

# Fc $\gamma$ RIIa defunctioning polymorphism in paediatric patients with renal allograft

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## Abstract

**Introduction:** Fc gamma receptor (Fc $\gamma$ R) IIa is considered the most widely distributed of the three classes of Fc receptors, and it expresses an allelic polymorphism. This type of polymorphism may modify the immune response and may be an important factor for some diseases. The aim of the study reported herein was to evaluate the association between the Fc $\gamma$ RIIa polymorphism and susceptibility to both end-stage renal disease (ESRD) and acute kidney graft rejection (AR) in children who have undergone renal transplantation.

**Material and methods:** The study evaluated 70 children who had undergone transplantation and 60 healthy subjects. AR was observed in 25 children.

**Results:** Fc $\gamma$ RIIa genotypes and alleles were significantly different between transplantation patients and the control group. The assessment for Fc $\gamma$ R of the groups in which AR was present showed that there was only a risk of having an acute rejection in homozygous genotype RR.

**Conclusions:** Fc $\gamma$ RIIa RR genotype and allele frequency was increased in paediatric renal transplant recipients. The present findings showed that Fc $\gamma$ RIIa genotype may be related to ESRD disease susceptibility, and Fc $\gamma$ RIIa polymorphisms seemed to affect AR.

**Key words:** Fc $\gamma$  receptors, Fc $\gamma$ RIIa, polymorphism, acute rejection, paediatric renal allograft.

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## Introduction

Acute rejection (AR) of the renal transplant recipient involves injury to interstitial and vascular endothelial cells within the organ and is mediated by macrophages, antibodies, and T lymphocytes. The majority of cases occur in the first few months, and the frequency reduces with time, although episodes can occur at any time after transplantation. The cell-mediated immune response is the result of antigen recognition and activation together with proliferation of CD4+ and CD8+ cells, and is mainly responsible for the occurrence of cellular rejection [1].

In the kidney graft, cellular rejection generally refers to 'borderline' changes or 'Grade I' acute rejection according to Banff criteria. This grade is characterised by a large influx of T cells into the interstitial space, causing inflammation and oedema, and infiltration of T-cells in tubular epithelium and in the lumen, resulting in what is known as tubulitis with degeneration of tubular epithelial cells. More severe forms of acute rejection are represented by Banff grades II and III and are determined by increasing degrees of vascular involvement. The arterial walls become

inflamed (intimal arteritis), so the vessel lumen becomes blocked due to thrombus formation, finally resulting in necrosis of the transplanted organ. This is often known as 'vascular' rejection and is mainly mediated by infiltrating macrophages and B-cell-derived antibody deposition (humoral immune response) [2].

The occurrence and the magnitude of severity of antibody-mediated graft pathology in both acute and chronic settings is variable, and it is likely that genetic polymorphisms, which affect the magnitude of the B-cell-derived antibody response and the effector functions of antibody in the transplant recipient, might lead to such pathologic variation.

Immunoglobulins (Ig) can interact with the effector mechanisms of the immune system by direct binding to effector cells via receptors for the Fc region of the immunoglobulin heavy chain or by activation of the complement cascade. Fc gamma receptors (Fc $\gamma$ R) combine the Fc portion of IgG antibodies and are expressed and represented by more immune cells, including natural killer (NK) cells, dendritic cells (DCs), macrophages, and neutrophils [3]. Families of Fc receptors are found in each of the immunoglobulin isotypes [4]. Immunoglobulin G binding to activat-

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ing Fc $\gamma$ R receptors (Fc $\gamma$ RIIa [CD32a], Fc $\gamma$ RIIIa [CD16a], and Fc $\gamma$ RIIIb [CD16b]) results in macrophage and neutrophil activation and immunogenic antigen presentation to T cells by DCs.

Fc $\gamma$ RIIa receptor is found in most immune-competent cells and demonstrates a genetically determined polymorphism [5]. This polymorphism results from a single base substitution of guanine to adenine at nucleotide 494 of the coding region in exon 4, which leads to a change in an amino acid from arginine to histidine at position 131. The H131 allele (494A) codes for histidine at position 131 and has a high affinity for human IgG2 and a low affinity for murine IgG1, whilst the R131 allele (494G) has arginine at position 131 and has little affinity for human IgG2 but has a high affinity for murine IgG1 [6, 7]. Genetic polymorphism of Fc $\gamma$ RIIa was also associated with release of cytokines (INF- $\gamma$ , IL-2, TNF- $\alpha$ ). A high degree of release of cytokines correlated with the presence of HH131 genotype [8, 9].

