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Freaquency of Fcγriiia-158v/F Polymorphism in Systemic Lupus Erythematosus Patients with Lupus Nephritis.

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Abstract

Background: Receptors for the IgG plays critical role in linking humoral and cellular immune response. The various FcγR genes may contribute to differences in infectious and immune related diseases in various ethnic populations. Allelic variants of FcγR confers distinct phagocytic capacities providing a mechanism for heritable susceptibility to immune complex disease. Numerous functionally relevant SNP variants and copy number variants have been characterized in the FcγR genes. Many of these variants have also been shown to associate with the risk to development of SLE and some have been associated with disease progression.

Aim: In this study we aimed to investigate whether the distribution of the FcγRIIIA polymorphism determines susceptibility to Systemic Lupus Erythematosus with lupus nephritis in Indian patients.

Methodology: A total of 32 patients that fulfilled American college of Rheumatology classification criteria for SLE were included in the study. FcγRIIIA genotypes were determined by polymerase chain reaction based allotyping method with allele specific primers.

Results: The results demonstrated that FcγRIIIA-158V/F polymorphism in 91% and FcγRIIIA-158V/V in 9% of the cases. It shows that FcγRIIIA-158 has susceptibility to SLE and lupus nephritis in Indian patients. To our knowledge this is the first study considering the frequency of FcγRIIIA polymorphism in Indian SLE patients.

Conclusion: To enhance our understanding of the functional role of the receptors in SLE future research will need to integrate the knowledge of SNP and CNV and the functional diversity of the receptors.

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Keywords: FcγRIIIA genotypes, Systemic Lupus Erythematosus, cellular immune response, IgG

INTRODUCTION

SLE is a prototypic autoimmune disease characterized by the presence of autoreactive B cells and the formation and deposition of antibody-antigen immune complexes consistent with the diathesis, which involves multiple organ systems. Evidence from familial aggregation studies[1-5] together with a high concordance among monozygotic twins [6-8] suggest a genetic contribution. However, a single gene with a clearly causal Mendelian effect has not been identified underscoring a multigenic mode of inheritance. Among the quantitative trait loci identified from candidate gene-association studies of murine lupus models and diverse human populations and the recently published genome-wide scan, consistent linkage to 1q21.1-24, a region that includes a functionally and structurally diverse group of receptors that recognize the constant (Fc) portion of specific immunologlobulin (Ig) isotypes has been demonstrated[9-15].

Consistent with a role for receptors for the Fc region of IgG (FcγR), the pathogenesis of SLE involves the production of autoantibodies resulting in immune complex (IC) formation. Altered or delayed clearance of these autoantibody containing IC results in deposition of these IC in various tissues, eliciting inflammation and damage by engaging IgG Fc receptors (FcγRs) and complement.

In addition, more recent data demonstrated that FcγR also function as receptors for innate immune opsonins (CRP and SAP) and provide a link between innate and acquired immunity. In human, the classical FcγR family is divided into three receptor families (FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16)) based on structural homology, difference in affinity and differences in specificity for IgG subclasses. These FcγRs are also defined as either activating receptors (FcγRI, FcγRIIA/C, FcγRIII) or inhibitory receptor (FcγRIIB) as they elicit or inhibit immune functions such as phagocytosis, cytotoxicity, degranulation, antigen presentation and cytokine production via immune tyrosine activating or inhibitory motifs (ITAM or ITIM). . The classic clearance studies[16,17] demonstrated delayed in vivo FcγR mediated clearance in patients with SLE and ex vivo studies demonstrated altered FcγR functions such as phagocytosis[18]. These alterations in FcγR function correlate with disease activity suggesting that disease activity may alter receptor function. However, extensive studies of FcγRs in both animal models and human population studies have since been performed[19,20] and several functional genetic polymorphisms have been identified and associated with SLE in several ethnic populations. Thus FcγR function in patients with SLE is influenced by both inherited genetic variation and by acquired differences in function attributable to disease activity. In addition, common variation in the genes that encode Fc receptors, capable of altering the efficiency of the mononuclear phagocyte system to clear Ig immune complexes, provides a mechanism for the heritable differences observed in the susceptibility to SLE and subsequent immune complex-mediated tissue injury[21,22].

