Original Article

Association of IRGM (rs1000113 C/T) Genetic Polymorphism with the Incidence of Acute Rejection in Iranian Liver Transplanted Patients

Malekpour Z, Kafilzadeh F*

Department of Biology, Jahrom Branch, Islamic Azad University, Jahrom, Iran

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Abstract

Background & Objective: Autophagy has been shown to be involved in organ transplantation. IRGM (human immunity-related GTPase) has a crucial role in autophagy complex activation and ROS and microorganism elimination during graft rejection. We examined the association between rs1000113 C/T genetic polymorphism of IRGM and the risk of liver rejection in liver transplanted patients.

Materials & Methods: The present study included 100 healthy people and 100 patients with liver disease that led to liver transplantation. Fifty patients were diagnosed with histologically proven acute liver rejection and the other 50 without any rejection. Both groups were matched for sex and age. To determine variants of rs1000113 C/T genetic polymorphism of IRGM, polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used.

Results: A significant association was observed between liver rejection and rs1000113 C/T genetic polymorphism of IRGM (TC: p-value=0.0098, OR=2.93 CI=1.2-7.22) and (CC: p-value=0.0098, OR=0.34 CI=0.138 -0.83). Also, a significant association was observed between this polymorphism and allelic frequency in liver rejection patients. (T: p-value=0.027, OR=2.14 CI=1.027-4.57) and (C: p-value= 0.027, OR=0.46 CI=0.218 -0.97). No significant difference was found in rs1000113 C/T genetic polymorphism of IRGM, sex, blood group, and underlying disease among the healthy groups and liver transplanted patients.

Conclusions: The data suggest that the rs1000113 C/T genetic polymorphism of IRGM, an autophagy-related polymorphic locus, influences liver rejection in liver transplanted patients, with the possible involvement of autophagy in transplantation. Recipients with TC genotype for IRGM are more likely to develop liver rejection compared to those with CC genotype.

Keywords: IRGM, Liver transplantation, Autophagy, Acute rejection

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Introduction

Liver transplantation is one the best and most effective remedies for a patient with end-stage liver disorders. Despite using an immunosuppressive agent and advanced methods, rejection is one of the major difficulties the patient often faces after liver transplantation. Although survival of patient is enhanced to 80% in one year, the prevalence of liver rejection is still 40%–80% (1, 2). Liver rejection is a complicated process where immune cells and reactive oxygen species (ROS) play the leading role. Immunosuppressive agents, such as cyclosporine can suppress calcineurin activity. Hence, T cells cannot be activated and rejection does not occur (3).

Noticeably, autophagy plays a crucial role in both innate and adaptive immune responses, including the elimination of intracellular

***Corresponding Author: Kafilzadeh Farshid,** Department of Biology, Jahrom Branch, Islamic Azad University, Jahrom, Iran.
Email: f.kafilzadeh@gmail.com
https://orcid.org/0000-0003-2506-7140

pathogen infections (4), presentation of exogenous and endogenous Ags by MHC class II molecules(5), ssRNA recognition of viruses IFN-a production by dendritic cells (6) and homeostasis of the organelle in lymphocytes (7).

Autophagy can be observed in all thymocyte subsets and naive T lymphocyte (8). Also, stimulation of TCR can induce extreme autophagy, which leads to T cell proliferation survival (9).

Autophagy plays a vital part in normal liver physiology and pathogenesis of liver disorders such as fibrosis, nonalcoholic and alcoholic fatty liver, protein conformational liver diseases, viral hepatitis, drug induced liver injury, aging, liver cancer, alpha-1-antitrypsin deficiency (ATD), and liver ischemia-reperfusion injury (I-R) (10-12).

Liver IR occurs during liver transplantation and hemorrhagic shock, leading to liver dysfunction and enhancement of morbidity and mortality after liver transplantation (13).