Many clinical research projects have suggested that this polymorphism may have an influence on susceptibility to diseases, mainly where IgG2 is the predominant antibody subclass produced. Fc $\gamma$ RIIa polymorphism may also be involved in the susceptibility to heparin-induced thrombocytopenia, lupus erythematosus (SLE), and bacterial diseases [10-12]. In a study done by Pawlik *et al.*, they have shown the prolonged graft survival in kidney graft recipients with genotype RR131 [13].

The aim of the present study was to evaluate the distribution of Fc $\gamma$ RIIa polymorphism in paediatric renal transplant recipients as well as healthy control children, and to study the association between the Fc $\gamma$ RIIa polymorphism and acute rejection of kidney allografts.

## Material and methods

Histories of 70 paediatric renal transplant recipients (43 males, 27 females) were revised with attention to the onset of acute graft rejection. All patients had received their first transplantation. All recipients had ABO-compatible renal transplants and received an allograft at the Centre of Paediatric Nephrology and Transplantation (CPNT), Children's Hospital, Cairo University, Egypt. Serum creatinine levels were in the range of normal values and there was an absence of hypertension and proteinuria. Subjects were not routinely screened for the development of the novel HLA antibodies post-transplant. Anatomical problems were excluded by ultrasound and nuclear scans. The most common aetiologies of end-stage renal disease (ESRD) were unknown ( $n = 12$ ), posterior urethral valve (PUV) ( $n = 12$ ), PUV with reflux nephropathy ( $n = 7$ ), nephronophthisis ( $n = 7$ ), and chronic pyelonephritis (45.71% in total).

Sixty healthy, age-matched, unrelated population controls (36 males, 24 females) were recruited from the Paediatric Clinic of the National Research Centre (NRC).

Creatinine was measured at least monthly post-transplant. Renal biopsies were only performed if there were clinical indications with suspicion of allograft dysfunction. The episodes of AR were detected in 25 cases. Among all the cases of AR, vascular rejection was seen in only one patient (4%) and cellular rejection in the remaining 24 (96%). Chronic allograft nephropathy (CAN) was detected in four (5.71%) patients. The study was approved by the local Ethics Committee of the NRC, and informed consent was obtained from all subjects.

Age; sex; transplant year; cold ischaemia time; presence of HLA-A, HLA-B, and HLA-DR mismatches; disease leading to renal failure; means of initial immunosuppression; serum creatinine level; number of rejection episodes; and details about allograft loss and transplantation outcome were recorded.

AR, which is cellular rejection due to T-cell activation encountered in the first post-transplant week, was defined and graded according to the Banff Criteria [14, 15]. It was defined as either borderline/suspicious or acute rejection, in patients with stable serum creatinine values at the time of biopsy [16].

## Immunosuppressive (IS) regimens

All children received intravenous methylprednisolone (5-10 mg/kg, 150-250 mg/m<sup>2</sup> up to 250 mg/dose) on the night before the operation, all the time of induction of anaesthesia, all the time of decamping, 6 h post-operation, and once on the day following the operation (20 mg/m<sup>2</sup> per day) on the first month of transplantation, and then oral prednisolone was tapered down to 2.5-7.5 mg/day during the first year of transplantation. Immunosuppressive treatment protocol included FK regimen ( $n = 43$ ) (prednisolone + FK506 + MMF), cyclosporine (CsA) regimen ( $n = 27$ ) (prednisolone + CsA + MMF) and FK/tori regimen ( $n = 3$ ) (prednisolone + CsA + sirolimus/everolimus). The initial CsA dose was 10 mg/kg per day by oral route (100-400 mg/day), and target trough levels ranged from 66 to 154 ng/ml in case-based immunosuppression. The initial FK506 dose was 0.16 mg/kg per day by oral route (1.5-6 mg/day), and target trough levels were 3-14 ng/ml in the first three months and 4.5 ng/ml in the FK506/everolimus group. The initial dose of MMF was 1200 mg/m<sup>2</sup> (800-1800 mg/m<sup>2</sup>) in 2-3 doses, and the dose was modified based on adverse effects such as diarrhoea or leucopenia. IL-2 receptor-blocking antibody (anti-IL-2R Ab, basiliximab) (Simulect – Novartis Pharmaceuticals, Basel, Switzerland) was given to 15 patients (BSX group) (CsA or FK506 based immune suppression) on day 0 and three days after renal transplantation (up to 20-mg doses). Anti-thymocyte globulin (ATG) (Thymoglobulin, Genzyme Transplant, Cambridge, MA) was given to 43 patients (THYMO induction) (CsA or FK506 based immune suppression) from days 0 to 3 (1.5 mg/kg per day, each day).