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AIMS AND OBJECTIVES

1. To study Fc gamma receptor polymorphisms in SLE patients with lupus nephritis.

2.To identify the predominant type of polymorphism in SLE patients with lupus nephritis.

MATERIALS AND METHODS

Study design and patient population:

This is a cross sectional study. The study was conducted in the Department of Biochemistry in collaboration with Department of Medical genetics Nizam‟s Institute of Medical Sciences, Punjagutta, Hyderabad and Diagnostics division CDFD (Centre for DNA fingerprinting and Diagnostics) Nampally Hyderabad from november 2015 to August 2016. 40 patients were recruited from the outpatient division of General medicine department and Medical Genetics outpatient division department of Nizam‟s Institute of Medical Sciences, Hyderabad.

Study Material:

Patients attending Rheumatology and Nephrology departments of NIMS with clinical suspicion of Lupus Nephritis were confirmed by Renal biopsy. FCGR polymorphisms (FCGR2A-R131H ,FCGR3A-F158V,) analysis by PCR amplification followed by sequencing. Based on the presence or absence of polymorphism patients were grouped into following groups:

- First group- Patients with FCGR2A-R131H polymorphism
- Second group- Patients with FCGR3A-F158V polymorphism

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Inclusion criteria:

Patients above 18 year of age who are diagnosed as having Lupus nephritis disease based on clinical history, haematological parameters and histopathological examination.

Exclusion criteria:

1)Subjects who are below 18 years of age.

2)Patients with other systemic autoimmune disease.

3)Patients with chronic kidney disease.

Sample collection:

Peripheral venous blood samples will be collected in EDTA containing tubes and the samples will be frozen at -20^0c.Genomic DNA will be extracted from white blood cells with phenol-chloroform.Two FCGR polymorphism(FCGR2A-R131H ,FCGR3A-F158V,) will be analysed by Polymerase Chain Reaction and sangers sequencing method.

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Institutional Ethics Committee approval:

The study was approved by the hospital's Institutional Ethical Committee (EC/NIMS/1544/2014) dated 22/08/2016.

BIOCHEMICAL ANALYSIS:

ANTI ds DNA antibodies:These are meaaured by enzyme linked immunosorbent assay (elisa) in human serum or plasma.Diluted patient serum is added to wells coated with purified ds dna antigen.specific antibody if presnt binds to antigen,all unbound materials are washed away and the enzyme conjugate is added to bind to antigen-antibody complex,if present.excess enzyme conjugate is washed off and substrarte is added .the plate incubated to allow the oxidation of the substarate by the enzyme.the intensity of the colour generated proportional to the amont of specific anti body in the sample.

ANTI cardiolipin antibodies:

these are measured by ELISA. Dilueted patient serum is added to wells coated with purified aCL antigen.acL specific ig M antibody if presents binds to the antigen. All unbound materials are washed away and the enzyme conjugate.

Genetic Analysis:

1.DNA extraction: DNA is extracted manually using QIAGEN kit method where silica membrane technology is used. This method is based on the selective adsorption of nucleic acids to a silica gel membrane in the presence of high concentrations of chaotropic salts. Use of optimized buffers in the lysis procedure ensures that only DNA is adsorbed while cellular proteins and metabolites remain in solution and are subsequently washed away. Combination of filtration and centrifugation procedures are needed.

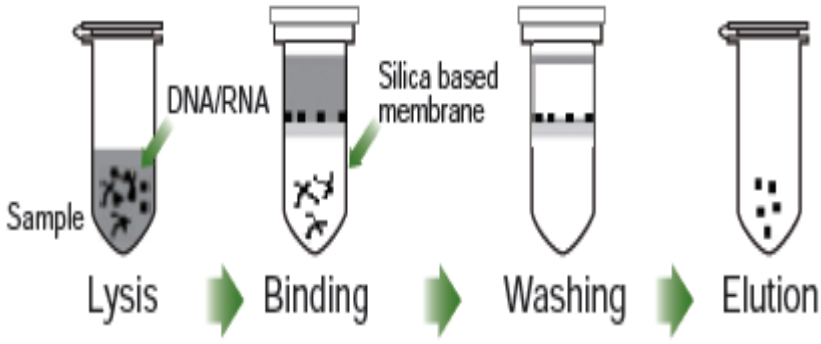

Figure : DNA or RNA released from sample treated by lysis buffer is bound to a silica gel membrane in the presence of high concentration of chaotropic salt. The purified genomic DNA on the membrane is eluted in the elution buffer.

