Clinical and Genetic Risk Factors of Recurrent Nonalcoholic Fatty Liver Disease After Liver Transplantation

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INTRODUCTION: **Nonalcoholic fatty liver disease (NAFLD) has been increasingly reported among recipients of liver transplantation (LT). We aimed to identify clinical and genetic risk factors responsible for the development of early recurrent NAFLD in nonalcoholic steatohepatitis transplant recipients.**

METHODS: **Forty-six total single nucleotide polymorphisms with known association with NAFLD were tested among both recipient and donor liver samples in 66 LT recipients with nonalcoholic steatohepatitis to characterize influences on NAFLD recurrence at ~1 year post-LT (median interval from LT to biopsy: 377 days).**

RESULTS: **Recurrent NAFLD was identified in 43 (65.2%) patients, 20 (30.3%) with mild recurrence, and 23 (34.8%) with moderate to severe NAFLD. On adjusted analysis, change in the body mass index (BMI) (ΔBMI) was significantly associated with NAFLD recurrence, whereas post-LT diabetes mellitus was associated with increased severity of NAFLD recurrence. ADIPOR1 rs10920533 in the recipient was associated with increased risk of moderate to severe NAFLD recurrence, whereas the minor allele of SOD2 rs4880 in the recipient was associated with reduced risk. Similar reduced risk was noted in the presence of donor SOD2 rs4880 and HSD17B13 rs6834314 polymorphism.**

DISCUSSION: **Increased BMI post-LT is strongly associated with NAFLD recurrence, whereas post-LT diabetes mellitus was associated with increased severity of NAFLD recurrence. Both donor and recipient *SOD2* rs4880 and donor HSD17B13 rs6834314 single nucleotide polymorphisms may be associated with reduced risk of early NAFLD recurrence, whereas presence of the minor allele form of ADIPOR1 rs10920533 in the recipient is associated with increased severity NAFLD recurrence.**

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) represents a dynamic spectrum of disease with potential transition from isolated hepatic steatosis to its progressive inflammatory form, nonalcoholic steatohepatitis (NASH), which may eventually lead to progressive fibrosis, cirrhosis, and increased propensity for hepatocellular carcinoma. With continued high rates of adult obesity and diabetes mellitus (DM) among an aging population, NAFLD-related liver disease and mortality will continue to increase in the United States (1). NAFLD cases are forecasted to increase 21%, from 83.1 million in 2015 to 100.9 million in 2030, whereas prevalent NASH cases will increase 63% from 16.52 million to 27.00 million cases. Consequently, the incidence of decompensated cirrhosis is projected to increase by 168% to 105,430 cases by 2030, hepatocellular carcinoma by 137% to 12,240 cases, and liver deaths by 178% to an estimated 78,300 deaths in 2030

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(1). Not surprisingly, NASH, currently the second most common indication for waitlisted adults in the United States (2), is expected to surpass other indications and become the leading cause of liver transplantation (LT) between 2020 and 2025 (3).

Reports of recurrent and *de novo* NAFLD/NASH in LT recipients have been increasingly recognized over the past decade (4). However, there remains wide variation in the reported prevalence of recurrent NAFLD after LT based on lack of standard inclusion criteria, protocol liver biopsies, diagnostic modalities, and follow-up intervals. As evidence of these large deviations between studies, prevalence of recurrent or *de novo* NAFLD has been reported as high as 100% recurrence after 5 years post-LT, although recurrent NASH is less common (5–8). On the other hand, one recent study demonstrated of 226 patients with NASH undergoing LT, 81 patients (36.6%) developed recurrent biopsy-proven NASH, with 15 (6.6%) developed bridging fibrosis, but only 4 patients (1.8%) progressed to recurrent NASH cirrhosis at mean 9 years of follow-up post-LT (9).

Several studies have attempted to identify clinical factors responsible for NAFLD recurrence post-LT. Initial studies have emphasized the role of obesity, metabolic syndrome, alcohol use, and donor graft steatosis at the crux of this mechanism (10,11). More recent data suggest a predilection toward allograft steatosis among female subjects, time-dependent body mass index (BMI), and hepatitis C virus diagnosis (8). Meanwhile, some data suggest NASH recurrence is less common and less severe among African American donors (9). Another clinical study among 88 LT recipients finds that BMI, triglyceride levels, and average steroid dose given at 6 months post-LT correlated with higher incidence of NAFLD recurrence at 5 years of follow-up (12). Finally, nuances among patients undergoing LT for NASH versus alcoholic liver disease [ALD] reveal some discordance among degree of steatosis and fibrosis on post-LT biopsy (13,14); however, recipient age and BMI seem to be independent risk factors of recurrent/*de novo* NAFLD.

There is a paucity of data characterizing genetic influences on NAFLD recurrence post-LT. Finkenstedt et al. (15) reported that recipient patatin-like phospholipase domain containing 3 (PNPLA3) rs738409 was associated with graft steatosis based on 5-year post-LT computed tomography imaging. More recent data by Trunecka et al. (16) revealed donor PNPLA3 rs738409 as a significant risk factor of graft steatosis based on histologic findings on liver biopsy. Another study performed by John et al. (17) recently demonstrated that recipient adiponectin [*ADIPOQ*] rs1501299 and rs17300539 polymorphisms are associated with *de novo* NAFLD among patient transplanted for hepatitis C. These small single-gene studies represent the only data regarding characterization of genetic influences on recurrent or *de novo* NAFLD to date.

In the wake of the obesity epidemic, the incidence of NAFLD and NASH is rising, and as a corollary, so too is recurrent and *de novo* NAFLD among post-LT patients. Select evidence presently has provided a foundation for clinical risk factors; however, there is a tremendous paucity of data categorizing genetic variants contributing to this phenomenon. Previous studies characterizing recurrent NAFLD/NASH post-LT can be challenging due to variable inclusion criteria, differing diagnostic modalities, lack of uniform protocol liver biopsies, and varying follow-up times seen among this patient population. Based on a 1-year protocol liver biopsy and the first study of its kind, we aim to provide novel insights into the prevalence of recurrent NAFLD/NASH among adult LT recipients and highlight clinical and genetic risk factors of recurrent NAFLD.

MATERIALS AND METHODS

Overall study design

A retrospective review of the electronic medical records from January 2006 to March 2015 identified 1,060 consecutive, adult LT recipients (at least 18 years of age) at the Methodist University Hospital Transplant Institute, University of Tennessee Health Sciences Center with follow-up to June 2018. Individual medical charts were reviewed for demographic characteristics, indication for LT, alcohol consumption, serial histology reports, laboratory data, comorbid conditions, and immunosuppressant medications.

We defined patients to meet the criteria for the diagnosis of NASH if they meet the following criteria: histological evidence of NASH in the pre-LT period or evidence of NAFLD in the explant or presence of DM and/or obesity (BMI $\geq$ 30), absence of significant alcohol use ($\leq$3 or more than 3 drinks in man and $\geq$ 2 drinks in woman), and exclusion of other etiologies. Patients diagnosed with cryptogenic cirrhosis (CC) were determined to be NASH phenotype whether their explant histopathology was suggestive of NAFLD. Alcohol history was determined by reviewing clinical notes including those of transplant social worker evaluations. As a policy of our center, all transplant candidates undergo thorough psychosocial evaluation by dedicated transplant social worker, during which, alcohol intake and other substance abuse history is recorded in the chart. Patients with significant alcohol use were excluded from the analysis despite a diagnosis of NASH.

