Importance of genetic polymorphisms in liver transplantation outcomes

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MINIREVIEWS

Importance of genetic polymorphisms in liver transplantation outcomes

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Abstract

Although, liver transplantation serves as the only curative treatment for patients with end-stage liver diseases, it is burdened with complications, which affect survival rates. In addition to clinical risk factors, contribution of recipient and donor genetic prognostic markers has been extensively studied in order to reduce the burden and improve the outcomes. Determination of single nucleotide polymorphisms (SNPs) is one of the most important tools in development of personalized transplant approach. To provide a better insight in recent developments, we review the studies published in the last three years that investigated an association of recipient or donor SNPs with most common issues in liver transplantation: Acute cellular rejection, development of new-onset diabetes mellitus and non-alcoholic fatty liver disease, hepatocellular carcinoma recurrence, and tacrolimus concentration variability. Reviewed studies confirmed previously established SNP prognostic factors, such as PNPLA3 rs738409 for non-alcoholic fatty liver disease development, or the role of CYP3A5 rs776746 in tacrolimus concentration variability. They also identified several novel SNPs, with a reasonably strong association, which have the potential to become useful predictors of post-transplant complications. However, as the studies were typically conducted in one center on relatively low-to-moderate number of patients, verification of the results in other centers is warranted to resolve these limitations. Furthermore, of 29 reviewed studies, 28 used gene candidate approach and only one implemented a genome wide association approach. Genome wide association multicentric studies are needed to facilitate the

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development of personalized transplant medicine.

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Core tip: Better stratification of risk before transplantation and/or selection of appropriate donor are crucial to reduce post-transplant complications and improve outcomes. The contribution of genetic risk associated with single nucleotide polymorphisms for the most common complications along with the immunosuppression after liver transplantation is briefly summarized in this review.

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INTRODUCTION

Liver transplantation (LT) is the only effective treatment for the end-stage liver failure regardless of its etiology. Although patients' survival following transplantation has markedly improved during the last decades, LT is still burdened with various complications, such as acute cellular rejection (ACR), development of metabolic disorders: New-onset diabetes mellitus (NODM), non-alcoholic fatty liver disease (NAFLD) and/or the recurrence of primary disease like hepatocellular carcinoma (HCC)[1]. Better stratification of risk before transplantation, selection of appropriate donor, and appropriate immunosuppressive therapy might be of crucial importance to reduce these complications and improve the outcomes[2].

The contribution of genetic risk associated with single nucleotide polymorphisms (SNPs) has been extensively investigated. In the present review, we briefly summarize the findings of older investigations for each of the most common complications after LT and give a detailed analysis of discoveries of the studies published in the last three years.

LITERATURE SEARCH

We searched PubMed for articles published after 2017 using a predefined search strategy. For acute cellular rejection we searched PubMed for: "Liver transplantation", rejection and polymorphism. For new-onset diabetes mellitus we searched PubMed for: "Liver transplantation", diabetes, and polymorphism. For NAFLD we searched PubMed for: "Liver transplantation", (NAFLD or steatosis), polymorphism. For HCC recurrence we searched PubMed for: "Liver transplantation", hepatocellular carcinoma, recurrence, and polymorphism. Finally for tacrolimus pharmacokinetic we searched PubMed for: "Liver transplantation", tacrolimus, and polymorphism. Similar search for everolimus and sirolimus returned no relevant studies. Books, dissertations, review articles, meta-analyses, non English articles, and unpublished reports were excluded. Studies non-relevant for the topic, as well as studies with data inconsistency, as assessed by the review of the abstracts or full text, were also excluded.

ACUTE CELLULAR REJECTION AFTER LIVER TRANSPLANTATION

ACR is a common complication after LT with the incidence of 10%-30%. A recently conducted large study showed that ACR is a clinically significant event, associated

with an increased risk of graft failure and death. Clinical risk factors for ACR development include younger recipient age, lack of renal impairment, higher AST levels before LT, longer cold ischemic times and older donors. However, genetic risk factors might play a contributory role[3,4]. ACR is a T-cell mediated reaction, therefore, majority of SNP studies are focused on molecules that participate in T-cell activation, signaling and trafficking.

