polymorphism was genotyped by DNA amplification using a touchdown polymerase chain reaction followed by polyacrylamide gel electrophoresis.*

Results

The distribution of VNTR polymorphisms within the FCGRT *gene in Chinese subjects was different to that in Caucasians. Analysis of allele and genotype frequencies revealed no significant difference between LN patients and controls. There was no significant difference in the clinical features or prognosis in LN patients when stratified by VNTR polymorphism.*

Conclusion

Our results suggest that VNTR polymorphisms within the FCGRT *promoter are not associated with LN in the Chinese population.*

Key words

Lupus nephritis, *FCGRT*, variable number of tandem repeats.

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Introduction

The occurrence and progression of systemic lupus erythematosus (SLE) – a prototypic systemic autoimmune disease – involves many types of factors (1). Multiple facets of disturbances of the immune system including immunoglobulin G (IgG) homeostasis breakdown, and especially the persistent presence of a diverse array of autoantibodies, are believed to be the key pathway leading to the destructive power and complexity of the disease (2-4).

The neonatal Fc receptor (FcRn) is a major histocompatibility complex (MHC) class I-related molecule, which regulates the half-life of IgG and albumin. It has been identified as the "IgG protection" receptor, given the pivotal role of FcRn in IgG homeostasis (5, 6). It regulates IgG homeostasis and thus controls serum levels of antibodies (7, 8).

Earlier studies have shown that lupus prone (MRL-lpr/lpr) mice, when deficient in all class I molecules owing to a deficiency in β2-microglobulin, were protected from SLE-like syndromes, showing reduced hypergammaglobulinemia, alleviation of renal pathology, and decreased anti-DNA, anti-Sm Abs, and rheumatoid factor (9, 10). It was hypothesized that this protection could be due to the lack of functional FcRn molecules to protect pathogenic IgG antibodies from catabolism (11-13). In other studies on autoimmune diseases, $FcRn^{-/-}$ mice were protected from experimentally-induced autoimmune arthritis and epidermolysis bullosa acquisita (EBA) (14, 15). In humans, the presence of FcRn was demonstrated on glomerular epithelial cells (GEC), as well as in the brush border of proximal tubular cells. Thus, FcRn may play a role in the clearance of immune complexes and the reabsorption of IgG (16). Recent data indicated that FcRn expressed in podocytes functions to internalize IgG from the glomerular basement membrane (GBM). In mice lacking FcRn, IgG was found to accumulate in the GBM with age; moreover, tracer studies have shown delayed clearance of IgG from the kidneys of FcRn-deficient mice (17). These studies suggest that FcRn may play important roles in autoantibody regulation and be involved in kidney diseases with autoimmune characteristics.

A variable number of tandem repeat (VNTR) regions within the *FCGRT* gene, which encodes the α chain of FcRn, have been observed and *in vitro* this polymorphism influences the expression of the FcRn receptor, leading to different IgG binding capacities. Monocytes from VNTR2/3 heterozygous individuals carried significantly less FcRn transcript and displayed a diminished IgG binding capacity compared to VNTR3/3 homozygotes (18). However, it was not clear whether the differential expression of FcRn due to the VNTR polymorphism influences IgG-dependent pathologies in humans.

Based on the above, we speculate that FcRn may play a pivotal role in human lupus nephritis (LN) by maintaining the levels of pathogenic autoantibodies and promoting the occurrence and/or progression of LN. In particular, according to this hypothesis individuals homozygous for VNTR3/3 would be more likely to show higher serum levels of autoantibodies and a higher binding capacity than those who are heterozygous for VNTR2/3; thus, the former may be more prone to LN or have more severe clinical manifestations. The aim of this study was first to determine the distribution of this polymorphism in the Chinese population, and then to evaluate the association of VNTR polymorphisms in *FCGRT* with LN. We sought to investigate the role of genetic variations of FcRn in human autoimmune disease, especially lupus nephritis.