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DNA quantification: The concentration of DNA is measured using nanodrop which works on the principle of spectrophotometry. For quantifying DNA and RNA, readings should be taken at wavelengths of 260 nm and 280 nm. The reading at 260 nm allows calculation of the concentration of nucleic acid in the sample. Pure DNA has an A_{260}/A_{280} ratio of 1.8–2.0 in 10 mM Tris·Cl, pH 8.5. Strong absorbance at A_{280} resulting in a low A_{260}/A_{280} ratio indicates the presence of contaminants, such as proteins. Strong absorbance at 270 nm and 275 nm may indicate the presence of contaminating phenol. Absorbance at 325 nm suggests contamination by particulates in the solution or dirty cuvettes.

PCR: The DNA is amplified using PCR technique. Both FCGR2A and FCGR3A promoter regions were being amplified using a thermo cycler. The thermal cycler heats and cools the reaction tubes to achieve the temperatures required at each step of the reaction. Thin-walled reaction tubes permit favorable thermal conductivity to allow for rapid thermal equilibration.

a) Primer designing a prerequisite for PCR: Proper primer design is important for applications in PCR, DNA sequencing, and hybridization. The ideal primer generally has the following characteristics:

1. Tm between 55 and 65°C (usually corresponds to 45-55 G+C for a 20-mer).
2. Absence of dimerization capability.
3. Absence of significant hairpin formation (usually >3 bp).
4. Lack of secondary priming sites in the template.
5. Low specific binding at the 3' end, to avoid mispriming.

c) PCR conditions for FCGR2A-R131H and FCGR3A-F158V Polymorphism:

A total of 10µl of reaction volume was used for this purpose. The reaction volume was composed of 2µl of the genomic DNA template,0.5µl of each of the two primers is used, 5µl of master mix which contains taq polymerase, dntp's, 2µl of Q solution which contains buffers, 0.4µl of distilled water. The program was run in a thermocycler at 94^0c for 5 mins for an initial denaturation, followed by 30 cycles of DNA denaturation at 94°C for 1 minute, annealing at 56°C for 1 minute, elongation at 72°C for 1 minute. After 30 cycles were over, the thermal cycler was set at 72°C for 7 minutes for final extension.

d) PCR conditions for FCGR 3A polymorphism- A total of 10µl of reaction volume was used for this purpose. The reaction volume was composed of 2µl of the genomic DNA template,0.5µl of each of the two primers is used (forward primer 5'-**GTCTTTCAGGCTGGCTGTTG** -3', reverse primer 5'-**GGACTGAAACAGAGCTGCAA** -3'), 5µl of master mix which contains taq polymerase, dntp's, 2µl of Q solution which contains buffers. The program was run in thermal cycler at 94°C for 6 minutes for an initial denaturation, followed by 34 cycles of DNA denaturation at 94°C for 1 minute, annealing at 55°C for 30 seconds, elongation at 72°C for 45 seconds. After 34 cycles were over, the thermal cycler was set at 72°C for 10 minutes for final extension.

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1) **Gel Electrophoresis:** After PCR amplification, PCR product was run in 2% agarose gel to check the purity and intactness of a DNA preparation. Agarose gel is used to separate molecules larger than 100bp.