Although positive association was reported for a relatively high number of SNPs, none of them was firmly and consistently associated with ACR. Studies typically report relatively wide 95% confidence interval (CI) for odds ratio (OR) with a limit close to 1 and lack a confirmation from studies conducted in other centers. The role of TNFa-308 and IL10-1082 SNPs remains controversial even after conducted meta-analyses and might depend on ethnicity[5-7].

Our search identified eight novel studies which are summarized in Table 1. All studies were on genes related to the immune system; seven studies were solely on recipients, while the study by Thude *et al*[8], investigated both donors and recipients. This study reported an association of ACR with incompatibility in human platelet antigen 3 (HPA-3) SNP between the donor and recipient, although on a relatively low number of patients (53 non-rejectors and 43 rejectors). One study investigated SNP (IL28B rs12979860) for which a previous study reported an association with ACR[9], but found no difference[10]. Valero-Hervás *et al*[11] found the association with complement C3 genotype (95%CI for OR 0.09-0.77) on large number of patients and confirmed independency by multivariate analysis. SNP for IL17 (rs2275913) was associated with risk for ACR, and also with IL-17 plasma concentration and cyclosporine metabolism[12]. Yu *et al*[13] found a weak association between ACR and CD276 polymorphism, with CI limits close to 1. The remaining studies found either no association or the association was present only in subgroup analysis[14-16].

Although reviewed studies provide some insight into genetic risk for ACR occurrence, no reliable association has been identified. The approach by Thude *et al*[8], who investigated the recipient-donor relationship, seems to be more promising and should be conducted on larger scale.

NEW-ONSET DIABETES MELLITUS AFTER LIVER TRANSPLANTATION

NODM is a common metabolic complication after liver transplantation with a reported prevalence of 17%-36% despite the improvements in immunosuppressive regimens[17-19]. NODM has a negative effect on recipient and graft survival, and it is associated with cardiovascular complications, infections, chronic rejection and renal failure[17-20]. So far, clinical parameters such as advanced age, ethnicity, family history, body mass index, hepatitis C virus and immunosuppressive drugs have been reported as risk factors for NODM after LT[21-23].

Identifying patients at high risk of developing NODM is rather necessary for preventing the disease, individualization of immunosuppressive protocols and improving the long-term outcomes after LT. The pathophysiology of NODM resembles that of type 2 diabetes mellitus (T2DM) and it is characterized by impaired insulin secretion and insulin resistance. Thus, the numerous genetic polymorphisms that are involved in T2DM may also be associated with the development of NODM[24]. However, these associations in the post-transplantation setting are only starting to be elucidated.

We reviewed four studies that were published in the last three years (Table 2). With the exception of the study by Husen *et al*[25], all were conducted on SNPs previously shown to be associated with T2DM in non-transplant patients. Cen *et al*[26] investigated twelve different recipient's SNPs and found an association with two different SNPs for adiponectin gene rs1501299 and rs82239, and further confirmed rs1501299 (minor allele frequency, MAF 24%) to be an independent risk factor by multivariate regression. For rs82239, MAF (4.7%) was too low for firmer conclusions[26]. Interestingly, they found no association for KCNJ11 rs5219 SNP for which Parvizi *et al*[27] previously reported significant association with NODM. Similarly, the lack of association for nine other SNPs previously associated with DM in non-transplant patients was reported in this study[26]. Zhang *et al*[28] investigated both donor's and recipient's SNPs for small ubiquitin-like modifier 4 (SUMO4) rs237025 and found both of them to be associated with NODM. A recent meta-analysis confirmed that this SNP contributes to DM risk in non-transplant patients[29]. The angiotensin gene polymorphism rs699 is well known to be associated with a risk for various cardiovascular conditions. Moreover, its association with insulin sensitivity has also been reported[30]. Mottaghi *et al*[31] found this SNP to be associated with NODM in liver

Table 1 Genes and their single nucleotide polymorphisms investigated in association with acute cellular rejection after liver transplantation