Whether autophagy can protect from or promote liver injury following warm and/or cold I-R remains to be further elucidated. R. Curcio et al. concluded that the enhancement of autophagy in the liver during warm and/or cold I-R may increase the graft survival via a delay of necrosis and apoptosis, hence increasing the possibility for novel therapeutic intervention to diminish the extent of warm/cold liver I-R injury. Autophagy-deficient cells show strong IR injury due to aggregation of apoptotic proteins and ROS (10).

The best example to understand the links between autophagy and human disorders is the genetic polymorphisms in ATG16L1 and IRGM that enhance the risk of Crohn's disease, an intestinal inflammatory disorder (14). The polymorphisms of IRGM have been linked to autophagy and directly influence antimicrobial immune response (15). In line with its autophagy-mediated antimicrobial function, IRGM is additionally a genetic risk factor for tuberculosis in various human populations (16) and may play a protective role in leprosy (17).

IRGM regulates autophagy via interaction with ULK1 and Beclin 1 and enhances their co-assembly, thus controlling the formation of initial complexes of autophagy. Moreover, IRGM interacts with NOD2 which is one of the pattern recognition receptors. All IRGM, NOD2, and ATG16L1 are Crohn's disease risk factors which form a complex to govern autophagic responses (18). NOD2 promotes K63-linked poly-ubiquitination of IRGM, which is needed for the activation and interaction of IRGM with the core autophagy factors and for microbial elimination. Hence, IRGM has a direct role in organizing the autophagy complex to endow it with antimicrobial, anti ROS, and anti-inflammatory functions (19).

Although the effects of autophagy on liver disorders and transplantation as well as the role of IRGM in autophagy have been well studied, the association of IRGM polymorphism underlying liver transplantation and liver rejection is still a matter of question and to the best of our knowledge, the possible effects of rs1000113 C/T genetic polymorphism of IRGM on rejection in liver transplanted patients have not yet been explored.

In this study, it is demonstrated for the first time that rs1000113 C/T genetic polymorphism is associated with graft rejection in liver transplanted patients.

Materials & Methods

Study Groups

In the current study, 100 healthy persons and 100 recipients of liver transplants between 2011 and 2016 were investigated. All of the patients were Iranian and transplanted at the Transplantation Center of Namazi Hospital, affiliated with Shiraz University of Medical Sciences, Shiraz, southern Iran. The study protocol was approved by Ethics Committees of Shiraz University and Shiraz University of Medical Sciences.

In the recipients, the graft outcome and rejection episode(s) for at least six months were investigated. Rejection episodes were determined by an expert team based on the accepted criteria such as enhanced serum liver enzymes levels and total serum bilirubin level in the absence of biliary problems, histological findings after biopsy of the liver and clinical and biochemical response to high doses of steroids, according to criteria for liver rejection described by Banff schema (20). The patients' immunosuppression regimen was tacrolimus or cyclosporine with mycophenolate mofetil and steroids. The dose of drug was adjusted to maintain a target therapeutic blood level of 200 ng/mL for CsA (5 mg/kg/day) or 2–3 mg twice a day for tacrolimus. Methylprednisolone was added to their immunosuppressive regimen for the patients with signs of rejection. The patients were classified into two groups according to

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presence or absence of acute rejection. Donors were selected on the basis of ABO blood group compatibility. HLA matching is not routinely checked for liver transplantation in our center.

DNA Extraction

The buffy coat of the whole blood from liver transplanted patients had already been isolated and was available in the sample bank of Transplant Research Center. DNA of Patients was extracted from their buffy coat using the DNP kit (CinnaGen, Iran) according to the manufacturer's instructions.

Genotyping analysis

The SNP of the study gene (IRGM) was evaluated by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) methods using a thermal cycler (Techne, Genius, UK) as previously described (21,22).