Patients and methods

Patients and controls

For this study 200 lupus nephritis patients from northern China – all of whom were diagnosed at Peking University First Hospital between 1997 and 2007 and met the revised and updated criteria established by the American College of Rheumatology (19, 20) – were enrolled. LN was confirmed by renal biopsy and classified according to the revised 2003 ISN/RPS classification system (21, 22). The mean age at diagnosis was 32.0±10.6 years (range, 14–60), and 84.5% of the patients were female. Geographically-matched healthy blood

donors (n=204; age range 9-52 years; mean ± SD, 28.2±8.7 years; proportion of females, 30.9%) served as controls. The data collected included: demographic information (age, sex), general clinical data (blood pressure, temperature), and data on the hematological system (blood count), kidneys (renal function and pathology), other organs (arthritis, skin, nervous system), immunological indicators (serum antibody and complement levels), and prognosis (renal function, for an average follow-up period of 5 years). Renal function was evaluated based on the serum creatinine level and the estimated glomerular filtration rate (eGFR) according to the abbreviated Modification of Diet in Renal Disease (MDRD) equation, suitably modified for the Chinese population (23).

The protocol for the genetic study was approved by the medical ethics committee of Peking University, and informed written consent was obtained from all the participants.

Determination of FCGRT *VNTR*

Genomic DNA was extracted from the peripheral white blood cells of whole blood samples by the salting out procedure (24). Primers for the *FCGRT* gene (GenBank accession number: AC010619) were designed for polymerase chain reaction (PCR) amplifications as follows: sense primer, 5′-TCTCGACACTGGGTCTGA-3′; anti-sense primer, 5′-TCACCCCT-GAACTGGATCTC-3′. The 20μL reaction volume contained 80–200 ng of template DNA, 3 pmol of each oligonucleotide primer, 2μL of 10×reaction buffer, 1.6μL of 2.5mM/L dNTP, 2μL 50% dimethyl sulfoxide (DMSO), and 1 unit of Taq LA DNA polymerase (Takara, Dalian, China). The amplification protocol included an initial denaturation at 94° for 10 min, 20 cycles of touchdown PCR of denaturation at 94° for 30 s, annealing at 60° for 30 s, and an extension at 72° for 30 s by decreasing the annealing temperature by 0.5° at every cycle, then 20 cycles of denaturation at 94° for 30 s, annealing at 50° for 30 s, and an extension at 72° for 30 s, followed by a final extension at 72° for 5 min. The products of PCR amplification were detected by 10% polyacrylamide gel electrophoresis. The specificity of the PCR products and the presence of tandem repeats were verified by sequencing.

Statistical analysis

Data were expressed as the mean ± standard deviation, geometric mean, ratio or proportion. Pearson's χ^2 was used to analyze the categorical data; continuity correction or Fisher's exact test were applied when necessary. Continuous variables were tested in each group for the normal distribution using the Kolmogorov-Smirnov test. Differences of the means between two groups were tested by Student's *t*-test. The Mann-Whitney U-test was applied for abnormal distributions. The analyses were performed using the SPSS 12.0 program. All tests were two-sided, and $p<0.05$ was considered statistically significant.

Results

Distributions of FCGRT *VNTR polymorphisms in patients and healthy controls*

Genotyping of 204 unrelated healthy subjects and 200 LN patients revealed three PCR products that differed in size (Fig. 1), consistent with two to four repeats of a 37-bp-long fragment. This result was subsequently verified by DNA sequencing and was in concordance with the earlier observation by Ulrich J. H. Sachs *et al.* (GenBank accession numbers: AF453514–AF453516).

VNTR3 was the most common allele in our Chinese cohorts; VNTR2 was less common and VNTR4 was rare. No VNTR1 or VNTR5 was observed. The calculated frequencies for the VNTR2, VNTR3, and VNTR4 alleles were 3.9%, 95.85% and 0.25% in the controls and 2.8%, 97.2% and 0% in the patients. A significant difference was observed in the distribution of these three polymorphisms in our subjects in comparison to the reported distribution in Caucasians ($p=1.21\times10^{-6}$) (Table I) (18). From this comparison it can be seen that the proportions of VNTR1, VNTR2, VNTR4, and VNTR5 in Chinese were relatively low, whereas the proportion of VNTR3 was relatively high.

There was no significant difference in the frequencies of *FCGRT* alleles and genotypes between the healthy controls and LN patients ($p=0.318$ and $p=0.326$). In addition, when the subjects were stratified by gender, no significant difference was observed in the frequencies of *FCGRT* alleles and genotypes between female ($p=1.000$ and 1.000) versus male ($p=0.881$ and 0.878) healthy controls and LN patients.