Ref.	Etiology/Population N (non-ACR/ACR)	Genes and best 95%CI OR	Key points
Yu *et al*[13]	Various Eastern Asian 334/54	Recipient CD276: rs2127015 (0.05-0.93); NS for: rs11072431, rs11574495, rs12593558, rs12594627, rs3816661 rs7176654; Recipient TREML2: rs4714431, rs6915083, rs7754593, rs9394767 NS[1]	Recipient's CD276 (rs2127015) T allele is weakly associated with ACR and with CD276 mRNA expression
Ostojic *et al*[14]	Alcoholic European 156/59	Recipient CXCL9: rs10336 NS; Recipient CXCL10: rs3921 NS	No association found. CXCL9 (rs10336) is associated with earlier ACR occurrence and higher plasma CXCL9 concentrations
Sun *et al*[12]	Various Eastern Asian 66/40	Recipient IL-17: rs2275913 (0.07-0.77)[2]	Associated with increased IL-17 plasma concentration and with cyclosporine metabolism (CYP3A4 and CYP3A5 expression)
Verma *et al*[16]	Various Asian 86/16	Recipient FOXP3: rs3761547, rs3761548, and rs2232365 NS	Association found only in a very small subgroup of steroid resistant ACR patients (N = 5) for rs3761548 Associated with the degree of mixed lymphocyte reaction
Thude *et al*[15]	Various European 163/178	Recipient KLRB1: rs1135816 NS	No association found
Thude *et al*[8]	Various European 53/43	Recipient HPA-3 a/b: rs5910 (1.749–41.8); Recipient/donor incompatibility: rs5910 (1.78–7.39); HPA-1, -2, -3, -5, -15 NS for all	HPA-3 incompatibility and HPA-3 b/b genotype were associated with higher incidence of ACR There was no difference in the time of ACR occurrence
Fereidooni *et al*[10]	Various Western Asian 101/39	Recipient IL28B: rs12979860 NS	No association found
Valero-Hervás *et al*[11]	Various European 277/185	Recipient C3 complement rs2230199 (0.09-0.77)	C3FF genotype is associated with lower incidence of ACR, independently after multivariate analysis for sex, HCV infection, therapy and donor type

[1]Although a statistical significance for rs6915083 and rs7754593 of TREML2 is noted in the manuscript, the 95% ORs include 1 and should not be considered a significant association.
[2]Calculated from study data by authors of this review. ACR: Acute cellular rejection; C3: Complement component 3; CD: Cluster of differentiation; CXCL: Chemokine (CXC motif) ligand; CYP: Cytochrome P450; FOXP3: Forkhead box P3; HCV: Hepatitis C virus; HPA: Human platelet antigen; IL: Interleukin; KLRB1: Killer cell lectin-like receptor B1; mRNA: messenger ribonucleic acid; N: Number; NS: Not significant; TREML2: Triggering receptor expressed on myeloid celllike transcript 2; 95%CI OR: 95% confidence interval for odds ratio.

recipients. Finally, Husen *et al*[25] found the recipient's mammalian target of rapamycin mTOR rs2295080 to be associated with NODM in everolimus-treated patients. However, considering that the NODM risk was not a primary study objective and that the number of NODM patients was very low, this result needs further verification.

NON-ALCOHOLIC FATTY LIVER DISEASE AFTER LIVER TRANSPLANTATION

NAFLD is now recognized as the most common etiology of chronic liver disease[32,33], and one of the most common indications for LT, with increasing trends[34,35]. The genetic background of NAFLD is well established and the strongest evidence is provided for PNPLA3 rs738409, which became a major genetic determinant of hepatic fat content[33]. Following liver transplantation NAFLD/non-alcoholic steatohepatitis (NASH) may reoccur or develop *de novo*, with almost 50% of recipients showing evidence of steatosis after 10 years[36].