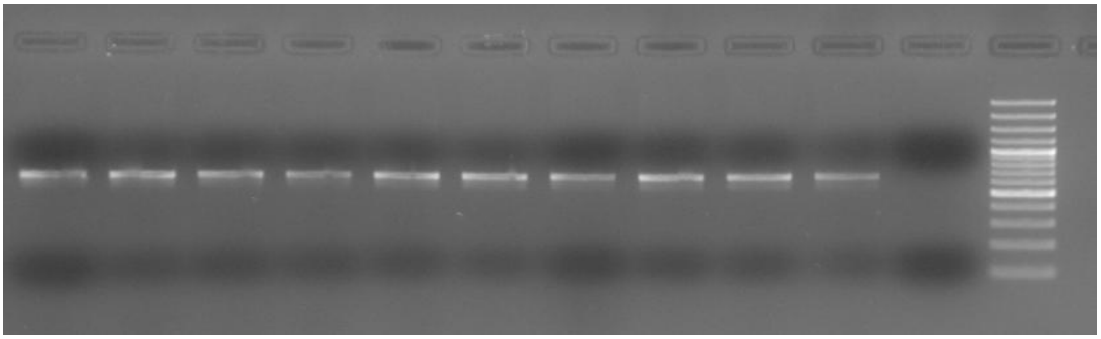

Figure : A photograph of agarose gel stained with ethidium bromide and illuminated with UV irradiation showing discrete DNA bands of PCR product of FCGR 3A-F158V polymorphism.

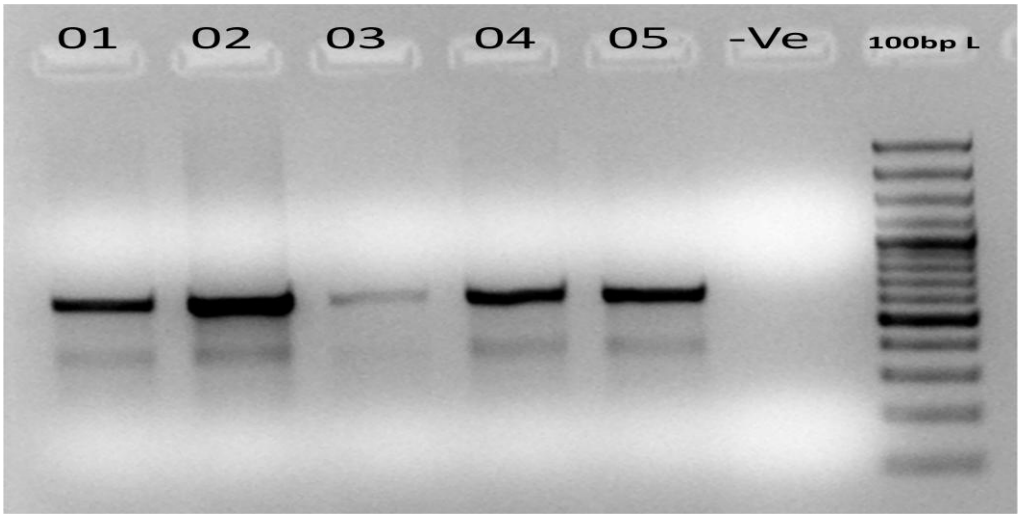

Figure : 1 Another photograph of agarose gel stained with ethidium bromide and illuminated with UV irradiation showing discrete DNA bands of PCR product of FCGR 3A-F158V polymorphism, a negative control and 100bp length ladder.

2) **Sequencing:** DNA sequencing is the process of determining the nucleotide order of a given DNA fragment. DNA is being sequenced by sanger sequencing.

Sanger sequencing- This method is a chain termination method developed by Frederick Sanger. In this sequencing, extension is initiated at a specific site on the template DNA by using a short oligonucleotide 'primer' complementary to the template at that region. The oligonucleotide primer is extended using a DNA polymerase, an enzyme that replicates DNA. Included with the primer and DNA polymerase are the four deoxynucleotide bases, along with a low concentration of a chain terminating nucleotide most commonly a di-deoxynucleotide. Limited incorporation of the chain terminating nucleotide by the DNA polymerase results in a series of related DNA fragments that are terminated only at positions where that particular nucleotide is used. The fragments are then size-separated by

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electrophoresis in a slab polyacrylamide gel, or more commonly now, in a narrow glass tube (capillary) filled with a viscous polymer.