FCGRT *VNTR polymorphisms, clinical manifestations and renal prognosis*

Based on the clarity of expression and functional significance between the VNTR2/3 heterozygote and the VNTR3/3 homozygote reported by others (18), we divided the patients into two groups by genotype – those with the VNTR2/3 heterozygote and those with the VNTR3/3 homozygote (the VNTR2 homozygote was never observed in our cohort).

The clinical characteristics of the LN patients at the time of renal biopsy and the results of the most recent follow-up urinalysis are reported in Table II. There was no significant difference in any of the clinical parameters between the two genotypes. Notably, although a higher white blood cell count was observed in VNTR2/3 patients compared to VNTR3/3 patients, values never fell outside the normal range and the weakly significant difference disappeared after adjustment by multiple comparisons.

VNTR2/3 patients appeared to have a better prognosis; however, the difference in comparison to VNTR3/3 patients was not statistically significant and the finding was difficult to interpret because of the limited data available — only 3 patients in our cohort had the VNTR2/3 genotype. The serum creatinine levels of the three VNTR2/3 patients were 50 μmol/L, 49 μmol/L, and 299 μmol/L at the time of renal biopsy, and 76 μmol/L, 57 μmol/L, and 84 μmol/L at the time of the most recent follow-up.

Discussion

SLE has strong genetic and environmental components (25). Several strategies have been developed to identify genes or gene intervals associated with SLE in humans (26, 27). These approaches

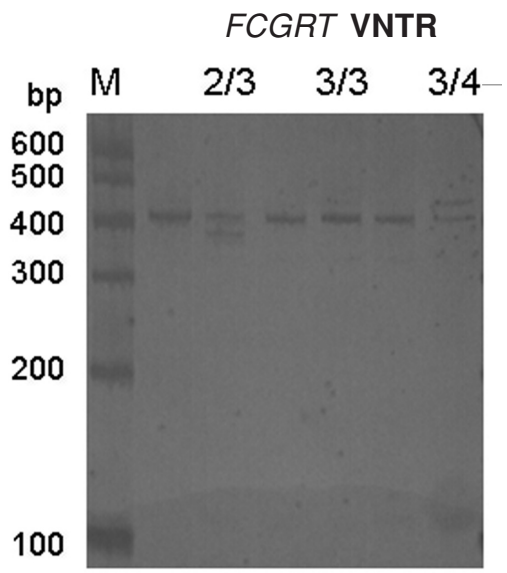

Fig. 1. VNTRs of the *FCGRT* gene in Chinese LN patients. Three types of alleles – the VNTR2/3, VNTR 3/3, and VNTR 3/4 genotypes – were detected by PCR. The numbers in the top row indicate the number of repeats of the tandem domain.