Recurrent and/or *de novo* allograft steatosis could also be genetically driven, and

Table 2 Genes and their single nucleotide polymorphisms investigated in association with new-onset of diabetes mellitus after liver transplantation

Ref.	Etiology/Population N (non-NODM/NODM)	Genes and best 95%CI OR	Key points
Mottaghi *et al*[31]	Various Iran 62/53	Recipient AGT: rs699 - 7.326 (2.0-26.8), rs4762 – NS	The presence of AGT rs699 T allele may significantly increase the NODM risk
Husen *et al*[25]	Various European 115/12[1]	Recipient Mtor: rs2295080 (1.48-23.4); rs12139042, rs2536 – NS	rs2295080 CC genotype is associated with a risk of DM on everolimus-based IS DM was a secondary objective, with a very low N of DM patients
Cen *et al*[26]	Hepatitis C, HCC China 181/75	Recipient ADIPOQ: rs1501299 (0.05-0.61)[2], rs822396 (0.13-0.70)[3]; NS for recipient SNPs: ADIPOR2 rs767870, TLR4 rs1927907, CCL5 rs2107538 and rs2280789, CYP3A5 rs776746, PPARA rs4823613, ACE rs4291, HSD11B1 rs4844880, KCNJ11 rs5219, KCNQ1 rs2237892	ADIPOQ rs1501299 and rs822396 are associated with a risk of NODM rs1501299 is an independent risk factor
Zhang *et al*[28]	Various China 102/24	Recipients SUMO4: rs237025 (1.42-5.91); Donors SUMO4: rs237025 (1.542–9.007)	Donor and recipient rs237025 G allele and their combination were independent predictive factors for NODM

[1]In the cited article the N of non-diabetic patients is wrongly stated to be 127, which is a total N.
[2]Calculated from study data for codominant model by authors of this review.
[3]Calculated from study data for dominant model by authors of this review. ACE: Angiotensin I converting enzyme; ADIPOQ: Adiponectin, C1Q and collagen domain containing; ADIPOR2: Adiponectin receptor 2; AGT: Angiotensinogen; CCL5: Chemokine (C-C motif) ligand 5; CYP: Cytochrome P450; DM: Diabetes mellitus; HCC: Hepatocellular carcinoma; HSD11B1: Hydroxysteroid 11-beta dehydrogenase 1; IS: Immunosuppression; KCNJ11: Potassium inwardly-rectifying channel, subfamily J, member 11; KCNQ1: Potassium voltage-gated channel, KQT: Like subfamily, member 1; mTOR: Mammalian target of rapamycin; N: Number; NODM: New-onset diabetes mellitus; NS: Not significant; PPARA: Peroxisome proliferator-activated receptor alpha; SNP: Single nucleotide polymorphism; SUMO4: Small ubiquitin like modifier 4; TLR4: Toll like receptor 4; 95%CI OR: 95% confidence interval for odds ratio.

our search identified 4 novel studies, summarized in Table 3, which had analyzed the association between donor and recipient SNPs with steatosis occurrence after LT. The donor PNPLA3 G allele was independently associated with steatosis occurrence in two studies from the same group of authors[37,38]. Míková *et al*[37] further reported that donor TM6SF2 rs58542926 A allele is associated with higher odds for steatosis development. Additionally, the strongest association was observed when both PNPLA3 G and TM6SF2 A alleles were present in the donor liver (95%CI for OR 2.01-13.0). However, it should be noted that two studies also reported a weak association between recipient PNPLA3 G allele and steatosis in the univariate model[38,39]. Furthermore, Kim *et al*[39] found that there are higher odds for steatosis development when donor and recipient have PNPLA3 G allele. However, the evidence is weak and CI limits extremely wide, mainly due to a small number of patients. Finally, recipient adiponectin gene SNPs were reported to be weakly associated with *de novo* steatosis in patients transplanted due to chronic hepatitis C virus (HCV) infection[40].

In summary, despite the small number of studies and a relatively small number of patients included, PNPLA3 rs738409 seems to be associated with post-LT steatosis, with novel studies providing stronger evidence for the donor rather than recipient polymorphism. However, based on previous "seed and soil" theory[41] and observations from studies shown in Table 3, we find that it would be of scientific interest to examine the possible interaction effect of donor and recipient genotypes on steatosis occurrence in an adequately powered study. Furthermore, the additive effect of TM6SF2 rs58542926 seems to increase the genetic risk for post-transplant steatosis further.