The first dose was given intra-operatively to be completed prior to decamping. Everolimus was administered 2 mg per day and sirolimus was loaded 6 mg per day and then an adjusted dose of 2 mg/day was maintained to target a trough level of 5-15 ng/ml.

**Genomic DNA preparation and continuation**

DNA was isolated from 2 ml EDTA blood by using a DNA Blood extraction kit (THERMOFISCHER, GERMANY) according to the manufacturer’s instructions.

**FcγRIIIa genotyping**

A 25 UL PCR reactions were performed, containing 3 ml of genomic DNA (approx. 50 mg), 250 mm of each dNTP, 1U Taq polymerase and 2.5 all of 10 × PCR buffer containing 1.5 mm MgCl<sub>2</sub> (Bioron, Germany). We used 0.5 ohm H131-specific sense primer (5’-ATCCCAG-AAATTCTCCCA-3’) or 0.5 um R131-specific sense primer (5’ ATCCCAGAAATTCTCCCG-3’) and 0.5 um common antisense primer (5’- CAATTTTGCTGCTAT-GGGC-3’). The resulting fragment was 253 bp in length. A thermal cycler (BioRad) was used to perform a hot start PCR as follows: 5 min at 95°C, 10 cycles of 1 min at 95°C, 2 min at 57°C, and a final extension step of 1 min at 72°C. The PCR amplification products were separated on 1.5% agarose and visualised using ethidium bromide [13].

**Statistical analysis**

Statistical analyses were performed by SPSS 16.0 computer program and Pearson’s Chi Square test. Data were

summarised as mean ± SD, range, or percentage. Histograms and normality plots were used for evaluating the normality of the data. For those data with skewed distribution, log transformation was performed before a *t*-test. Power analysis was used to calculate the minimum sample size required to accept the outcome of a statistical test with a particular level of confidence. A sample size of 20 gave us approximately 80% power ( $\alpha = 0.05$ , two-tail) to reject the null hypothesis of zero correlation. We used power calculations performed by the Power and Precision program (Biostat) to determine the number of chromosomes required to detect a significant difference between the polymorphism frequency in the reference population and the expected frequency. Power commonly sits at 80%; however, at that level, a polymorphism would be missed 20% of the time. In qualitative data, inferential analyses for independent variables were done using Chi square test for differences between proportions and Fisher’s exact test for variables with small expected numbers.

The calculated power of our study was 86.1% based on difference in mutation proportion using the method mentioned before [17], and the minimum detectable difference (MDD) was 50.0%. Data were evaluated between the experimental groups by independent t-test. The Hardy-Weinberg equilibrium (HWE) assumption was assessed in case and control groups by comparing the observed numbers of different genotypes with those expected under HWE for the estimated allele frequency and comparing the Pearson goodness-of-fit statistic with a distribution with one degree of freedom. A *p* value < 0.05 was considered statistically significant.