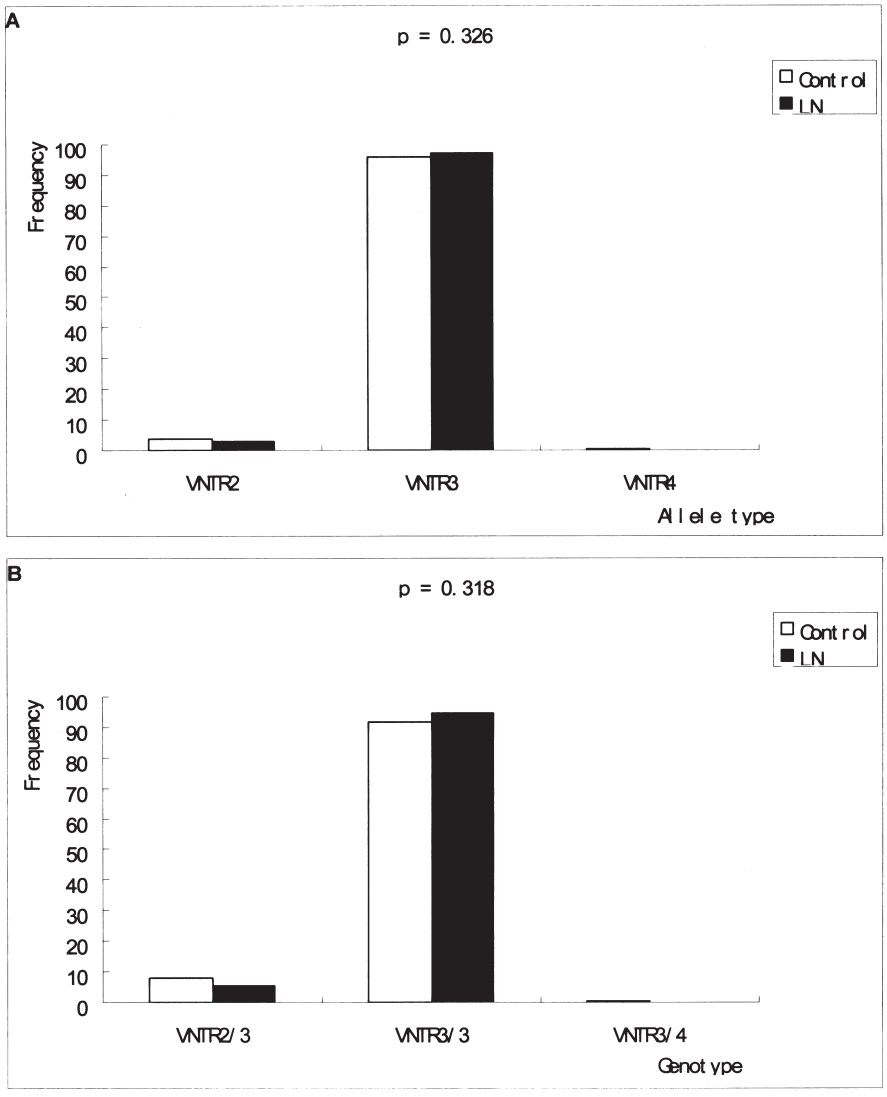

Fig. 2. Distribution of *FCGRT* alleles (**A**) and genotypes (**B**) between healthy controls and LN patients. No significant difference was found in the frequency of *FCGRT* alleles (p=0.318) and genotypes (p=0.326) between healthy controls and LN patients.

include: (a) candidate gene association studies, (b) linkage analysis in multiplex families, and (c) genome-wide association (GWA) studies. Candidate gene analysis focuses on specific genes, identified based on their location in a disease-associated interval or because of their potential physio-pathological importance. Although many loci and candidate genes have been reported to be associated with SLE (28-32), a genetic predisposition to the development of the disorder cannot be attributed to a monogenic defect; it appears instead to be polygenic, with multiple factors interacting in additive, epistatic or redundant ways. Thus, identifying genes and the pathways that they regulate could also lead to a better understanding of the pathogenesis of this complex disease.

The *FCGRT* gene has been located on 19q13.3 which is within an SLE-associated region by replicated linkage studies (28, 33). Its encoded molecule, FcRn, plays important roles in autoimmune diseases and may be a potential therapeutic target linking the initial and effector phases of humoral autoimmune disease (7, 34). All of this suggests that genetic variations in *FCGRT* may influence the occurrence and/or progression of SLE.

Gregory *et al*. found that multiple indicators of MRL-lpr/lpr SLE syndrome show considerable dependence on MHC I molecules. In particular, the severe glomerulonephritis characteristic of lpr/lpr B2m$^{+/-}$ was reduced significantly in lpr/lpr B2m0$^{-/-}$ mice, approaching levels equivalent to those of non-lpr homozygotes. This finding indicates that the presence of MHC class I is a prerequisite for the development of characteristic LN – the omnipresent and principal cause of morbidity in MRL-lpr/lpr mice (10). The expression of FcRn in the kidneys indicates that it may play a functional role under physiologic conditions and/or in some cases of human glomerulonephritis, especially LN, where IgG deposits have been found in the glomeruli, IgG has been detected in the urine, and a variety of autoantibodies are present (16, 17).

The disease model of gene knockout mice has recently emerged as a tool to elucidate the role of the *FCGRT* gene; however, the association of polymor-

Table I. Comparison of the VNTR distribution between Chinese and Caucasians*.

Allele type (%)	VNTR1	VNTR2	VNTR3	VNTR4	VNTR5
Chinese (n=404)	0	3.34	96.54	0.12	0
Caucasians (n = 427)	0.1	7.5	92	0.2	0.2

*Compared with data from U.J. Sachs *et al*. (18).

Table II. General clinical parameters for Chinese lupus nephritis patients, grouped by genotype (VNTR2/3 or VNTR3/3).