PCR mixture included MgCl2 (0.75 mM), PCR buffer (10 mM, pH of 8.3), dNTP (0.2 mM), each primer (4 µM), Taq DNA polymerase (1 U) (all from CinnaGen, Iran) and DNA samples. The PCR program consisted of an initial pretreatment at 95 °C for 5 min, with 35 cycles followed by denaturation at 95 °C for 1 min, annealing at 65 °C for 40 sec and extension at 72 °C for 1 min. Then, 2.5 µL buffer and 1 U RsaI enzyme were added to each PCR product tube and incubated at 37 °C for 3 hours. The PCR products were analyzed by electrophoresis in 3% agarose gel stained with safe stain and finally detected by a UV transilluminator.(Primers, fragment sizes and restriction enzymes are summarized in Table 1).

Table1. The primer, fragment size and restriction enzymes for the IRGM

Locus	Primer	Fragment sizes (bp)	Restriction enzymes
IRGM (rs1000113 C/t)	Forward primer : - CGATAATCTTTGAGTTTCAGTTCT Reverse primer CCCAGTCTGTCCATCTTG	280	RsaI

Statistical Analyses

All the statistical analyses were performed using the SPSS® for Windows® version 16.0 (SPSS Inc., Chicago, IL, USA) and Epi Info (CDC, Atlanta, USA) software.

The frequencies of the alleles/genotypes were compared in the patients with or without transplant liver and controls by $\chi 2$ test or Fisher's exact test. A $\chi 2$ test was used for IRGM polymorphism to determine whether the distribution followed the Hardy-Weinberg equilibrium. Regardless of rejection, the investigated gene was in Hardy-Weinberg equilibrium ($P>0.05$).

Besides, the relationship between genetic polymorphism and the incidence of acute liver rejection were estimated by odds ratio (OD) with assuming 95% confidence interval (CI).

Results & Discussion

The study groups were composed of liver rejection including 50 persons, 32 males and 18 females, and non-rejection groups including 50 persons, 37 males and 13 females, with the mean age of 33.96±18.99 and 33.96±18.99 years respectively. Also, 100 healthy subjects were included as a control group (mean±SD age of 36.3 ± 3.7 years). The T allele frequency was 29% in rejection group, 16% in no- rejection group and 75% in healthy one.

Among the patients, 14% were with cryptogenic, 22 % with HBV, 9% with HBV+HCV, 10% with autoimmune hepatitis, 13% with PSC+PBC, 9% with primary pediatric liver disease, 7% with genetic disorders and 15% with other diseases (Table2).

The amplified fragment length for this polymorphism is 280 bp. When this fragment is affected by the Rsa restriction enzyme, For CC, wild genotype, a fragment of 280 bp, for TC, hetrozygote case, three fragments of 280 bp, 150 bp and 135 bp and for TT, homozygote, two fragments with 150 bp and 135 bp were seen (Figure 1).

The results revealed no significant differences between sex, underlying disease and blood type in patients with liver transplantation (with or without transplant rejection).

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Table2. Underlying disease of liver transplanted patients

underlying diseases	N	TT	TC	CC
HBV	24	0	10	12
HBV+HCV	9	0	3	6
HCV	2	0	2	0
Wilson	3	0	2	1
Autoimmune Hepatitis	10	0	6	4
Budd-Chiari	2	0	1	1
PSC+PBC	13	0	5	8
Primary pediatric Liver disease	9	0	4	5
Genetic Disorder	7	0	3	4
NASH	2	0	0	2
HCC	2	0	1	1
Metastatic tumor	3	0	1	2
Cryptogenic	14	0	7	7
Fulminant Hepatitis	2	0	1	1
Total	100	0	46	54