An alternative to the labelling of the primer is to label the terminators instead, commonly called 'dye terminator sequencing'. The major advantage of this approach is the complete sequencing set can be performed in a single reaction, rather than the four needed with the labeled-primer approach. This is accomplished by labelling each of the dideoxynucleotide chain-terminators with a separate fluorescent dye, which fluoresces at a different wavelength. This method is easier and quicker than the dye primer approach, but may produce more uneven data peaks, due to a template dependent difference in the incorporation of the large dye chain-terminators. This problem has been significantly reduced with the introduction of new enzymes and dyes that minimize incorporation variability.

Other types include- pyrosequencing

True single molecule sequencing

Large-scale sequencing.

STATISTICAL ANALYSIS:

Descriptive statistics will be used to describe continous variables and expressed in mean±SD. Frequency tables will be used to describe the categorical variables.Chi-square test will be used to analyse the groups. p value of <0.05 will be taken as significant.

RESULTS

This is a study which includes 32 SLE patients(males-2, females-30) with lupus nephritis proved by renal biopsy. Of the 32 patients 18 were of stage 4 lupus nephritis, 7 and 4 were in stage 3 & 5 respectively. 2 cases were with indeterminant biopsy report (as shown in Fig 1). Their characteristic routine SLE profile was shown in Table 1.

Fig 1: Stage wise distribution of SLE patients with Lupus nephritis.

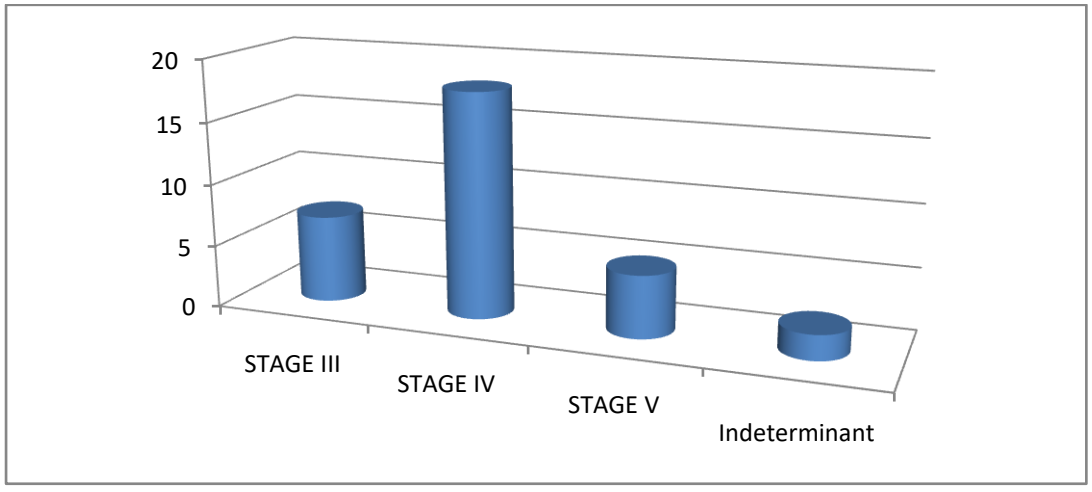

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Table 1: CHARACTERISTICS OF SLE PATIENTS WITH LUPUS NEPHRITIS