**Table 1.** Cross-sectional analysis: baseline and clinical characteristics of kidney transplant recipients and healthy controls

	All kidney transplant recipients (n = 70)	Healthy controls (n = 60)	<i>p</i> -value
<b>General characteristics</b>			
Recipient gender (males/females)	43 (61.43%)/27 (38.57%)	36 (60%)/24 (40%)	0.55
Mean recipient age at transplant (years)	9.63 ±3.33	8.7 ±4.51	0.64
Donor organ source			
Deceased	0		
Living, related	54 (77.14%)		
Living, unrelated	16 (22.86%)		
Number of HLA mismatch	2.28 ±1.8		
Ischemia time (mean ±SD; min)	44.47 ±3.49		
<b>Clinical characteristics</b>			
AR (%)	25 (35.71%)		
Immunosuppression at the time of the study			
FK506/CsA (%)	43 (61.43%)/27 (38.57%)		
Sirolimus/everolimus	3 (4.29%)		
MMF	70 (100%)		
Prednisone	70 (100%)		

FK506 – tacrolimus; CsA – cyclosporine; AR – acute rejection  
*P* was significant if < 0.05

**Table 2.** Distribution of FcγRIIIa genotypes and alleles in transplant recipients and controls

Genotypes		Case (n = 70)	Controls (n = 60)	χ <sup>2</sup> value	^P value	OR (95% CI)
Types	Wild (HH)	5 (7.1%)	20 (33.3%)		Reference	
	Heterozygous (HR)	34 (48.6%)	29 (48.3%)	8.369	0.004*	4.690 (1.564-15.062)
	Homozygous (RR)	31 (44.3%)	11 (18.3%)	18.252	< 0.001*	11.273 (3.404-37.326)
Mutation	Wild (HH)	5 (7.1%)	20 (33.3%)		Reference	
	Mutant (HR + RR)	65 (92.9%)	40 (66.7%)	4.286	< 0.001*	6.500 (2.261-18.690)
RR vs. (HH + HR)	(HH + HR)	39 (55.7%)	49 (81.7%)		Reference	
	RR	31 (44.3%)	11 (18.3%)	9.950	0.002*	3.541 (1.581-7.930)
Alleles	Wild (H)	44 (31.4%)	69 (57.5%)		Reference	
	Mutant (R)	96 (68.6%)	51 (42.5%)	17.874	< 0.001*	2.952 (1.776-4.907)

^P-value of chi-square test

\*Significant

Values were presented as percentages.

FcγRIIIa – Fc gamma receptors

## Results

Baseline characteristics of patients are shown in Table 1. In KT recipients, the renal function was excellent (serum creatinine 0.80 ±0.24 mg/dl) at the time of the research.

FcγRIIIa genotypes were significantly different between transplantation paediatric patients and the control group. RR genotype was present in 44.3 and 18.3% of the transplantation and control groups, respectively ( $p = 0.001$ ). Frequencies of HR and HH genotypes were 48.6 and 7.1% in the transplantation group and 48.3 and 33.33%, respectively, in the control group ( $p = 0.004$ ) (Table 2). The risk of being an ESRD patient in heterozygous gene carriers is about four times higher than those who have wild genotype, and the risk is more than double in homozygous genotype. Hardy-Weinberg equilibrium equations are balanced (equal to 1) in each group. Furthermore, we analysed the data by pooling the HR + RR genotypes with HH genotype, and a highly significant difference was observed ( $p = 0.001$ ). This may suggest that patients with RR genotype are at high risk of developing renal disease (OR = 6.500, 95% CI = 2.261-18.690). Also, we analysed the data by pooling the HR + HH genotypes with RR genotype, and a highly significant difference was observed ( $p = 0.002$ ). This may confirm the importance of RR genotype in the risk of developing renal disease (OR = 3.541, 95% CI = 1.581-7.930).

The frequencies of FcγRIIIa genotypes were significantly different between the patients who had acute rejection and those who did not. Frequencies of RR, HR, and HH genotypes were 72.0, 28.0, and 0.0% in the rejection group while those in the group without rejection were 28.9, 60.00, and 11.1%, respectively. There was a risk of having an acute rejection only in homozygous genotype RR ( $p = 0.045$ ). Hardy-Weinberg equilibrium equations were

balanced (equal to 1) in each condition. Furthermore, we analysed the data by pooling the HR + RR genotypes with HH genotype, and no significant difference was observed ( $p = 0.152$ ), but when pooling the HR + HH genotypes with RR genotype, a significant difference was observed ( $p = 0.001$ ) (Table 3).