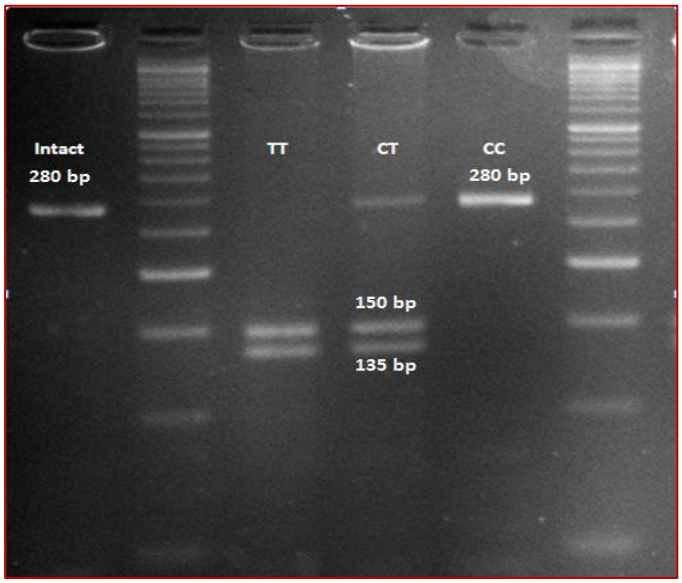

Figure1. Genotyping IRGM (rs1000113 C/T) polymorphism by RsaI via RFLP method
From right to left the lanes are the DNA size marker (50-bp ladder), CC genotype (280-bp), CT genotype (280-bp, 150-bp, and 135-bp), TT genotype (135-bp and 150-bp), the DNA size marker (50-bp ladder) and intact (280-bp), respectively

There was a significant relationship between IRGM (rs1000113 C/t) polymorphism and liver rejection; Increases in T allele enhanced the likelihood of liver rejection (T: p-value=0.027, OR=2.14 CI=1.027 - 4.57) while increases in C allele decreased the risk of rejection (C: p-value = 0.027, OR=0.46 CI=0.218 -0.97). Also a significant association between IRGM genotypes and liver rejection (TC: p-value=0.0098, OR=2.93 CI=1.2 -7.22) and (CC: p-value=0.0098, OR=0.34 CI=0.138 -0.83) were observed (Table 3 and Chart1).

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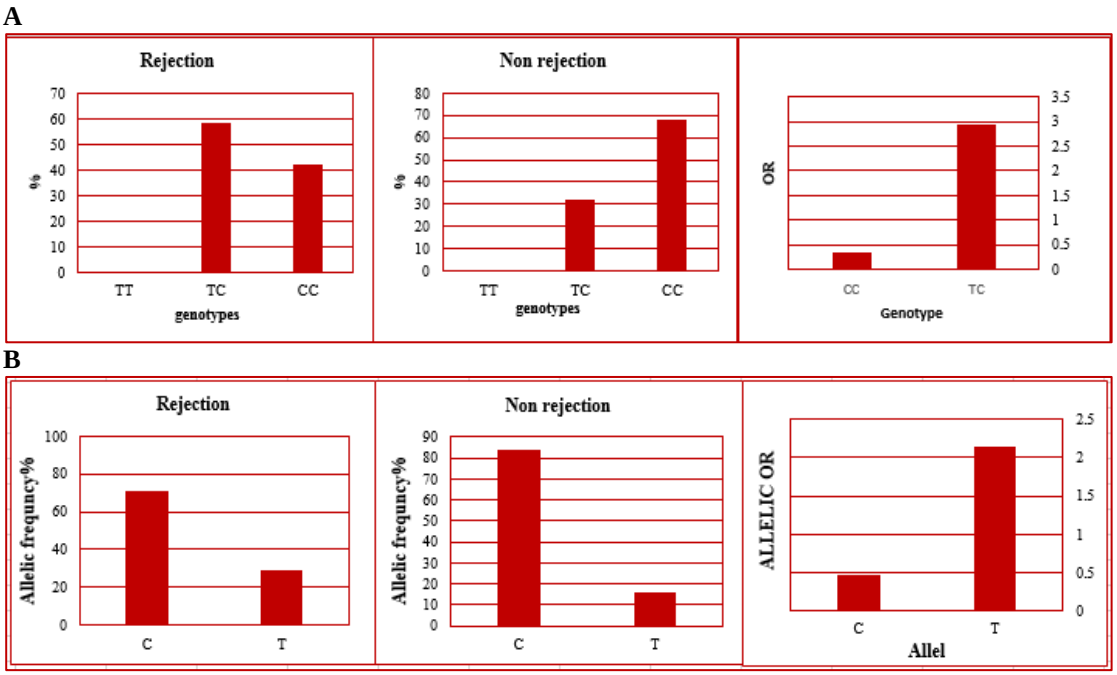