HEPATOCELLULAR CARCINOMA AFTER LIVER TRANSPLANTATION

HCC is the most common type of primary liver cancer and the second leading cause of tumor-related deaths worldwide[42]. Several HCC risk factors including alcohol

Table 3 Genes and their single nucleotide polymorphisms investigated in association with non-alcoholic fatty liver disease after liver transplantation

Ref.	Etiology/Population N (no steatosis/steatosis)	Genes and best 95%CI OR	Key points
Míková *et al*[37]	Various European 139/129	Donor TM6SF2: rs58542926 (1.28-4.42); Donor PNPLA3: rs738409 (1.28-3.27); Additive: TM6SF2 + PNPLA3 (2.01-13.0); Recipient NS for all	Donor TM6SF2 A allele and PNPLA3 G allele are associated with steatosis in both univariate and multivariate adjusted analyses The additive effect of donor TM6SF2 A allele and donor PNPLA3 G allele is strongly associated with steatosis No association when recipients SNPs were analyzed
John *et al*[40]	HCV North American 72/39	Recipient adiponectin: rs1501299 (1.09-5.5), rs266729 (0.14-0.75); rs2241766, rs17300539 – NS; Donor – NS for all	Recipient but not donor adiponectin rs1501299 GG genotype is significantly, but weakly associated with *de novo* steatosis after adjustment for race and HCV genotype
Kim *et al*[39]	Various Eastern Asian 23/9	Recipient PNPLA3: rs738409 (1.00-9.34)[1]; Donor – NS; Additive donor + recipent: (1.32-117.0)[2]	If both, donor and recipient have G allele, the recipient has higher risk for steatosis weak association, small number of patients
Trunečka *et al*[38]	Various European 89/87	Donor PNPLA3: rs738409 (1.05-1.75); Recipient PNPLA3: rs738409 (1.02-1.57)	PNPLA3 G allele in donors [OR (95%CI) = 1.62 (1.12-2.33)], but not in recipients is independently associated with steatosis after adjustment for age, disease etiology, BMI, diabetes, hypertension, therapy and lipids

[1]Calculated from study data for log-additive model by authors of this review.
[2]Calculated from study data by authors of this review. BMI: Body mass index; HCV: Hepatitis C virus; N-number; NS: Not significant; OR: Odds ratio; PNPLA3: Patatin-like phospholipase domain-containing 3; SNP: Single nucleotide polymorphism; TM6SF2: Transmembrane 6 superfamily member 2; 95%CI OR: 95% confidence interval for odds ratio.

consumption, HCV, hepatitis B virus (HBV), obesity and T2DM can be addressed through a variety of prevention and treatment methods[43]. Nevertheless HCC is an increasing indication for liver transplantation (LT) worldwide, regardless of the etiology[44,45]. LT provides a highly effective treatment option in selected patients, whereas the post-transplant HCC recurrence still remains a negative predictor of post-transplant survival in a substantial part of recipients[46,47]. Significant efforts have been made to identify risk factors for the HCC recurrence, and some of them as tumor size and number of lesions are implemented in selection criteria and prognostic models[48,49]. Mechanisms involved in the HCC development and recurrence are being extensively investigated, but our current knowledge is still limited, restricting our diagnostic and therapeutic options.

Genetic risk factors play an important role in HCC development. Recent investigations indicate an important role of PNPLA3, EGF and TM6SF2 SNPs in HCC susceptibility[50]. A recently conducted genome-wide association study (GWAS) identified rs2431 SNP for fibronectin type III domain containing 3b (FNDC3B) to be associated with the overall survival of HCC patients who underwent liver resection[51]. However, data on HCC recurrence in patients treated with liver transplantation, where both donor and recipient SNPs might contribute to the genetic risk of HCC reoccurrence are scarce. Our search identified three novel studies (Table 4). All three studies were conducted on genes associated with immune system activity. Zhang *et al*[52] found the recipient's SNP for IL-15 (rs10519613) to be associated with the risk of post-transplant HCC recurrence in a cohort of HBV infected patients. Two different studies on toll-like receptor- (TLR) related genes have reported an increased risk of HCC recurrence for donor's TLR4 (rs1927914) and recipient's TLR9 (rs187084) polymorphism, respectively[53,54]. Noteworthy, for TLR4 (rs1927914) polymorphism, previous case-control study reported an association with the HCC development[55]. These studies further emphasize the important role of innate immunity activation in liver carcinogenesis[56].