Post-LT liver biopsies were performed per protocol at our center at 1, 3, and 5 years after LT in addition to clinically indicated liver biopsies. We obtained hematoxylin and eosin–stained and trichrome-stained slides in addition to obtaining paraffin embedded liver biopsy specimen available closest to 1-year post-LT (median interval from LT: 377 days). Of all the 66 patients included in the study, only 2 patient had biopsies beyond 2 years (one at 2 years and the second one at 2 years and 9 months after LT), and 10 patients had relatively early biopsy ($<$300 days). Most patients had liver biopsies under institutional liver biopsy protocol ($>$75%). The stained slides were rereviewed by a single experienced hepatopathologist [D.K.] who was blinded of the clinical information of the patient and was graded/staged per NASH-Clinical Research Network (CRN) scoring system (18) and Ishak scoring system (19). The NAFLD activity score (NAS) was calculated as per NASH-CRN criteria with score ranging from 0 to 8 according to the sum of the scores for steatosis (0–3), lobular inflammation (0–3), and ballooning (0–2) (20). Diagnostic categorization into NAFLD without features of NASH, borderline steatohepatitis, and definite steatohepatitis was made based on standard histological criteria (20). Steatosis was defined as presence of at least 5% macrovesicular steatotic hepatocytes. Mild steatosis was defined as 5%–33% steatosis, moderate steatosis 33%–66%, and severe steatosis was defined as $>$66% macrovesicular steatosis. Isolated steatosis was defined as presence of steatosis alone without features suggesting steatohepatitis. Multiple additional features were also reviewed in the liver biopsy including presence or absence of mega-mitochondria, acidophil bodies, distribution of fat (zonal, azonal, or panacinar]) presence or absence of microvesicular steatosis, cholestasis, bile duct injury, and acute or chronic cellular rejection. Portal fibrosis was also staged according to the method by Ishak et al. (19). Liver

biopsy adequacy was assessed, and suboptimal biopsies were defined as those that were either small (≤10 mm) or had histological artifacts that impeded scoring.

Other components of metabolic syndrome were analyzed. Components of obesity, hypertension, hyperlipidemia, and DM were defined using the following criteria:

1. Obesity: BMI >30 kg/m^2, as per Centers for Disease Control and Prevention guidelines. Waist circumference was not available for the study.
2. DM: DM was defined based recorded history of DM in the chart with further confirmation with requirement of insulin, oral hypoglycemic agents, or based on HgA1C level of > 6.5 per American Diabetic Association criteria for the diagnosis of DM (21).
3. Hypertension: >140/90 mm Hg, >130/80 mm Hg with DM, or requirement of antihypertensive medications, as per Joint National Committee 7 guidelines (22).
4. Dyslipidemia: low-density lipoprotein >130 mg/dL, triglycerides >150 mg/dL, or requirement of lipid-lowering agents as per established guidelines by National Cholesterol Education Program III (23).

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The University of Tennessee Health Science Center Institutional Review Board approved the study *a priori* (15-03830-XP).

Immunosuppression regimen

All patients received steroid sparing immunosuppression consisting of rabbit antithymocyte globulin induction, 1.5 mg/kg given during the anhepatic phase and on posttransplant day 2. A single intravenous dose of methylprednisolone (500 mg) was administered before the first dose of rabbit antithymocyte globulin to minimize cytokine release. Mycophenolate mofetil (MMF) was initiated on posttransplant day 1 at a dose of 1,000 mg 2 times per day for a total of 3 months and then discontinued; MMF was continued indefinitely for autoimmune hepatitis, primary biliary cirrhosis, or primary sclerosing cholangitis. MMF dose and administration frequency adjustments were made for gastrointestinal side effects or the development of cytopenias. Tacrolimus was started between postoperative day 3 and 7 when the serum creatinine was less than 2.0 mg/dL. Sirolimus is used in lieu of tacrolimus if the creatinine level remains over 2.0 mg/dL beyond posttransplant day 7; patients received an initial dose of 5 mg daily with daily trough levels after the first dose. Goal trough levels for tacrolimus and sirolimus during the first 3 months postoperatively were 6–8 and 8–10 ng/dL, respectively.

DNA extraction

Genomic DNA from formalin-fixed paraffin-embedded liver tissues of recipients and their corresponding donors were purified using GeneRead DNA formalin-fixed paraffin-embedded kits (cat: 180134; Qiagen, Germany). Sections of 10 μm were cut and processed after Qiagen protocol for DNA purification. DNA was collected in 25 μL of ATE buffer. DNA concentration was determined using Thermo Scientific NanoDrop spectrophotometers.

TaqMan polymerase chain reaction assay

We focused on 46 single nucleotide polymorphisms (SNPs) that were known in the literature to be associated with either NAFLD or NASH. Genotyping for select SNPs was performed using Custom TaqMan SNP genotyping assays (Applied Biosystems, Foster City, CA) in which a fluorogenic probe, consisting of an oligonucleotide labeled with a fluorescent reporter dye (FAM or VIC) (Part # 4351379). Each primer and probe set was used in the TaqMan SNP genotyping assays in accordance with the information on the Applied Biosystems website (http://www.appliedbiosystems.com).

The polymerase chain reaction was performed according to the manufacturer's instructions provided by Applied Biosystems using a LightCycler 480 system (Roche Diagnostics, Switzerland). Each 96-well plate contained 46 paired of samples of an unknown genotype and 2 negative control samples (reaction mixtures containing the reagents, but no DNA). The genotypes were determined visually based on the dye component fluorescent emission data depicted in the X-Y scatterplot of the SDS software.

Association analysis

The allele frequency and genotyping rate of the recurrent and nonrecurrent NAFLD/NASH cases were determined using PLINK (v 1.9 www.cog-genomics.org/plink/1.9/), a whole-genome association resource tool (24).

Statistical analyses

Descriptive statistics were calculated for all key variables. Frequencies and percentages were calculated for categorical variables; median or mean along with standard deviation were calculated for continuous variables. Comparisons for continuous variables were made using the Wilcoxon signed-rank sum tests and Kruskal-Wallis test. Categorical variables were compared using Pearson χ^2 test and Fisher exact test as appropriate.

We analyzed the association of the SNPs using a logistic regression analysis approach in 3 different models, additive (wild type, heterozygous, and homozygous separately), recessive (wild type + heterozygous vs homozygous), and dominant (heterozygous + homozygous vs wild type) models to assess the effect of the minor allele.

A P value < 0.05 was considered as statistically significant. Odds ratios were given with the 95% confidence intervals. All data were analyzed using IBM SPSS statistics (version 21.0, IBM Corp, Armonk, NY).

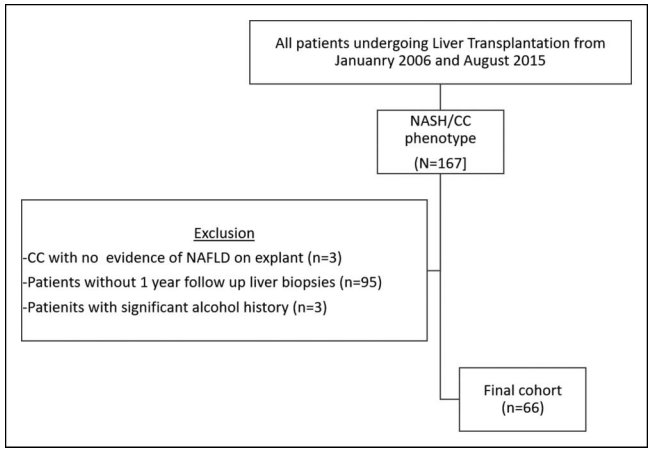

Figure 1. Attrition figure for developing the study cohort based on the inclusion and exclusion criteria.