## Frequencies of FcγRIIIa alleles

The frequency of the R allele in transplant patients was significantly higher than that in the control group (68.6% vs. 42.5%,  $p = 0.001$ ) (Table 2). Comparison of the FcγRIIIa alleles among transplanted children with and without acute rejection showed a significant difference ( $p = 0.001$ ) (Table 3).

## Discussion

Renal transplantation is the preferred method of treatment for children with end-stage renal disease. Its success is related to tissue matching, recovery of age-adjusted care, and the appropriate immunosuppressive treatment. The survival rate obtained by renal transplantation is better than with dialysis in all age groups of paediatric patients [4].

AR is the most relevant cause of graft loss within one year post transplantation [18]. The frequency of AR was 30% when cadaver kidneys were transplanted, compared with 27% with organs from living related donors in the late 1990s. With the recognition of risk factors and the development of immunosuppressive therapy, these rates have been reduced to less than 10%-15% in most centres. In most clinical studies, AR is viewed as a risk factor for chronic rejection (CR) [19, 20]. As the frequency and severity of AR increase, CR and graft loss also increase. Some studies have even reported that CR will not appear without prior AR [18].

**Table 3.** Distribution of FcγRIIIa genotype alleles in transplant recipients with and without rejection

Genotypes		Rejection (n = 25)	Not (n = 45)	χ <sup>2</sup> value	p value	OR (95% CI)
Types	Wild (HH)	0 (0.0%)	5 (11.1%)		Reference	
	Heterozygous (HR)	7 (28.0%)	27 (60.0%)		#0.563#	–
	Homozygous (RR)	18 (72.0%)	13 (28.9%)		0.045**	–
Mutation	Wild (HH)	0 (0.0%)	5 (11.1%)		Reference	
	Mutant (HR + RR)	25 (100.0%)	40 (88.9%)		0.152#	–
RR vs. (HH + HR)	(HH + HR)	7 (28.0%)	32 (71.1%)		Reference	
	RR	18 (72.0%)	13 (28.9%)	12.106	^ 0.001*	6.330 (2.138-18.737)
Alleles	Wild (H)	7 (14.0%)	37 (41.1%)		Reference	
	Mutant (R)	43 (86.0%)	53 (58.9%)	10.963	^ < 0.001*	4.288 (1.739-10.574)

#P-value of Fisher's Exact test

^P-value of chi-square test

\*Significant values were presented as percentages

FcγRIIIa – Fc gamma receptors

It has been proposed that, even in the presence of adequate immunosuppression, rejection continues sub-clinically, resulting in CR [21, 22]. Recipients who exhibit vascular rejection in the immediate post-transplantation period demonstrate early parenchymal injury and consequently CR [23, 24]. Laboratory evidence of an alloimmune reaction, as detected by a proliferative response to allopeptides or increased circulating anti-donor antibodies, is found in cases with CAN [25, 26].

In the study reported herein, AR was observed in 25 children. Among all the cases of AR, vascular rejection was seen in only one patient and cellular rejection in the remaining 24. CAN was detected in four patients. We examined the association between the FcγRIIIa polymorphism and acute kidney allograft rejection. It has been reported that there is a correlation between the presence of FcγR blockers in recipient serum and AR. As a result, the prediction of graft survival among transplant recipients is possible using molecular biology [26]. Among these FcγR blockers, FcγRII, the most common form, is expressed on cells, both in soluble form and as a transmembrane. It is expressed on monocytes, macrophages, and thrombocytes. FcγRII is the only FcγR that has an efficient relation to IgG2. Although FcγRII<sub>g</sub>-131R binds IgG2 weakly, FcγRIIa-131H is the only human FcγR that binds IgG2 effectively [27, 28].