Table 4 Genes and their single nucleotide polymorphisms investigated in association with hepatocellular carcinoma recurrence after liver transplantation

Ref.	Etiology/Population N (non HCC/HCC)	Genes and best 95%CI OR	Key points
Shi *et al*[53]	Various Eastern Asian 49/34	Donor TLR 4: rs1927914 (1.886-12.5)[1]; Recipient TLR 4: rs1927914 NS	Donor TLR4 TT variant is an independent risk factor for HCC recurrence [OR 95%CI = 6.499 (1.799-23.481), after correction], and is associated with shorter recurrence free survival and overall survival
Zhang *et al*[52]	HBV Eastern Asian 74/38	Recipient IL-15: rs10519613 (1.636–16.168), rs13122930 NS; Donor IL-15: rs10519613 NS; rs13122930 NS	Recipient IL-15 rs10519613 CA/AA genotype is an independent risk factor for shorter tumor free survival and overall survival after correcting for histologic grade, tumor thrombus, tumor stage and UCSF criteria OR 95 CI for tumor free survival = 2.214 (1.041–4.708), for overall survival = 3.152 (1.358–7.315)
de la Fuente *et al*[54]	Various European 139/20	Recipient TLR9: rs187084 (0.01–0.87); rs5743836 – NS	TLR9 rs187084 TT genotype was associated with a decreased risk of HCC recurrence

[1]Calculated from study data by authors of this review for dominant model. HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; IL: Interleukin; N: Number; NS: Not significant; OR: Odds ratio; TLR: Toll like receptor; UCSF: University of California San Francisco; 95%CI OR: 95% confidence interval for odds ratio.

TACROLIMUS PHARMACOGENOMICS

One of the most important aspects in patient and graft survival is adequate immunosuppressive therapy. Introduction of calcineurin inhibitors to immunosuppressive regimen has greatly improved the outcomes after liver transplantation, even more so with tacrolimus[57,58]. However, this is a drug with a narrow therapeutic window and many factors may influence its pharmacokinetic and pharmacodynamic profile. For adequate graft and patient survival it is of crucial importance to avoid both, under and over immunosuppression[59,60]. Tacrolimus is metabolized in liver by cytochrome P450 (CYP) isoforms CYP3A4 and CYP3A5[61]. The most important SNP in estimating the achieved tacrolimus plasma concentration is rs776746, also known as 6986A > G. Patients with GG genotype (also known as CYP3A5*3) are CYP3A5 non-expressors and achieve greater tacrolimus concentration than patients with A allele – CYP3A5 expressors (also known as CYP3A5*1)[62,63]. As CYP3A5 is not expressed only in the liver, but also in the intestine and kidney, both donor and recipient genotypes may influence tacrolimus metabolism and subsequently alter the drug dose-normalized concentration[59,63,64]. Recipient genotype appears to be more important in the early post-transplant period, and donor genotype in later post-transplant period[65].

Our search identified ten novel studies (Table 5). All studies determined the CYP3A5 6986A>G (rs776746) SNP confirming its key role and tried to determine contributory SNPs or to provide additional insight into CYP3A5 6986A>G effects. Liu *et al*[66] conducted GWAS study on 115 patients and identified several novel SNPs associated with tacrolimus concentration. In early post-transplant period the tacrolimus concentration was associated with donor FAM26F (rs1057192) and rs1927321 SNPs. These two SNPs together with preoperative creatinine concentration explained 22% of variation in tacrolimus concentration. In later post-transplant period the tacrolimus concentration was associated with donor CYP3A5 (rs776746), TELO2 (rs266762), ESYT1 (rs7980521), rs4903096, and also with recipient CYP3A5 (rs776746) and rs7828796. These six SNPs explained 47.8% of variation. Kato *et al*[67] showed that the variability of tacrolimus concentration caused by CYP3A5 6986A>G (rs776746) genotype can be diminished if the drug is applied intravenously instead of orally. Three studies aimed to identify other important CYPs polymorphisms. The first investigated 29 various SNPs and found two additional SNPs for CYP3A5 (rs4646450 CC genotype and rs15524 TT genotype) to be associated with increased tacrolimus concentration[65], while the second study indicated that rare CYP3A4 SNPs (CYP3A4*20 and CYP3A4*22) may additionally increase tacrolimus concentration[68]. The third study developed a population pharmacokinetic model and found recipient