Table 1. Pretransplant clinical and demographic baseline characteristics of the cohort with and without recurrent NAFLD

	All patients (n = 66)	No NAFLD recurrence (n = 23)	Mild NAFLD recurrence (n = 20)	Moderate to Severe NAFLD (N = 23)	*P* value[a]
Sex (female), n (%)	33 (50.0)	14 (60.9)	10 (50)	9 (39.1)	0.337
Race (Caucasian), n (%)	66 (100)	23 (100)	20 (100)	23 (100)	1.000
Obese, n (%)	39(59.1)	15 (65.2)	15 (75)	9 (39.1)	0.044
BMI categories, n (%)					0.118
<25 kg/m^2	10 (15.1)	2 (8.7)	3 (15)	5 (21.7)	
25–30 kg/m^2	17 (25.8)	6 (26.1)	2 (10)	9 (39.1)	
>30 kg/m^2	39 (59.1)	15 (65.2)	15 (75)	9 (39.1)	
Hypertension, n (%)	36 (51.5)	13 (56.5)	12 (60)	9 (39)	0.330
Diabetes, n (%)	31 (47)	10 (40.0)	9 (45)	12 (52)	0.821
Age at transplant (in yr)	57 ± 9	57 ± 10	57 ± 9	56 ± 8	0.766
Smoker, n (%)	13 (19.7)	3 (13.0)	5 (25)	5 (22)	0.589
Bilirubin level (mg/dL)	5.9 ± 6.9	6.6 ± 8.1	6.3 ± 6.9	4.9 ± 6.0	0.415
ALT (IU/mL)	54 ± 72	42 ± 35	83 ± 115	42 ± 38	0.650
AST (IU/mL)	89 ± 103	90 ± 110	101 ± 109	77 ± 94	0.626
Alkaline phosphatase	132 ± 75	127 ± 57	140 ± 106	130 ± 60	0.947
HgA1C level	5.1 ± 1.1	4.8 ± 0.9	5.3 ± 1.4	5.1 ± 0.9	0.546
FBS (mg/dL)	130 ± 60.4	126 ± 66	147 ± 75	118 ± 34	0.250
Cholesterol level (mg/dL)	142 ± 55	139 ± 52	138 ± 42	149 ± 70	0.981
Triglyceride level (mg/dL)	95 ± 60	80 ± 30	122 ± 90	87 ± 42	0.315
HDL (mg/dL)	44 ± 28	43 ± 36	39 ± 16	49 ± 29	0.499
LDL (mg/dL)	76 ± 34	78 ± 29	74 ± 29	74 ± 44	0.786
INR	1.9 ± 0.6	2 ± 0.7	1.8 ± 0.6	1.8 ± 0.5	0.650
MELD-Na score	21 ± 8	23 ± 9	21 ± 7	20 ± 7	0.360

ALT, alanine aminotransferease; BMI, body mass index; FBS, fasting blood sugar; HDL, high-density lipoprotein; INR, International Normalized Ratio; LDL, low-density lipoprotein; MELD-Na, model for end-stage liver disease; NAFLD, nonalcoholic fatty liver disease.
[a]Comparisons for continuous variables were made using the Kruskal-Wallis test, and categorical variables were compared using Pearson χ^2 test and Fisher exact test as appropriate.

RESULTS

Cohort characteristics

Of the 167 transplant recipients with NASH or CC, as outlined in Figure 1, 72 patients had 1-year protocol liver biopsy. Six patients of these 72 patients were further excluded based on significant alcohol history (n = 3) and CC whose explant was not consistent with NAFLD (n = 3), with a final total of 66 patients who formed the final analysis cohort.

Demographic and clinical data from 66 transplant recipients are summarized in Table 1. The overall cohort consisted of 33 (50%) female subjects, all from Caucasian decent (100%), with mean age at transplant 57.± 9 years. The mean Model For End-Stage Liver Disease Score (MELD-Na) at the time of LT was 21 ± 8. A history of tobacco (defined as any previous use) use was noted among 13 (19.7%) LT recipients. Pretransplant comorbidities of DM, hypertension, and obesity were noted in 47%, 51.5%, and 59.1% of patients, respectively.

The 66 patients in the final cohort were stratified based on the presence of mild NAFLD (n = 20), moderate to severe NAFLD (N = 23), or absence (n = 25) of recurrent NAFLD based on 1-year protocol liver biopsy. Between these 3 groups, there were no observed significant differences of baseline characteristics among patients who developed NAFLD recurrence versus those who did not except for the prevalence of baseline obesity seemed to be lower in the groups who developed moderate to severe recurrent NAFLD compared those with mild NAFLD recurrence. Median follow-up time posttransplant was 4.7 years (range 0.8–7.6 years).

Histological findings on 1-year protocol liver biopsy

Histologic characteristics of the 66 transplant recipients with NASH or CC are presented in Table 2. Recurrent NAFLD was identified in 43 patients 20 with mild recurrence and 23 with moderate to severe NAFLD based on liver biopsy of the recipient (allograft biopsy) at a median of 377 days after LT. Of these, 36

Table 2. Distribution of histological characteristics among patients who had liver transplantation with and without recurrent NAFLD based on NASH CRN staging criteria

	All patients (n = 66), n (%)	No NAFLD recurrence (n = 23), n (%)	NAFLD recurrence (n = 43), n (%)	*P* value
Steatosis (% of cohort)				<0.001
None (<5%)	23 (34.9)	23 (100)	0	
Mild (5%–33%)	20 (30.3)	0	20 (46.5)	
Moderate (33%–66%)	12 (18.2)	0	12 (27.9)	
Severe (>66%)	11 (16.7)	0	11 (25.6)	
Distribution of steatosis				<0.001
Zone 3	35 (62.5)	4 (30.8)	32 (72.1)	
Zone 1	0	0	0	
Azonal	13 (23.2)	9 (69.2)	4 (9.3)	
Panacinar	8 (14.3)	0	8 (18.6)	
Microvesicular fat				0.294
None	64 (97.0)	23 (100)	41 (95.4)	
Yes	2 (3.0)	0	2 (4.7)	
Lobular inflammation				0.280
Absent	2 (3.0)	1 (4.4)	1 (2.3)	
<2 foci/field	41 (62.1)	14 (60.9)	27 (62.8)	
2–4 foci/field	12 (18.2)	2 (8.7)	10 (23.3)	
>4 foci/field	11 (16.7)	6 (26.1)	5 (11.6)	
Cytological ballooning				0.171
None	60 (90.9)	23 (100)	37 (86.1)	
Few	4 (6.1)	0	4 (9.3)	
More than few	2 (3.0)	0	2 (4.7)	
Portal inflammation			0.347	
None	9 (13.6)	4 (17.4)	6 (11.6)	
Mild	31 (47.0)	8 (34.8)	23 (53.5)	
More than mild	26 (39.4)	11 (47.8)	15 (34.9)	
NAS				0.001
None (NAS 0)[a]	1 (1.5)	1 (4.4)	0	
Mild (NAS 1–2)	27 (40.9)	16 (69.6)	11 (25.6)	
Moderate (NAS 3–4)	31 (47.0)	6 (26.1)	25 (58.1)	
Severe (NAS 5–8)	7 (10.6)	0	7 (16.3)	
NASH diagnosis category				<0.001
No NAFLD	23 (34.9)	23 (100)	0	
NAFLD but not NASH	36 (54.6)	0	36 (83.7)	
Borderline NASH	3 (4.6)	0	3 (7.0)	
Definite NASH	4 (6.1)	0	4 (9.3)	
Fibrosis NASH CRN				0.789
Stage 0 (Absent)	45 (69.2)	18 (78.3)	27 (64.3)	
Stage IA (mild (delicate) zone 3 perisinusoidal fibrosis)	1 (1.5)	0	1 (2.4)	
Stage 1B (moderate (dense) zone 3 perisinusoidal fibrosis)	1 (1.5)	0	1 (2.4)	
Stage 1C (portal/periportal fibrosis only)	12 (18.5)	4 (17.4)	8 (19.1)	