Parameters#	Genotype 2/3 (n=11)	Genotype 3/3 (n=189)	*p*-value
Demography			
Gender, female/male	9/2	160/29	0.804
Age (years)	27.09 ± 7.34	32.35 ± 10.70	0.117
General			
Presence of fever	10% (1/11)	36% (63/175)	0.18
Systolic blood pressure (mm Hg)	125.45 ± 14.40	129.29 ± 22.06	0.570
Diastolic blood pressure (mm Hg)	79.55 ± 11.50	81.93 ± 14.16	0.585
Hematological system			
Red blood cell count ($\times 10^{12}$/L)	3.21 ± 0.80	3.60 ± 0.75	0.098
White blood cell count ($\times 10^{9}$/L)	7.94 ± 4.88	5.75 ± 3.20	0.035
Blood platelet count ($\times 10^{9}$/L)	157.09 ± 73.24	181.08 ± 80.43	0.336
Hemoglobin (g/L)	96.00 ± 25.36	107.65 ± 22.96	0.106
Kidney			
Urinary protein excretion (g/day)	5.38 ± 4.07	4.40 ± 4.07	0.438
Serum creatinine (μmol/l)	104.18 ± 73.86	110.86 ± 108.05	0.840
eGFR* (ml/min/1.73m2)	94.84 ± 48.09	92.10 ± 43.55	0.841
Active proliferative glomerulonephritis (class IV + III)	64% [(6+1)/11]	61% [(77+38)/189]	0.853
Other systems			
Presence of arthritis	50.0% (5/10)	41.2% (73/177)	0.828
Presence of hydrohymenitis	22.2% (2/9)	17.9% (31/173)	1.000
New presence of erythema	66.7% (6/9)	56.1% (97/173)	0.779
Headache	11.1% (1/9)	6.3% (11/174)	1.000
Immunological indicators			
Serum IgG (g/l)	10.36 ± 6.58	11.89 ± 6.08	0.424
Serum IgA (g/l)	2.48 ± 1.34	2.77 ± 1.33	0.491
Serum IgM (g/l)	1.18 ± 0.65	1.17 ± 0.68	0.948
Serum C3 (g/l)	0.41 ± 0.17	0.50 ± 0.27	0.271
Serum C4 (g/l)	0.09 ± 0.04	0.12 ± 0.09	0.218
Antinuclear antibody titres	1:339	1:460	0.411
Anti-ds DNA antibody titres	1:26	1:34	0.446
Renal prognosis## (n=76)			
Latest serum creatinine on follow-up (μmol/l)	72.33 ± 13.87 (n=3)	136.49 ± 159.76 (n=73)	0.492

#All parameters except prognosis were measured at the time of renal biopsy in the 200 LN patients (VNTR2/3 group, n=11; VNTR3/3 group, n=189).
##Renal prognosis was analyzed in the 76 patients for whom data were available (VNTR2/3 group, n=3; VNTR3/3 group, n=73).
*eGFR: estimated glomerular filtration rate.

phisms of human *FCGRT* with human phenotypes has rarely been investigated (35). VNTR polymorphisms within the *FCGRT* promoter were found to influence the expression of the FcRn receptor, leading to different IgG binding capacities. In the present study we investigated VNTR polymorphisms of the *FCGRT* gene in healthy Chinese subjects and in Chinese patients with LN. The repeat numbers of the domain varied from 2 to 4. The most frequent allele was VNTR3, and the most frequent genotype was VNTR3/3. We found the distribution of VNTR in Chinese subjects to be different from that in Caucasians. We furthermore demonstrated that there was no significant difference in the genotypes frequencies of *FCGRT* between LN patients and healthy controls. These results indicate that individuals with different VNTR polymorphisms of the *FCGRT* gene do not have different susceptibilities to LN. Our study also found no significant difference in the clinical, pathological, and renal prognosis indicators between LN patients with different VNTR polymorphisms. In particular, no association of genotypes with serum autoantibody levels was observed. These results suggest that the genotypes of the *FCGRT* gene are not associated with the general manifestations or prognosis of LN.

Despite the functional importance and apparently significant position of *FCGRT*, various reasons could account for the lack of an association between this polymorphism and LN. Firstly, MHC class I dependence occurs in the later phase of the disease, whereas the kinetics of the disease phases differ depending on genetic and/or environmental parameters. The role of genetics in the disease may be attenuated by many factors, thus making it difficult to confirm the hypothesis (10). Secondly, considering the prevalence of VNTR3/3 in our patient population and the low percentage of the VNTR2/3 genotype – analogous to what has been reported for Caucasians – we speculate that despite its functional significance, this polymorphism may not be an important contributing factor to the risk of developing LN.