ABCB1 rsl045642 (C3435T), but not CYP3A5 rs776746 (6986A>G) to be independently associated with tacrolimus metabolism. However, as data on donor CYP3A5 SNPs were not included into the model, conclusion should be taken cautiously[69].

CYP non-related SNPs may affect tacrolimus concentration indirectly by changing CYP expression. This was demonstrated by Ou *et al*[70] who showed that lower levels of tacrolimus in TLR9 rs352139 G allele patients were associated with higher CYP3A5 mRNA expression in the liver. Similarly, SUMO4 rs237025 AA genotype was shown to be independently associated with decreased tacrolimus concentration and also with higher CYP3A5 mRNA expression[71]. The association with decreased tacrolimus concentration independent on CYP3A5 genotype was found for the donor FMO3 SNPs (rs1800822 allele T and rs909530 allele T)[72] and also for the sixth complement component (recipient C6 rs9200 G allele and donor rs10052999 CC/TT genotype), but the exact mechanism remains to be investigated[73]. Deng *et al*[74] analyzed association between tacrolimus metabolism related SNPs and early renal injury and found that CYP3A5*3 was associated with the risk of early glomerular lesion, while CYP2C8*3 was associated with the risk of tubulointerstitial injury.

In summary the reviewed studies confirmed the dominant role of CYP3A5 rs776746, (6986A>G) polymorphism, but also identified few novel SNPs involved in tacrolimus metabolism which might be a promising tool to reduce variability in tacrolimus concentration.

CONCLUSION

Reviewed studies confirmed previously established SNP prognostic factors such as the PNPLA3 rs738409 for NAFLD development and the role of CYP3A5 rs776746 in tacrolimus metabolism. They also identified several novel SNPs, which have the potential to become useful predictors of ACR, NODM, NAFLD, HCC recurrence, and post-transplant tacrolimus concentration variability. However, as the studies were typically conducted in one center on relatively low-to-moderate number of patients, verification of the results in other centers is warranted to resolve these limitations. Furthermore, of 29 reviewed studies, 28 used gene candidate approach and only one implemented a GWAS approach. GWAS multicentric studies are needed to facilitate the development of personalized transplant medicine.

Table 5 Genes and their single nucleotide polymorphisms investigated in association with tacrolimus metabolism after liver transplantation