Table 2. (*continued*)

	All patients (n = 66), n (%)	No NAFLD recurrence (n = 23), n (%)	NAFLD recurrence (n = 43), n (%)	*P* value
Stage 2 (zone 3 perisinusoidal fibrosis with portal/periportal fibrosis)	2 (3.1)	0	2 (4.8)	
Stage 3 (bridging fibrosis)	3 (4.6)	1 (4.4)	2 (4.8)	
Stage 4 (cirrhosis)	1 (1.5)	0	1 (2.4)	
Other incidental histological features				
Mega-mitochondria				0.802
None	61 (92.4)	21 (91.3)	410 (93.0)	
Yes	5 (7.6)	2 (8.7)	3 (7.0)	
Acidophil bodies				0.175
None	47 (71.2)	14 (60.9)	33 (76.7)	
Yes	19 (28.8)	9 (39.1)	10 (23.3)	
Cholestasis				1.000
None	64 (92.8)	23 (92.0)	41 (93.2)	
Present	5 (7.3)	2 (8.0)	3 (6.8)	
Mallory bodies				0.195
None	63 (95.5)	23 (100)	40 (93.0)	
Present	3 (4.6)	0	3 (7.0)	
Bile duct injury				0.028
Absent	55 (83.3)	16 (69.6)	39 (90.7)	
Present	11 (16.7)	7 (30.4)	4 (9.3)	

CRN, Clinical Research Network; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NAS, NAFLD activity score.
[a]Variables were compared using Pearson χ^2 test and Fisher exact test as appropriate.

(83.7%) subjects had NAFLD without features of NASH. Only 3 (7%) patients had findings consistent with borderline NASH, and 4 (9.0%) patients demonstrated histologic features of definite NASH. Among the subjects with recurrent NAFLD, grade-based NASH CRN criteria categorized mild hepatic steatosis (5%–33%) in 20 (46.9%) subjects, moderate steatosis (33%–66%) in 12 (27.9%), and severe steatosis (>66%) in 11 (25.6%). Lobular inflammation, cytological ballooning, and portal-based inflammation were not significantly different in the subjects with and without recurrent NAFLD. Patients with NAFLD recurrence had a higher zone 3 distribution of steatosis (72.1%) when compared with patients without NAFLD recurrence (30.8%) among this cohort ($P < 0.001$). Moreover, the presence of bile duct injury was more prevalent among patients without (30.4%) versus those with NAFLD recurrence (9.3%; $P = 0.028$). Significant fibrosis (≥2) was noted in 5 of the 43 patients with recurrent NAFLD, 2 (4.8%) subjects with stage 2 fibrosis, 2 (4.8%) individuals with stage 3 fibrosis, and 1 (2.4%) patient with stage 4 fibrosis. Overall NAS in the subjects with recurrent NAFLD was recorded as mild (NAS = 1–2) in 11 (25.6%) patients, moderate (NAS = 3–4) in 25 (58.1%), and severe (NAS = 5–8) in 7 (16.3%) subjects. Interestingly, a significant proportion of the patients without recurrent NAFLD also had NAS that was graded as mild or moderate in 16 (69.6%) and 6 (26.1%) LT recipients, respectively. These cases lacked steatosis, and the presence of lobular inflammation resulted in a mild to moderate NAS scores.

Clinical factors associated with recurrent NAFLD/NASH

Univariate logistic regression analysis of pretransplant demographic variables (age at transplant, sex, and race), comorbidities (obesity, DM, hypertension, and history of smoking), biochemical profile (HgA1c, AST, ALT, alkaline phosphatase, total bilirubin, low-density lipoprotein, HDL, cholesterol, and triglyceride), and MELD-Na score are detailed in Table 3. No pre-LT variables were determined to serve as significant predictors for histological NAFLD recurrence on 1-year protocol liver biopsy. However, moderate to severe NAFLD recurrence was less likely associated with pre-LT obesity.

Univariate logistic regression analysis of posttransplant demographic variables, comorbidities, biochemical data, and immunosuppressive regimens at the time of liver biopsy are detailed in Table 4. A significant correlation with any NAFLD recurrence was found about both the presence of post-LT DM ($P = 0.02$) and ΔBMI (change in the BMI from the baseline pre-LT to 1-year follow-up post-LT) ($P = 0.008$). The presence of post-LT diabetes was also observed in the predicting the recurrence of moderate to severe NAFLD on univariate logistic regression analysis, but the association was less apparent with ΔBMI. On multivariate logistic regression analysis, change in the BMI (ΔBMI) was significantly associated with NAFLD recurrence post-LT (OR 1.17; 95% confidence interval (CI): 1.02–1.40, $P = 0.03$, Table 5). In addition, post-LT DM (OR 3.68, 95% CI: 1.09–12.39, $P = 0.035$ (Table 5) was associated with increased risk of moderate to severe NAFLD recurrence.

Table 3. Univariate analysis of pretransplant factors on developing recurrent NAFLD

	Any NAFLD		Moderate to severe NAFLD	
Pretransplant factors/variables[a]	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Demographic data				
Age at transplant	0.99 (0.94–1.05)	0.74	0.98 (0.94–1.05)	0.70
Male sex	0.51 (0.18–1.43)	0.19	0.51 (0.18–1.43)	0.19
Medical history				
Hypertension	0.73 (0.27–2.03)	0.55	0.46 (0.17–1.30)	0.14
Diabetes mellitus	1.24 (0.45–3.44)	0.68	1.38 (0.50–3.81)	0.54
Obese (BMI≥ 30 kg/m^2)	0.59 (0.20–1.74)	0.34	0.26 (0.09–0.75)	0.01
History of smoking	2.02 (0.49–8.23)	0.32	0.22 (0.35–4.26)	0.76
Laboratory parameters				
Total bilirubin (mg/dL)	0.98 (0.91–1.05)	0.57	0.96 (0.89–1.05)	0.39
ALT (IU/mL)	1.01 (0.99–1.02)	0.34	0.99 (0.98–1.01)	0.32
AST (IU/mL)	1.00 (0.99–1.01)	0.95	0.99 (0.99–1.00)	0.49
ALP (IU/mL)	1.00 (0.99–1.01)	0.71	0.99 (0.99–1.01)	0.86
HgA1c	1.50 (0.79–2.81)	0.21	1.07 (0.64–1.77)	0.81
FBS (mg/dL)	1.00 (0.99–1.01)	0.72	0.99 (0.98–1.01)	0.28
Cholesterol (mg/dL)	1.00 (0.99–1.01)	0.76	1.00 (0.99–1.01)	0.53
Triglyceride (mg/dL)	1.01 (0.99–1.02)	0.19	0.99 (0.98–1.01)	0.45
HDL (mg/dL)	1.00 (0.98–1.02)	0.92	1.01 (0.99–1.03)	0.38
LDL (mg/dL)	0.99 (0.98–1.01)	0.72	0.99 (0.98–1.02)	0.90
INR	0.62 (0.28–1.41)	0.25	0.68 (0.28–1.66)	0.39
MELD-Na	0.95 (0.89–1.02)	0.16	0.97 (0.90–1.04)	0.35