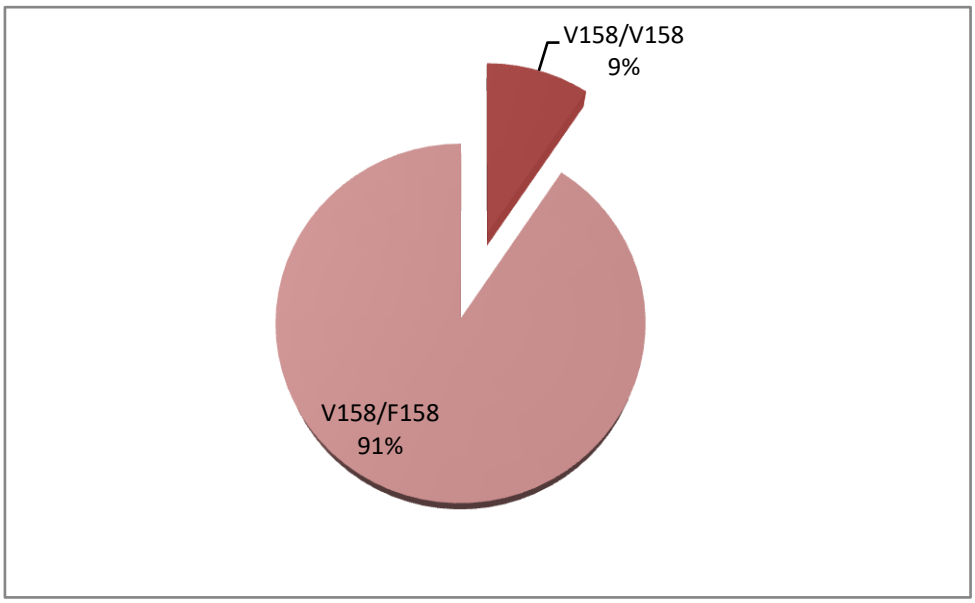
	Mean ± SD
NUMBER OF SUBJECTS	**32, M=2; F=30**
AGE (YRS)	**30.2 ± 9.5**
Ds DNA	**2.5±0.5**
Ac IgG (GPL)	**25.9 ± 9.9**
AcIgM (MPL)	**10.8 ± 7.8**
Complement C3 (mg/dl)	**33.3 ± 12.7**
Complement C4 (mg/dl)	**8.5 ± 5.5**
Urine Protein/creatinine	**1.3 ± 0.7**

Distribution of FcγRIIIA alleles in Indian Lupus Nephritis patients was shown Table 2. Homozygosity for the FcγRIIIA V158 alleles was found only in 9% where as heterozygosity was seen 91% of cases.

Table 2: Distribution of FcγRIIIA alleles in Indian SLE patients with Lupus Nephritis.

	LUPUS NEPHRITIS N=32
GENOTYPE	**No. of subjects (%)**
V158/F158	29(91)
V158/V158	3(9)
Alleleic frequency	
V158	55%
F158	45%

Figure 2: DISTRIBUTION OF FcγIIIA 158 V/F POLYMORPHISM IN INDIAN SLE PATIENTS WITH LUPUS NEPHRITIS.



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DISCUSSION:

In the Indian scenario, no studies have been undertaken to look for the association of Fc γ receptor polymorphism in patients with SLE and their role in pathophysiology of the disease. It will be interesting to know Fc γ receptor polymorphism in our country as no substantial data is yet available.

Two genes, FCGR3A and FCGR3B encode the two receptors of the FcγRIII family (FcγRIIIa and FcγRIIIb). FcγRIII is also considered low affinity, however, FcγRIIIA can bind monomeric IgG with an intermediate affinity and both FcγRIIIA and FcγRIIIB bind multimeric IgG and IC efficiently. FcγRIIIa ligand binding is further influenced by receptor glycosylation. Different glycoforms of FcγRIIIa are expressed on human NK cells and monocytes/ macrophages and these glycoforms have different abilities to bind IgG ligand.

The FcγRIIIa protein is expressed as a transmembrane protein on monocytes, tissue specific macrophages, dendritic cells, δ/γT cells, and natural killer cells[19]. On these cells γ-chain (or the TCR ζ-chain on NK cells) is necessary for both stable expression of the protein on the cell surface and for signal transduction through the FcγRIIIa receptor complex. A key function of these activating FcγR is the removal or clearance of immune complexes. As noted above, this function is known to be altered in patients with SLE. Of all FcγRs, FcγRIIIa is thought to play an important role in immune complex clearance. The intermediate affinity of this receptor on macrophages (fixed tissue macrophages) makes it ideally suited as a capture receptor to facilitate clearance. Of course, this does not preclude a role for other FcγR in IC handling and it is likely that IC clearance represents the integrated function of multiple FcγR working in concert with complement receptors.