In conclusion, our study represents the first investigation of the distribution of *FCGRT* promoter VNTR polymorphisms in Chinese subjects. This was found to be different from the distribution in Caucasians. We show for the first time an association of *FCGRT* polymorphism with LN in a case-control study, and demonstrate that it is not associated with susceptibility to SLE in the Chinese Han population. Future efforts directed at examining other *FCGRT* gene polymorphisms such as copy number variants and single nucleotide polymorphisms (SNPs), or other candidate genes may provide further insight into the genetic mechanisms underlying the pathogenesis of this disease.

References

1. JONSEN A, BENGTSSON AA, NIVED O, TRUEDSSON L, STURFELT G: Gene-environment interactions in the aetiology of systemic lupus erythematosus. *Autoimmunity* 2007; 40: 613-7.
2. ALBA P, BENTO L, CUADRADO MJ *et al*.: Anti-dsDNA, anti-Sm antibodies, and the lupus anticoagulant: significant factors associated with lupus nephritis. *Ann Rheum Dis* 2003; 62: 556-60.
3. GOMEZ-PUERTA JA, BURLINGAME RW, CERVERA R: Anti-chromatin (anti-nucleosome) antibodies: Diagnostic and clinical value. *Autoimmun Rev* 2008.
4. YUNG S, CHAN TM: Anti-DNA antibodies in the pathogenesis of lupus nephritis--the emerging mechanisms. *Autoimmun Rev* 2008; 7: 317-21.
5. TAKAI T: Fc receptors and their role in immune regulation and autoimmunity. *J Clin Immunol* 2005; 25: 1-18.
6. TAKAI T: Roles of Fc receptors in autoimmunity. *Nat Rev Immunol* 2002; 2: 580-92.
7. AKILESH S, PETKOVA S, SPROULE TJ, SHAFFER DJ, CHRISTIANSON GJ, ROOPENIAN D: The MHC class I-like Fc receptor promotes humorally mediated autoimmune disease. *J Clin Invest* 2004; 113: 1328-33.
8. HE W, LADINSKY MS, HUEY-TUBMAN KE, JENSEN GJ, MCINTOSH JR, BJORKMAN PJ: FcRn-mediated antibody transport across epithelial cells revealed by electron tomography. *Nature* 2008; 455: 542-6.
9. CHRISTIANSON GJ, BLANKENBURG RL, DUFFY TM *et al*.: Beta2-microglobulin dependence of the lupus-like autoimmune syndrome of MRL-lpr mice. *J Immunol* 1996; 156: 4932-9.
10. CHRISTIANSON GJ, BROOKS W, VEKASI S *et al*.: Beta 2-microglobulin-deficient mice are protected from hypergammaglobulinemia and have defective antibody responses because of increased IgG catabolism. *J Immunol* 1997; 159: 4781-92.
11. ISRAEL EJ, WILSKER DF, HAYES KC, SCHOENFELD D, SIMISTER NE: Increased clearance of IgG in mice that lack beta 2-microglobulin: possible protective role of FcRn. *Immunology* 1996; 89: 573-8.
12. MIXTER PF, RUSSELL JQ, DURIE FH, BUDD RC: Decreased CD4-CD8- TCR-alpha beta + cells in lpr/lpr mice lacking beta 2-microglobulin. *J Immunol* 1995; 154: 2063-74.
13. OHTEKI T, IWAMOTO M, IZUI S, MACDONALD HR: Reduced development of CD4-8-B220+ T cells but normal autoantibody production in lpr/lpr mice lacking major histocompatibility complex class I molecules. *Eur J Immunol* 1995; 25: 37-41.
14. MATSUMOTO I, STAUB A, BENOIST C, MATHIS D: Arthritis provoked by linked T and B cell recognition of a glycolytic enzyme. *Science* 1999; 286: 1732-5.
15. SESARMAN A, SITARU AG, OLARU F, ZILLIKENS D, SITARU C: Neonatal Fc receptor deficiency protects from tissue injury in experimental epidermolysis bullosa acquisita. *J Mol Med* 2008; 86: 951-9.