AST, aspartate aminotransferase; ALT, alanine aminotransferease; BMI, body mass index; CI, confidence interval; FBS, fasting blood sugar; HDL, high-density lipoprotein; INR, international normalized ratio; LDL, low-density lipoprotein; MELD-Na Score, model for end-stage liver disease; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio.
[a]Race was not analyzed in the analysis as 99% of the included patients are of Caucasian origin.

Genetic variants linked to recurrent NAFLD/NASH

Tissue samples were isolated from liver biopsies obtained from both the recipient and donor. Subsequently, both samples underwent genotyping, and an association analysis was performed to calculate the influence of each SNP on NAFLD recurrence post-LT. We have unmasked several SNPs this way (Table 6). In this study, we report the proportion of phenotypic variance using 46 SNPs attributed to NAFLD recurrence after liver transplant in additive, recessive, and dominance genetic variation models. First, we analyzed predictors for any NAFLD recurrence and then reanalyzed for moderate to severe NAFLD recurrence. Using this approach, we have unsurfaced the following SNPs that seems to be associated with NAFLD recurrence: recipient or donor SOD2 rs4880 polymorphism, donor HSD17B13 rs6834314, and recipient ADIPOR1 rs10920533. We noted a dominant protective effect of the minor allele of SOD2 rs4880 polymorphism (G/G) (OR 0.05, 95% CI 0.01–0.42, $P = 0.006$) for moderate to severe NAFLD recurrence. Similar protective effect for NAFLD recurrence was noted in the presence of donor SOD2 rs4880 polymorphism in both the additive (OR 0.10, 95% CI 0.01–0.79, $P = 0.035$) and dominance phenotypic variation models (OR 0.15; 95% CI 0.03–0.93, $P = 0.041$). Presence of the minor allele form of the HSD17B13 rs6834314 phenotype also showed a strong protective effect for moderate to severe NAFLD recurrence in the additive model (OR 0.11, 95% CI 0.01–0.88, $P = 0.036$). Finally, we found a strong association for moderate to severe NAFLD recurrence in the presence of minor allele form (A/A) of ADIPOR1 rs10920533 in the recipient (OR 4.49, 95% CI 1.11–18.23, $P = 0.036$) in the dominant genetic variation model. A comprehensive list of the genetic variants and SNPs tested, and their association with NAFLD recurrence is provided in Table 7.

DISCUSSION

Several important observations can be concluded from this study. First, this study, using liver biopsy predominantly obtained through institutional protocol around 1-year post-LT clearly demonstrates that early recurrent NAFLD occurs in almost two-thirds of the NASH patients undergoing LT, 30% with mild recurrence, and 35% with moderate to severe NAFLD recurrence but recurrent NASH is relatively infrequent, occurring in approximately 11% of our cohort. Second, we demonstrated that ΔBMI and the presence of post-LT DM are important clinical predictors of recurrent NAFLD. Third, using a comprehensive translational approach, we performed genotyping for 46 SNPs, with known association with NAFLD, obtained from DNA extracted from the donor (through allograft biopsies in the posttransplant period) and recipient liver samples (explant liver tissue). Through this novel design, we have noted preliminary findings suggesting potential association between recipient or donor SOD2 rs4880 polymorphism, donor HSD17B13

Table 4. Univariate analysis of the association of posttransplant factors and early immunosuppression on development of recurrent NAFLD

	Any NAFLD		Moderate to severe NAFLD	
Posttransplant factors/variables	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Medical comorbidities				
Hypertension	0.83 (0.29–2.38)	0.73	0.52 (0.18–1.52)	0.24
Diabetes mellitus	3.58 (1.18–10.84)	0.02	3.50 (1.21–10.13)	0.02
Anthropometric and laboratory parameters				
BMI (kg/m^2) at 1 yr	1.09 (0.99–1.21)	0.08	0.94 (0.85–1.04)	0.22
ΔBMI	1.20 (1.05–1.37)	0.008	1.11 (0.99–1.24)	0.07
Total bilirubin (mg/dL)	1.04 (0.90–1.19)	0.61	0.98 (0.88–1.10)	0.76
ALT(IU/mL)	1.00 (0.99–1.01)	0.99	0.99 (0.99–1.01)	0.81
AST(IU/mL)	1.00 (0.99–1.01)	0.60	1.00 (0.99–1.01)	0.19
ALP (IU/mL)	1.00 (0.99–1.00)	0.81	1.00 (0.99–1.01)	0.31
HgA1c	2.35 (0.37–14.92)	0.37	2.08 (0.54–8.01)	0.29
FBS	1.01 (0.99–1.03)	0.10	1.00 (0.99–1.01)	0.40
Cholesterol (mg/dL)	1.01 (0.99–1.02)	0.56	1.01 (0.99–1.02)	0.50
Triglyceride (mg/dL)	1.00 (0.99–1.01)	0.70	1.00 (0.99–1.01)	0.55
HDL (mg/dL)	1.04 (0.98–1.10)	0.23	1.04 (0.98–1.10)	0.23
LDL (mg/dL)	0.99 (0.98–1.02)	0.89	0.99 (0.98–10.02)	0.76
INR	0.78(0.09–6.55)	0.82	0.16 (0.01–5.39)	0.31
Immunosuppression regimen				
Tacrolimus (no use vs use)	1.56 (0.37–6.52)	0.55	1.03 (0.23–4.60)	0.97
Mycophenolic acid (no use vs use)	0.41(0.09–1.84)	0.25	0.54 (0.10–2.93)	0.47
mTor inhibitor (no use vs use)	0.93 (0.24–3.59)	0.91	1.72 (0.46–6.43)	0.42

BMI, body mass index; CI, confidence interval; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio.

rs6834314, and recipient ADIPOR1 rs10920533 as genetic risk factors influencing recurrent NAFLD post-LT. Although the presence of the minor allele form of ADIPOR1 rs10920533 was strongly associated with NAFLD recurrence, those with recipient or donor SOD2 rs4880 polymorphism and donor HSD17B13 rs6834314 seems to be have a protective effect.