Chart 1. Association of (A) genotypic and (B) allelic frequency of IRGM (rs1000113 C/T) polymorphism and liver rejection

Table 3. Association of IRGM (rs1000113 C/T) polymorphism and liver rejection

Genotype frequency	N (N%) NR	N (N%) R	P-value	OR	95%CI
TT	0	0		undefined	
TC	16 (32)	29 (58)	0.0098	2.93	1.2-7.22
CC	34 (68)	21 (42)	0.0098	0.34	0.138-0.83
Allelic frequency					
T	16 (16)	29 (29)	0.027	2.14	1.027-4.57
C	84 (84)	71 (71)	0.027	0.46	0.218-0.97

NR: no rejection, R: rejection

We observed that with an increase in T allele, the rejection was enhanced so that the patients with TC genotype are 2.9 times more likely to have liver rejection than those with CC genotype. C allele can decrease the possibility of liver rejection and it seems to play a protective role in liver transplanted patients.

When we compared the healthy group and liver transplanted patients in terms of IRGM (rs1000113 C/T) polymorphism, we did not observe any association between genotypes of IRGM (rs1000113 C/T) polymorphism and incidence of liver disease leading to transplantation (TC: p-value = 0.328, OR=0.75 CI=0.4 -1.38) and (CC: p-value=0.832, OR=1.06 CI=0.5 -1.9). Moreover, we did not observe any significant results in allelic frequency (T: p-value=0.65, OR=1.11 CI=1.83 - 0.77 and CC: p-value=0.65, OR=0.89 CI=1.47 -0.5) (Table 4).

Several studies have shown the association of IRGM polymorphisms with various diseases. Genetic polymorphisms in ATG16L1 and IRGM enhance the risk of Crohn's disease, an intestinal inflammatory disorder (14). Also, the importance

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Table 4. association of IRGM (rs1000113 C/T) polymorphism and risk of liver disorders that leading to liver transplantation

Genotype frequency	N (N%) Healthy	N (N%) LT	P-value	OR	95%CI
TT	5 (5.4)	0		undefined	
TC	35 (38)	45 (45)	0.328	0.75	0.4-1.38
CC	52 (56.5)	55 (55)	0.832	1.06	0.5-1.9
Allelic frequency					
T	45 (25)	45 (22)	0.65	1.11	0.67-1.38
C	139 (75)	155 (78)	0.65	0.89	0.5-1.47

LT: Liver transplanted

of autophagy in organ transplantation was investigated in several studies (23). The golden rule of IRGM in autophagy was previously proved (19,24). To the best of our knowledge, the association of IRGM (rs1000113) and liver transplantation has not been studied before.

In the current study, we showed that TC heterozygosis at the IRGM (rs1000113) SNP locus, an autophagy-related genetic polymorphism, was associated with a significantly higher rejection rate in a liver-transplanted patient in Iranian population.

Our data showed that the polymorphism IRGM (rs1000113) cannot affect the autophagy and liver physiology in healthy people. Therefore, IRGM (rs1000113) seems to have no role in the incidence of liver disease that leads to transplantation. It could be possible that other processes support this autophagy inefficiency in healthy people.

Autophagy has been reported in a number of cases of liver diseases and transplantation, playing a major role in liver function or dysfunction (25). IR in the liver is due to oxygen deficiency caused by vascular occlusion during liver resection, hemorrhagic shock or liver transplantation (26) leading to adenosine triphosphate depletion and in ROS production and finally resulting in cell death and graft rejection. It seems that increases in autophagy can enhance ROS elimination and apoptosis and necrosis inhibition due to IR.