16. HAYMANN JP, LEVRAUD JP, BOUET S *et al*.: Characterization and localization of the neonatal Fc receptor in adult human kidney. *J Am Soc Nephrol* 2000; 11: 632-9.
17. AKILESH S, HUBER TB, WU H *et al*.: Podocytes use FcRn to clear IgG from the glomerular basement membrane. *Proc Natl Acad Sci USA* 2008; 105: 967-72.
18. SACHS UJ, SOCHER I, BRAEUNLICH CG, KROLL H, BEIN G, SANTOSO S: A variable number of tandem repeats polymorphism influences the transcriptional activity of the neonatal Fc receptor alpha-chain promoter. *Immunology* 2006; 119: 83-9.
19. TAN EM, COHEN AS, FRIES JF *et al*.: The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; 25: 1271-7.
20. HOCHBERG MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 1725.
21. WEENING JJ, D'AGATI VD, SCHWARTZ MM *et al*.: The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol* 2004; 15: 241-50.
22. WEENING JJ, D'AGATI VD, SCHWARTZ MM *et al*.: The classification of glomerulonephritis in systemic lupus erythematosus revisited. *Kidney Int* 2004; 65: 521-30.
23. MA YC, ZUO L, CHEN JH *et al*.: Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. *J Am Soc Nephrol* 2006; 17: 2937-44.
24. MILLER SA, DYKES DD, POLESKY HF: A simple salting out procedure for extracting DNA from human nucleated cells. *Nucleic Acids Res* 1988; 16: 1215.
25. ALARCON-SEGOVIA D, ALARCON-RIQUELME ME, CARDIEL MH *et al*.: Familial aggregation of systemic lupus erythematosus, rheumatoid arthritis, and other autoimmune diseases in 1,177 lupus patients from the GLADEL cohort. *Arthritis Rheum* 2005; 52: 1138-47.
26. RHODES B, VYSE TJ: General aspects of the genetics of SLE. *Autoimmunity* 2007; 40: 550-9.
27. SHEN N, TSAO BP: Current advances in the human lupus genetics. *Curr Rheumatol Rep* 2004; 6: 391-8.
28. HARLEY JB, ALARCON-RIQUELME ME, CRISWELL LA *et al*.: Genome-wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in ITGAM, PXK, KIAA1542 and other loci. *Nat Genet* 2008; 40: 204-10.
29. AKSU K, KITAPCIOGLU G, KESER G *et al*.: Fc-gamma RIIa, IIIa and IIIb gene polymorphisms in Behçet's disease: do they have any clinical implications? *Clin Exp Rheumatol* 2008; 26 (Suppl. 50): S77-83.
30. HOSHI D, OKAMOTO H, KANEKO H *et al*.: Association of a polymorphism in the monocyte chemoattractant protein-1/CCL2 gene and lupus nephritis in systemic lupus erythematosus patients. *Clin Exp Rheumatol* 2008; 26: 972-3.
31. MOSTOWSKA M, WUDARSKI M, CHWALINSKA-SADOWSKA H, JAGODZINSKI PP: The programmed cell death 1 gene 7209 C > T polymorphism is associated with the risk of systemic lupus erythematosus in the Polish population. *Clin Exp Rheumatol* 2008; 26: 457-60.
32. PIOTROWSKI P, LIANERI M, WUDARSKI M, LACKI JK, JAGODZINSKI PP: Contribution of the R620W polymorphism of protein tyrosine phosphatase non-receptor 22 to systemic lupus erythematosus in Poland. *Clin Exp Rheumatol* 2008; 26: 1099-102.
33. KANDIL E, EGASHIRA M, MIYOSHI O, NIIKAWA N, ISHIBASHI T, KASAHARA M: The human gene encoding the heavy chain of the major histocompatibility complex class I-like Fc receptor (FCGRT) maps to 19q13.3. *Cytogenet Cell Genet* 1996; 73: 97-8.
34. LIU L, GARCIA AM, SANTORO H *et al*.: Amelioration of experimental autoimmune myasthenia gravis in rats by neonatal FcR blockade. *J Immunol* 2007; 178: 5390-8.
35. BROWN EE, EDBERG JC, KIMBERLY RP: Fc receptor genes and the systemic lupus erythematosus diathesis. *Autoimmunity* 2007; 40: 567-81.