To date, major challenges in accurately characterizing recurrent NAFLD/NASH post-LT were primarily related to variable inclusion criteria, differing diagnostic modalities, lack of uniform protocol liver biopsies, varying follow-up times, and lack of evidence identifying genetic targets. At the recent 2019 meeting of International Liver Transplantation Society NASH consensus, it was agreed that female sex, hypertension, hyperlipidemia, DM, renal dysfunction, obesity, weight gain, PNPLA3 genetic polymorphisms, and tacrolimus-based immunosuppression regimens are potential risk factors of NAFLD recurrence post-LT (25). However, there was a call for improved definitions of NAFLD recurrence post-LT and risk factors of this phenomenon. More importantly, the authors challenged future studies to not only provide more long-term, prospective data but also target basic science and genomic influences at play in addition to optimizing the immunosuppression regimen among this patient population. We hope to target and identify genetic polymorphisms that may alert patients at higher risk of post-LT NAFLD recurrence based on their genetic predilection. In this study, we identified clinical and genetic risk factors and assessed overall patient survival based on liver biopsy predominantly obtained using institutional protocol closest to 1-year post-LT in an effort to more accurately characterize recurrent NAFLD/NASH post-LT.

Numerous studies have characterized risk factors and prevalence of posttransplant NAFLD and NASH recurrence (26). A recent study showed that recurrent NAFLD post-LT occurred in 88% of patients, with nearly one-fourth patients having advanced

Table 5. Multivariate analysis of the association of clinical factors in early development of NAFLD

Variables	OR (95% CI)	*P* value
Any NAFLD recurrence		
Diabetes mellitus at follow-up (ref = no diabetes)	2.23 (0.66–7.50)	0.20
ΔBMI	1.17 (1.02–1.40)	0.03
Moderate to severe NAFLD recurrence		
Diabetes mellitus at follow-up (ref = no diabetes)	3.68 (1.09–12.39)	0.035
ΔBMI	1.06 (0.94–1.20)	0.32

BMI, body mass index; CI, confidence interval; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio

Table 6. Association of SNPs with NAFLD recurrence using a logistic regression analysis in additive, recessive, and dominant models to assess the effect of the minor allele

SNPs, dominant allele, frequencies of the allele	Model	Allele	Any NAFLD		Moderate to severe NAFLD	
			Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Recipient SOD2 rs4880	Additive	A/A	REF		REF	
"A" allele is WT		A/G	0.16(0.02–1.47)	0.123	0.03(0.003–0.32)	0.004
A/A = 8, A/G = 32, G/G = 13		G/G	0.23(0.02–2.46)	0.480	0.09(0.01–0.96)	0.383
	Recessive	A/G+A/A	REF		REF	
		G/G	1.07(0.30–3.85)	0.922	1.30(0.35–4.76)	0.694
	Dominant	A/A	REF		REF	
		A/G+G/G	0.18(0.02–1.57)	0.121	0.05(0.01–0.42)	0.006
Donor SOD2 rs4880	Additive	A/A	REF		REF	
"A" allele is WT		A/G	0.50(0.11–2.37)	0.514	1.13(0.29–4.33)	0.277
A/A = 15, A/G = 21, G/G = 7		G/G	0.10(0.01–0.79)	0.035	0.25(0.02–2.64)	0.202
	Recessive	A/G+A/A	REF		REF	
		G/G	0.15(0.03–0.93)	0.041	0.23(0.03–2.15)	0.199
	Dominant	A/A	REF		REF	
		A/G+G/G	0.33(0.08–1.45)	0.143	0.83(0.23–3.03)	0.782
Donor HSD17B13 rs6834314	Additive	A/A	REF		REF	
"A" allele is WT		A/G	0.37(0.04–3.84)	0.880	0.33(0.04–2.27)	0.979
A/A = 6, A/G = 20, G/G = 17		G/G	0.18(0.02–1.86)	0.109	0.11(0.01–0.88)	0.036
	Recessive	A/G+A/A	REF		REF	
		G/G	0.40(0.11–1.40)	0.150	0.25(0.06–1.08)	0.064
	Dominant	A/A	REF		REF	
		A/G+G/G	0.26(0.03–2.47)	0.243	0.21(0.03–1.33)	0.098
Recipient ADIPOR1 rs10920533	Additive	G/G	REF		REF	
"G" allele is the WTA/A = 9,		A/G	1.23(0.37–4.03)	0.265	3.91(0.91–16.81)	0.494
A/G = 26, G/G = 19		A/A	7.20(0.75–69.38)	0.090	6.67(1.10–40.43)	0.113
	Recessive	A/G+G/G	REF		REF	
		A/A	6.40(0.74–55.52)	0.092	2.77(0.64–11.89)	0.171
	Dominant	G/G	REF		REF	
		A/G+A/A	1.73(0.55–5.39)	0.348	4.49(1.11–18.23)	0.036

CI, confidence interval; NAFLD, nonalcoholic fatty liver disease; SNP, single nucleotide polymorphism.

fibrosis (27). Contos et al. cited a 100% recurrence rate of NASH post-LT among 27 patients within 5 years follow-up; however, the rate of cirrhosis and graft failure was quite low (6). In this study, we noted an overall NAFLD recurrence in 43 patients (65.2%). Of the 66 total subjects, 36 patients (54.5%) had NAFLD recurrence without evidence of NASH, 3 patients (4.5%) with borderline NASH, and 4 patients (6.1%) with definite NASH recurrence based on histologic findings. Advanced fibrosis (stage 3 and 4] was evident in 3 patients (4.5%) with NAFLD recurrence, in addition to 1 patient (1.5%) without NAFLD recurrence.

Type 2 DM is an important risk factor of NAFLD and has been shown to accelerate the progression of liver disease in NAFLD. A recent meta-analysis has shown high prevalence of NAFLD and NASH in patients with DM (28). Liver transplant recipients with NASH have a higher risk of *de novo* posttransplant DM (29). Considering known association of NAFLD and DM, a higher prevalence of NAFLD is expected in the post-LT period (30). We have noted a clear association of recurrent NAFLD and presence of posttransplant DM on univariate analysis. Presence of diabetes in the posttransplant period was associated with 4.4-fold increased risk of moderate to severe NAFLD recurrence after adjusting for pre-LT obesity and ΔBMI.

Several genetic variants have shown an association with NAFLD through genome-wide association study, meta-analyses, and retrospective case–control studies. PNPLA3 rs738409 and TM6SF2 rs58542926 are the 2 genetic variants providing the strongest evidence for association with NAFLD (31). However, data on its association in post-LT NAFLD have not been well-characterized. PNPLA3 is a well-known SNP associated with development of NAFLD in both transplant and nontransplant settings (16,32). Recently, this polymorphism in donor graft has been associated with increased risk of post-LT NAFLD as well (16). In a novel study design comparing genotypes of both recipient and donor liver samples, the genetic link with PNPLA3 and TM6SF2 was not replicated in this study; however, we noted a potential association with donor SNP rs4880 polymorphism with post-LT recurrent NAFLD.

In NAFLD, increased fatty acid oxidation produces high levels of reactive oxygen species. Manganese-dependent superoxide dismutase, encoded by the *SOD2* gene, plays an important role in protecting cells from oxidative stress. *SOD2* has previously been implicated in the pathogenesis of NASH through aberrant antioxidant compensation and mitochondrial dysfunction. A common nonsynonymous polymorphism in *SOD2* (C47T; rs4880) is associated with decreased manganese-dependent superoxide dismutase mitochondrial targeting and activity (33). In contrast to these earlier observations, we noted a protective effect of the *SOD2* (A > G; rs4880] polymorphism for NAFLD recurrence.