Liver fibrosis is formed in response to chronic liver injury. Its end-stage cirrhosis leads to high rates of morbidity and mortality in patients. Investigations showed that autophagy can restrict the liver fibrosis development via its anti-inflammatory effects in macrophages and protective effects on hepatocytes (12).

ATD is a genetic cause of liver disorders which is created by aggregation of mutant alpha-1-antitrypsin Z (ATZ) within hepatocytes. ATZ accumulation causes activation of autophagy. Inefficient autophagy cannot eliminate ATZ from liver cells while efficient autophagy could be a new strategy for liver diseases resulting from ATD and genetic liver diseases, such as inherited hypofibrinogenemia, caused by the proteotoxic effects of misfolded protein (27).

Furthermore, autophagy has a crucial role in nonalcoholic and alcoholic fatty liver, protein conformational liver diseases, viral hepatitis, drug-induced liver injury and aging (10,11).

IRGM was originally described as a molecule with an important function in autophagy by forming an initial complex of autophagy. We believe the present work could have major implications for the broader field of liver transplantation. Brest et al. showed the possible role of IRGM polymorphism in Crohn's disease development, an inflammatory bowel disease.

The variants of IRGM (+313) locus play a crucial role in infections of intestinal epithelia of individuals with Crohn's disease. Investigations

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showed IRGM is controlled by a family of microRNAs that are overexpressed under inflammatory conditions. MicroRNAs form a complex with IRGM mRNA to regulate IRGM production (15). In line with our data, in 2014, Kimura et al. demonstrated that TT genotype of IRGM (+313) is associated with high mortality in sepsis patients while the mRNA expression of IRGM in TT patients was lower than other patients (28).

IRGM polymorphism has also been showed to have a role in mitochondrial dysfunction as it enters the inner membrane of mitochondria and regulates mitochondrial-nuclear fission that results in membrane depolarization and cell death (24). The role of IRGM in cell death due to mitochondrial depolarization was proved by Carre et al. They reported that the activation of mitochondrial biogenesis in septic patients leads to a favorable outcome (29).

In line with our data about the role of autophagy in liver, Watanabe et al. demonstrated that liver cells of septic showed reproducible mitochondrial injury patterns and enhanced autophagic vacuolization (30). Furthermore, an investigation showed the mitochondrial injury and formation of autophagosome in renal proximal tubules of septic patients (31) .

Autophagy and organ failure have recently been investigated in the surgical fields. Insufficient autophagy causes the accumulation of different unsuitable factors, ROS, and injuries at cells, which, in turn, lead to organ dysfunction. These undesirable factors would ultimately affect each other (32).

Because of the role of autophagy in IR and liver dysfunction, we hypothesized that the 'physiologic' autophagy flux is disturbed in liver transplantation and this impaired autophagy causes liver rejection through IR enhancement and ROS accumulation. It was previously reported that T allele from IRGM (rs1000113) polymorphism is a mutant and risk allele that influences the IRGM activity (33).

Less functionality in IRGM SNP, i.e., TC heterozygotes of IRGM (rs1000113), might cause the undesirable effects on the pathophysiology of transplanted liver in patients. It seems that with an increase in T allele, the functionality of IRGM decreases and autophagy reduces too. Reduction in autophagy in the liver could cause the aggregation of ROS, IR and undesirable factors in the liver, resulting in rejection.

The results of the study could be further confirmed with a larger population and patient groups with the same underlying disease.

Conclusions

IRGM has a major role in autophagy via interaction with ULK1 and Beclin 1 and enhances their co-assembly, thus controlling the formation of initial complexes of autophagy. Our data showed that IRGM (rs1000113) polymorphism can affect autophagy in liver-transplanted patients and cause liver rejection to increase in a patient with TC genotype. We observed the risk of rejection enhanced with an increase in T allele while C allele plays a protective role in liver rejection.