Ref.	Etiology/Population/N	Genes	Key points
Liu *et al*[66]	Various Eastern Asian 115	Recipient, donor GWAS, association found for: CYP3A5 (rs776746), TELO2 (rs266762), ESYT1 (rs7980521), FAM26F (rs1057192), chr14: 39860228 (rs4903096) chr9: 118304139 (rs1927321), chr8: 83368297 (rs7828796)	Donor FAM26F (rs1057192) and rs1927321 were associated with Tac concentration in recovery phase (first 2 wk) Donor CYP3A5 (rs776746), TELO2 (rs266762), ESYT1 (rs7980521) and rs4903096 were associated with Tac concentration in stabilizing phase (third to fourth post-transplantation week) Recipient CYP3A5 (rs776746) and rs7828796 were associated with Tac concentration in stabilizing phase (third to fourth post-transplantation week)
Ou *et al*[70]	Various Eastern Asian 297	Recipient, donor: CYP3A5 (rs776746)[1], TLR 1 (rs574361, rs4833095), TLR2 (rs4696480), TLR3 (rs5743316, rs3775291), TLR4 (rs1927907), TLR7 (rs3853839), TLR9 (rs187084, rs352139, rs5743836)	Donor and recipient CYP3A5*3 genotype were associated with increased Tac concentration Donor TLR9 rs352139 AA genotype and TLR4 rs1927907 GG genotype were associated with increased Tac concentration Patients with donor TLR9 rs352139 G allele had increased CYP3A5 mRNA expression in transplanted liver tissue No significant association was found for other eight SNPs
Deng *et al*[74]	Not stated Eastern Asian 136	Recipient: CYP3A5 (rs776746)[1], CYP2C8 (rs11572080), ABCB1 (rs1045642, rs1128503)	Association with early renal injury was monitored CYP3A5*3 was associated with the risk of early renal glomerular lesion CYP2C8*3 was associated with the risk of the tubulointerstitial injury No association between ABCB1 SNPs and renal injury
Kato *et al*[67]	Various Eastern Asian 61	Recipient, donor: CYP3A5 (rs776746)[1]	Differences between administration routes of Tac were investigated CYP3A5 genotype influenced Tac concentration when Tac was applied orally, but not when applied intravenously
Gómez-Bravo *et al*[68]	Not stated European 90	Recipient, donor: CYP3A4 [rs67666821 (CYP3A4*20), rs35599367 (CYP3A4*22)], CYP3A5 (rs776746)[1]	CYP3A5*3 genotype was associated with increased Tac concentration The presence of rare CYP3A4 SNPs (CYP3A4*20 and CYP3A4*22) in donor liver increases Tac plasma concentrations Recipient CYP3A4*22 is also associated with increased Tac concentration
Liu *et al*[65]	Not stated Eastern Asian 373	Recipient, donor: CYP2B6 (rs3745274), CYP3A4 (rs4646437), CYP3A5 (rs776746, rs15524, rs4646450, rs3800959)[1]	CYP3A5 rs776746 GG (CYP3A5*3), rs4646450 CC and rs15524 TT genotypes were associated with higher Tac concentrations In the short term both donor and recipient CYP3A5 genotype contributed equally, but later the donor genotype had greater effect No significant association for the remaining 5 SNPs was found, 13 other SNPs were determined, but excluded from analysis because of low MAF

Zhang *et al*[71]	Various	Recipient, donor: CYP3A5 (rs776746)[1], SUMO4 (rs237025)	Donor and recipient CYP3A5*3 genotype are associated with increased Tac concentration
	Eastern Asian 297		Donor SUMO4 rs237025 AA genotype was independently associated with decreased Tac concentration and with higher CYP3A5 mRNA expression
Chen *et al*[69]	Not stated Eastern Asian	Recipient: CYP3A5 (rs776746), ABCB1 (rs1128503, rs2032582, rsl045642)	In a population pharmacokinetic model recipient ABCB1 rsl045642 (C3435T) was independently associated with Tac pharmacokinetic
	125		As data on donor CYP3A5 (rs776746) were not included into the model conclusion should be taken cautiously
Ren *et al*[72]	Not stated	Recipient, donor: CYP3A5 (rs776746)[1], FMO3 (rs1800822, rs2266782, rs1736557, rs909530, rs2266780)	Donor and recipient CYP3A5*3 genotype were associated with increased Tac concentration
	Eastern Asian 110		Donor FMO3 rs1800822 allele T and rs909530 allele T were associated with decreased Tac concentration, independently on CYP3A5 genotype
Liao *et al*[73]	HCC	Recipient, donor: CYP3A5 (rs776746)[1], C6 (rs9200, rs10052999)	Donor and recipient CYP3A5*3 genotype were confirmed to be associated with greater Tac concentration
	Eastern Asian 135		Recipient C6 rs9200 G allele and donor rs10052999 CC/TT genotype were associated with decreased Tac concentration

[1]for CYP3A5 (rs776746) CYP3A5*3 denotes GG genotype, patients with that genotype are CYP3A5 non-expressors. ABCB1: ATP binding cassette subfamily B member 1; C6: Complement C6; CYP: Cytochrome P450; ESYT1: Extended synaptotagmin 1; FAM26F: Gene family with sequence similarity 26, member F; FMO3: Flavin containing monooxygenase 3; MAF: Minor allele frequency; SUMO4: Small ubiquitin like modifier 4; Tac: Tacrolimus; TELO2: Telomere maintenance 2; TLR: Toll like receptor.

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