Table 7. Association of SNPs with NAFLD recurrence using a logistic regression analysis in additive, recessive, and dominant models to assess the effect of the minor allele

	SNPs, dominant allele, frequencies of the allele	Model	Genotype	Any NAFLD		Moderate to severe NAFLD	
				Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
1	Recipient SOD2 rs4880	Additive	A/A	REF		REF	
	"A" allele is WT		A/G	0.16 (0.02–1.47)	0.123	0.03 (0.003–0.32)	0.004
	A/A = 8, A/G = 32, G/G = 13		G/G	0.23 (0.02–2.46)	0.480	0.09 (0.01–0.96)	0.383
		Recessive	A/G+A/A	REF		REF	
			G/G	1.07 (0.30–3.85)	0.922	1.30 (0.35–4.76)	0.694
		Dominant	A/A	REF		REF	
			A/G+G/G	0.18 (0.02–1.57)	0.121	0.05 (0.01–0.42)	0.006
	Donor SOD2 rs4880	Additive	A/A	REF		REF	
	"A" allele is WT		A/G	0.50 (0.11–2.37)	0.514	1.13 (0.29–4.33)	0.277
	A/A = 15, A/G = 21, G/G = 7		G/G	0.10 (0.01–0.79)	0.035	0.25 (0.02–2.64)	0.202
		Recessive	A/G+A/A	REF		REF	
			G/G	0.15 (0.03–0.93)	0.041	0.23 (0.03–2.15)	0.199
		Dominant	A/A	REF		REF	
			A/G+G/G	0.33 (0.08–1.45)	0.143	0.83 (0.23–3.03)	0.782
2	Recipient PNPLA3 rs738409	Additive	C/C	REF		REF	
	"C" allele is WT		C/G	0.82 (0.23–2.93)	0.984	1.03 (0.29–3.74)	0.989
	C/C = 17, C/G = 25, G/G = 11		G/G	0.66 (0.14–3.08)	0.638	1.05 (0.22–5.09)	0.965
		Recessive	C/G+C/C	REF		REF	
			GG	0.74 (0.19–2.82)	0.658	1.03 (0.26–4.09)	0.968
		Dominant	C/C	REF		REF	
			C/G+G/G	0.76 (0.23–2.52)	0.658	1.04 (0.31–3.46)	0.954
	Donor PNPLA3 rs738409	Additive	C/C	REF		REF	
	"G" allele is WT		C/G	1.04 (0.23–4.77)	0.969	2.67 (0.56–12.62)	0.966
	C/C = 22, C/G = 10, G/G = 1		G/G	NA		NA	
		Recessive	C/G+C/C	REF		REF	
			GG	NA		NA	
		Dominant	C/C	REF		REF	
			C/G+G/G	1.21 (0.27–5.40)	0.801	NA	
3	Recipient HSD17B13 rs6834314 A/A = 0,G/A-2, G/G = 4	NA	NA	NA		NA	
	Donor HSD17B13 rs6834314	Additive	A/A	REF		REF	
	"A" allele is WT		A/G	0.37 (0.04–3.84)	0.880	0.33 (0.04–2.27)	0.979
	A/A = 6, A/G = 20, G/G = 17		G/G	0.18 (0.02–1.86)	0.109	0.11 (0.01–0.88)	0.036
		Recessive	A/G+A/A	REF		REF	
			G/G	0.40 (0.11–1.40)	0.150	0.25 (0.06–1.08)	0.064
		Dominant	A/A	REF		REF	
			A/G+G/G	0.26 (0.03–2.47)	0.243	0.21 (0.03–1.33)	0.098
4	Recipient ADIPOQ_rs266729	Additive	C/C	REF		REF	
	"C" Allele is WT		C/G	1.84 (0.60–5.65)		0.99 (0.31–3.16)	0.968
	C/C = 28, C/G = 25, G/G = 1		G/G	NA		NA	0.968
		Recessive	C/G+C/C	REF		REF	

Table 7. (*continued*)

	SNPs, dominant allele, frequencies of the allele	Model	Genotype	Any NAFLD		Moderate to severe NAFLD	
				Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
			G/G	NA		NA	0.986
		Dominant	C/C	REF		REF	
			C/G+G/G	1.95 (0.64–5.95)	0.241	1.12 (0.36–3.47)	0.847
	Donor ADIPOQ_rs266729	Additive	C/C	REF		REF	
	"C" Allele is WT		C/G	3.51 (0.99–12.36)	0.146	2.17 (0.66–7.12)	0.719
	C/C = 25, C/G = 24, G/G = 2		G/G	0.92 (0.05–16.46)	0.626	2.57 (0.14–47.01)	0.701
		Recessive	C/G+C/C	REF		REF	
			G/G	0.53 (0.03–9.03)	0.662	1.72 (0.10–29.24)	0.707
		Dominant	C/C	REF		REF	
			C/G+G/G	3.08 (0.92–10.25)	0.067	2.20 (0.69–7.06)	0.184
5	Recipient MTTP rs3816873	Additive	T/T	REF		REF	
	"T" allele is WT		C/T	0.91 (0.14–6.16)	0.936	1.15 (0.31–4.26)	0.517
	C/C = 5, C/T = 13, T/T = 37		C/C	0.97 (0.27–3.57)	0.979	0.46 (0.04–4.57)	0.469
		Recessive	C/T+T/T	REF		REF	
			C/C	0.92 (0.14–6.01)	0.930	0.44 (0.05–4.29)	0.483
		Dominant	T/T	REF		REF	
			C/T+C/C	0.96 (0.30–3.04)	0.940	0.92 (0.28–3.03)	0.895
	Donor MTTP rs3816873	Additive	T/T	REF		REF	
	"T" allele is WT		C/T	1.13 (0.33–3.83)	0.966	0.88(0.25–3.07)	0.933
	C/C = 3, C/T = 21, T/T = 22		C/C	NA		0.88 (0.07–11.24)	0.958
		Recessive	C/T+T/T	REF		REF	
			C/C	NA		0.93 (0.08–11.16)	0.957
		Dominant	T/T	REF		REF	
			C/T+C/C	1.39 (0.42–4.60)	0.595	0.88 (0.26–2.95)	0.829
6	Recipient ABCC2 rs17222723	Additive	T/T	REF		REF	
	"T" allele is WT		A/T	NA		1.94 (0.35–10.72)	0.967
	A/A = 1, A/T = 6, T/T = 47		A/A	1.13 (0.19–6.85)	0.967	NA	0.969
		Recessive	A/T+T/T	REF		REF	
			A/A	NA		NA	0.987
		Dominant	T/T	REF		REF	
			A/T+A/A	0.76 (0.15–3.78)	0.733	1.45 (0.29–7.30)	0.650
	Donor ABCC2 rs17222723	Additive	T/T	REF			
	"T" allele is WT		A/T	2.21 (0.23–21.46)	0.964	1.10 (0.17–7.25)	0.969
	A/A = 1, A/T = 5, T/T = 45		A/A	NA		NA	0.969
		Recessive	A/T+T/T	REF		REF	
			A/A	NA		NA	0.987
		Dominant	A/T+A/A	1.10 (0.18–6.70)	0.915	REF	
			T/T	REF		0.82 (0.14–4.99)	0.833
7	**Recipient FDFT1 rs2645424**	Additive	A/A	REF		REF	
	"A" allele is WT		A/G	1.67 (0.29–9.52)	0.357	1.77 (0.17–18.32)	0.758
	A/A = 12, A/G = 28, G/G = 15		G/G	0.77 (0.09–6.45)	0.556	0.77 (0.09–6.45)	0.556
		Recessive	A/G+A/A	REF		REF	