African Americans and afro caribbeans are recognized as a group with greater prevalence and more severe SLE than Caucasians[23,24]. Though the basis for these differences is likely to reflect both geneticand environmental factors, Recognition of the relative importance of inherited factors among various ethinic groups may provide insight into the clinical differences described for ethnically defined population and enhance understanding of the mechanism of disease in SLE. FcγRIIIa is thought to play a critical role in immune complex clearance. In addition, this receptor is an important mediator of antibody-dependent cell-mediated cytotoxicity (ADCC) functions on NK cells. A non-synonymous SNP (rs396991) that encodes a T to G change at nt559 that results in a phenylalanine (F) to valine (V) amino acid change at position 158 in the second extracellular domain of the FcγRIIIa protein. These alleles of FcγRIIIA have differing binding affinity for IgG. The FcγRIIIA-158V allele binds IgG1, IgG3 and IgG4 with higher affinity relative to the 158F allele. In addition, the increased binding capacity of the 158V allele results in more robust downstream functional effects. Using peripheral blood NK cells from genotyped donors, individuals homozygous for the 158V allele demonstrate higher calcium transients, higher induction of CD25 expression and more rapid apoptosis when compared to donors homozygous for 158F[25,26]. Consistent with a critical role for FcγRIIIa in IC clearance, the lower IgG binding allele 158F is

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associated with SLE susceptibility in several case-control studies in multiple ethnic groups (Caucasian and African-American).

A role for FcγRIIIa in disease severity has also been demonstrated. Within patients with renal disease, the higher biding 158V allele is associated with development of ESRD. This result, in conjunction with the SLE susceptibility studies of FCGR3A, demonstrates that this gene can influence not only disease susceptibility but also disease progression. In patients with renal disease, progression to ESRD[27] is associated with the higher binding allele of FcγRIIIA consistent with a role for this receptor in promoting more vigorous local inflammatory responses in the kidney.

A meta analysis report in Thai, Chinese and Japanese populations in patients with SLE with lupus nephritis and without nephritis suggests that the FcγRIIIA –V/F 158 polymorphism has a significant impact on the development of lupus nephritis where a comparision of patients with lupus nephritis with patients with non nephritis SLE revealed a significant over presentation of the low binding F 158 allele among patients with SLE who developed renal disease[29,30,31].

Several in vitro studies argue in favor of direct involvement of *FCGR3A*-158V/F polymorphism. First, Koene et al [28] have shown that the previously reported differences in IgG binding among the 3 Fc RIIIA isoforms are a consequence of the linked Fc RIIIa-158V/F polymorphism, and several teams have demonstrated that NK cells from individuals homozygous for the *FCGR3A*-158V allotype have a higher affinity for human complexed IgG1 and are more cytotoxic toward IgG1-sensitized targets.

In an independent, large, case controlled replication study, the association between Fc γ RIIIA and SLE was found to be stronger than the association of Fc γ RIIA with SLE. The data for Fc γ RIIIA satisfy the recommendations for evidence of linkage, a demonstrated association in both family based and independent case controlled cohorts, and functional relevance to disease as recently outlined for the definition of a true genetic effect. It is proposed that there could be a common susceptibility gene in the Asian population. India has diverse populations, ethnic groups, and isolated tribal areas.

CONCLUSION

Activating and inhibitory Fc γIIIA receptors polymorphisms seem to play an important role in the pathogenesis of SLE, both in initiation of autoimmunity and in subsequent development of inflammation. Though the mechanisms underlying the initiation of autoimmunity are yet to be elucidated, the ensuring development and maintenance of inflammatory processes could potentially be influenced at the level of Fc γ receptors. Our study shows that FcγRIIIA-158 has susceptibility to SLE and lupus nephritis in Indian patients. Modulating Fc γIIIA-158V/F receptor signaling mechanisms could influence the response to immune complexes and the course of the disease, making Fc γIIIA receptors a potential candidate for immunotherapy. Characterization of Fc γIIIA-158V/F receptor genotypes, in conjunction with other properties of the humoral immune response such as antibody subclass and complement status, may provide essential insights into vaccine

effectiveness and disease risk.

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Conflict of Interest

None

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Nil

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