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Conflict of Interests

The authors declare no conflicts of interest.

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مقاله پژوهشی

ارتباط پلی‌مورفیسم ژن IRGM (rs1000113 C/T) با رد حاد در بیماران پیوند کبد در ایران

زهرا ملک پور، فرشید کفیل زاده*

گروه زیست شناسی، واحد جهرم، دانشگاه آزاد اسلامی، جهرم، ایران

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چکیده

زمینه و هدف: مسیر اتوفاژی با بیماری‌های التهابی و پیوند اعضا مرتبط می‌باشد. ژن IRGM نقشی اساسی در فعال کردن کمپلکس اصلی اتوفاژی، حذف رادیکال‌های آزاد اکسیژن (ROS) و میکروارگانیسم‌ها در طی رد پیوند اعضا ایفا می‌کند. با توجه به نقش مهم اتوفاژی در پیوند اعضا و همچنین نقش حیاتی ژن IRGM در اتوفاژی، این مطالعه به بررسی ارتباط پلی مورفیسم rs1000113 C/T در ژن IRGM و احتمال خطر رد پیوند کبد در بیماران پیوندی می‌پردازد.

مواد و روش ها: در این مطالعه ۱۰۰ نفر از افراد سالم با۱۰۰ نفر از بیماران گیرنده پیوند کبد که از نظر جنسیت و گروه خونی یکسان بودند مورد بررسی قرار گرفتند. گروه بیماران شامل ، ۵۰ بیمار پیوندی بدون رد حاد که به عنوان گروه شاهد و ۵۰ بیمار همراه با رد پیوند کبد بودند. پلی مورفیسم rs1000113 ژن IRGM توسط تکنیک PCR-RFLP تعیین گردید.

نتایج: نتایج به دست آمده ارتباط معنی داری را بین ژنوتیپ TC و خطر افزایش رد پیوند کبد در بیماران را نشان می‌دهد (TC:p-۰/۰۰۹۸, value=۷/۲۲- ,CI =۱/۲ ,OR =۲/۹۳) و (CC:p-value=۰/۰۰۹۸, ۰/۸۳- ,CI =۰/۱۳۸ ,OR =۰/۳۴). هم چنین آنالیزهای آماری نشان می‌دهد ارتباط ارتباط معنی دار بین فرکانس آللی در این پلی مورفیسم و احتمال خطر رد پیوند کبد وجود دارد به طوری که با افزایش آلل T احتمال رد پیوند کبد افزایش می‌یابد(C:p-value=۰/۰۲۷ , ۰/۹۷- ,CI =۰/۲۱۸ ,OR =۰/۴۶) با بررسی‌های آماری بین افراد سالم و پیوندی، هیچ گونه ارتباط معنی داری بین این پلی مورفیسم و گروه خونی، جنسیت و بیماری‌های زمینه‌ای مشاهده نگردید.

نتیجه گیری: نتایج به دست آمده از این مطالعه نشان می‌دهد که پلی مورفیسم rs1000113 ژن IRGM می‌تواند حفظ بافت کبد بعد از پیوند را در بیماران پیوندی تحت تاثیر قرار دهد که این موضوع تایید کننده‌ی نقش اتوفاژی در پیوند اعضا می‌باشد. بیمارانی با ژنوتیپ TC نسبت به بیمارانی با ژنوتیپ CC بیشتر در معرض خطر رد پیوند کبد می‌باشند.

کلمات کلیدی: IRGM، پیوند کبد، اتوفاژی، رد حاد

***نویسنده مسئول: فرشید کفیل زاده،** گروه زیست شناسی، واحد جهرم، دانشگاه آزاد اسلامی، جهرم، ایران.
Email: f.kafilzadeh@gmail.com
https://orcid.org/0000-0003-2506-7140

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