The present study showed that FcγRIIIa RR genotype and allele frequency showed significant difference between renal transplant recipients and healthy controls. Furthermore, we analysed the data by pooling the HR + RR genotypes with HH genotype, and a highly significant difference was observed. Fc receptors, the genes of which are located in clusters across mammalian genomes, functionally link the cellular and humoral branches of the immune system and play an important role in the activation and modulation of the immune response [29]. FcγR poly-

morphisms are now considered to be heritable risk factors for infectious and many autoimmune diseases, and support for a key role of these polymorphisms has been obtained in previous studies [30, 31]. Disease susceptibility linked to FcγR polymorphisms has been reported for autoimmune diseases including SLE, rheumatoid arthritis (RA), multiple sclerosis, and anti-neutrophil cytoplasmic auto-antibody-positive systemic vasculitis [32]. Griffiths *et al.* investigated FcγRIIIa polymorphism in RA. They reported that the incidence of illness was greater among patients with the R/R and R/H genotypes. The effect of FcγRIIIa on the expression of RA is thought to be related to the immune functions of this receptor. FcγR plays a relevant role in a spectrum of immune responses, such as endocytosis, ADCC, phagocytosis, variations in antigen presentation, and release of inflammatory mediators. FcγRIIIa R/R has low affinity, and causes less phagocytosis of IgG2-opsonised particles, than FcγRIIIa H/H. Therefore, Griffiths *et al.* suggested that the excretion of immune complexes (IC) may decrease in homozygote individuals for the R allele; this immune complex may constitute an important factor that contributes to inflammation in RA [33]. In some research studies, it has been reported that FcγRIIIa-H131R polymorphism was related more to clinical symptoms than to the development of SLE. In the literature, this allele has been reported to accompany severe organ injury in patients with SLE [34]. Most studies have reported that the FcγRIIIa-H131R allele shows a low affinity for IgG2 and is related to lupus nephritis [27, 35]. It is likely that the polymorphism of this gene plays a certain role in the aetiology of renal failure, leading to the need for transplantation. Importantly, some studies have reported that antigen presentation is much more efficient if the IC is internalised by FcγR rather than by nonspecific uptake mechanisms such as fluid phase pinocytosis [36].

Pawlik *et al.* investigated the role of FcγRIIa polymorphism in renal allografts, reporting that graft survival time was longer among renal transplant recipients who show the RR allotype. In this study, cytokine release was higher in individuals with the HH131 allotype or the RR131 allotype. Therefore, it has been reported that patients with low-affinity FcγR show a decreased immune response, consequently with longer graft survival, and in patients with RR131 genotype the probability of graft survival over seven years was almost two-fold greater as compared with the HH131 genotype [13].

The relevance to transplantation of Fcγ-receptor-blocking antibodies was first raised in the early 1970s in studies of passive enhancement of rodent renal allografts [37]. Evidence for an association between Fcγ receptors and class II antigens was allied to evidence associating anticlass II antibody activity with passive enhancement, although neither of these proposed associations was undisputed [38]. Early findings were not encouraging. Studies by one group on pre- and post-transplant sera found that Fcγ inhibitory activity was associated with graft loss, while others found no significant differences in allograft outcome between recipients with or without pre-transplant serum Fcγ-receptor-blocking activity against B-enriched donor lymphocytes.

In the present study, a significant difference was found among FcγRIIa genotype frequency and allele frequency between rejecters and non-rejecters. There was only a risk of having an acute rejection in homozygous genotype. Also, when pooling the HR + HH genotypes with RR genotype, a significant difference was observed. Acute rejection can be summarised as an inflammatory process leading to intra-graft infiltrates that are comprised of a variety of cell types. Through a cascade of interrelated events that involve cytokines, chemokines, their receptors, adhesion molecules, and many others, these cells act together to specifically injure the allograft. Other studies with more patients may demonstrate the relationship of other FcγRs to rejection, yielding predictive knowledge about graft survival times. Pawlik *et al.* [39] revealed that there is no correlation between FcγRIIa polymorphism and acute rejection of renal transplant recipients.

Limitations of this study include moderate sample size, but it can be suitable as we searched in a paediatric population. Furthermore, the results represent a single-centre experience of a racially homogeneous cohort and may not be generalisable to other populations.

## Conclusions

In paediatric renal transplant recipients, FcγRIIa genotypes and alleles were significantly different as regards to the control group. Our present study showed that FcγRIIa polymorphisms were related to the incidence of ESRD, and they affected the renal-allograft function. If other studies are conducted with more patients to demonstrate the relationship of other FcγRs to rejection, the resultant predictive

knowledge about the value of genotypes may lead to improved outcomes following renal transplantation.

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*The authors declare no conflict of interest.*

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