Table 7. (*continued*)

	SNPs, dominant allele, frequencies of the allele	Model	Genotype	Any NAFLD		Moderate to severe NAFLD	
				Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
			G/G	1.33 (0.38–4.64)	0.651	0.93 (0.27–3.26)	0.908
		Dominant	A/A	REF		REF	
			A/G+G/G	0.77 (0.20–2.94)	0.696	3.27 (0.64–16.80)	0.156
	Donor FDFT1 rs2645424	Additive	A/A	REF		REF	
	"A" allele is WT		A/G	NA		>99.99 (<0.01–>99.99)	0.979
	A/A = 6, A/G = 23, G/G = 16		G/G	NA		>99.99 (<0.01–>99.99)	0.970
		Recessive	G/G	REF		REF	
			A/G+A/A	2.12 (0.55–8.18)	0.277	3.14 (0.86–11.50)	0.084
		Dominant	A/G+G/G	REF		REF	
			A/A	4.50 (0.72–28.01)	0.107	2.80 (0.30–26.42)	0.369
8	Recipient NCAN rs2228603	Additive	C/C	REF		REF	
	"C" allele is WT		C/T	2.83 (0.53–15.04)	0.123	1.93 (0.48–7.80)	0.962
	C/C = 41, C/T = 10, T/T = 3		T/T	0.35 (0.03–4.23)	0.229	NA	0.965
		Recessive	C/T+C/C	REF		REF	
			T/T	0.30 (0.02–3.50)	0.335	NA	0.977
		Dominant	C/C	REF		REF	
			C.T + T/T	1.59 (0.42–6.04)	0.493	1.21 (0.33–4.38)	4.38
	Donor NCAN rs2228603	Additive	C/C	REF		REF	
	"C" allele is WT		C/T	1.30 (0.22–7.64)	0.772	1.03 (0.20–5.26)	0.970
	C/C = 38, C/T = 7, T/T = 0		T/T	NA		NA	
		Recessive	T/T	REF		REF	
			C/T+C/C	NA		NA	
		Dominant	C/C	REF		REF	
			C.T + T/T	1.30 (0.22–7.64)	0.772	1.03 (0.20–5.26)	0.970
9	Recipient KLF6 rs3750861	Additive	C/C	REF		REF	
	"C" allele is WT		C/T	0.83 (0.23–3.06)	0.779	0.56 (0.13–2.39)	0.436
	C/C = 38, C/T = 7, T/T = 0		T/T	NA		NA	
		Recessive	C/T+C/C	REF		REF	
			T/T	NA		NA	
		Dominant	C/C	REF		REF	
			CT + T/T	0.83 (0.23–3.06)	0.779	0.56 (0.13–2.39)	0.436
	Donor KLF6 rs3750861	Additive	C/C	REF		REF	
	"C" allele is WT		C/T	1.19 (0.10–14.14)	0.893	0.93 (0.08–11.16)	0.957
	C/C = 43, C/T = 3, T/T = 0		T/T	NA		NA	
		Recessive	C/T+C/C	REF		REF	
			T/T	NA		NA	
		Dominant	C/C	REF		REF	
			CT + T/T	1.89 (0.10–14.14)	0.893	0.93 (0.08–11.16)	0.957
10	Recipient COL13A1 rs1227756	Additive	G/G	REF		REF	
	"G" allele is WT		A/G	2.45 (0.63–9.49)	0.368	1.14 (0.29–4.55)	0.701
	A/A = 17, A/G = 22, G/G = 15		A/A	2.10 (0.51–8.67)	0.635	0.83 (0.19–3.72)	0.696
		Recessive	A/G+G/G	REF		REF	

Table 7. (*continued*)

	SNPs, dominant allele, frequencies of the allele	Model	Genotype	Any NAFLD		Moderate to severe NAFLD	
				Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
			A/A	1.25 (0.38–4.12)	0.714	0.77 (0.22–2.67)	0.679
		Dominant	G/G	REF		REF	
			A/G+A/A	2.29 (0.68–7.69)	0.182	1.00 (0.28–3.54)	1.00
	Donor COL13A1 rs1227756	Additive	G/G	REF		REF	
	"G" allele is WT		A/G	0.82 (0.20–3.37)	0.960	0.38 (0.09–1.54)	0.048
	A/A = 4, A/G = 29, G/G = 12		A/A	NA		3 (0.24–37.67)	
		Recessive	A/G+G/G	REF		REF	
			A/A	NA		5.79 (0.55–60.87)	0.144
		Dominant	G/G	REF		REF	
			A/G+A/A	1.00 (0.25–4.06)	1.000	0.5 (0.13–1.92)	0.312
11	Recipient GCKR rs780094	Additive	T/T	REF		REF	
	"T" allele is WT		C/T	1.18 (0.32–4.42)	0.330	1.83 (0.40–8.49)	0.942
	C/C = 16, C/T = 24, T/T = 14		C/C	4.33 (0.85–22.23)	0.056	3.67 (0.73–18.33)	0.117
		Recessive	C/T+T/T	REF		REF	
			C/C	3.90 (0.95–15.94)	0.058	2.45 (0.74–8.19)	0.144
		Dominant	T/T	REF		REF	
			C/T+C/C	1.86 (0.54–6.37)	0.325	2.44 (0.59–10.16)	0.219
	Donor GCKR rs780094	Additive	T/T	REF		REF	
	"T" allele is WT		C/T	NA		NA[a]	
	C/C = 17, C/T = 21, T/T = 5		C/C	NA		NA[a]	
		Recessive	C/T+T/T	REF		REF	
			C/C	1.27 (0.34–4.75)	0.722	0.74 (0.21–2.63)	0.646
		Dominant	T/T	REF		REF	
			C/T+C/C	NA		NA[a]	
12	Recipient ACSL4 rs7887981	Additive	T/T	REF		REF	
	"T" allele is WT		C/T	1.65 (0.37–7.37)	0.272	0.54 (0.12–2.38)	0.787
	C/C = 9, C/T = 11, T/T = 34		C/C	0.50 (0.11–2.19)	0.217	0.18 (0.02–1.59)	0.211
		Recessive	C/T+T/T	REF		REF	
			C/C	0.44 (0.10–1.88)	0.269	0.21 (0.02–1.79)	0.152
		Dominant	T/T	REF		REF	
			C/T+C/C	0.93(0.30–2.88)	0.898	0.36(0.10–1.30)	0.118
	Donor ACSL4 rs7887981	Additive	T/T	REF		REF	
	"T" allele is WT		C/T	0.89 (0.27–3.11)	0.459	0.21 (0.05–0.93)	0.330
	C/C = 5, C/T = 17, T/T = 26		C/C	2.50 (0.24–25.68)	0.403	0.25 (0.03–2.55)	0.601
		Recessive	C/T+T/T	REF		REF	
			C/C	2.62 (0.27–25.44)	0.408	0.42 (0.04–4.11)	0.458
		Dominant	T/T	REF		REF	
			C/T+C/C	1.09 (0.34–3.54)	0.881	0.22 (0.06–0.84)	0.027
13	Recipient PEMT rs7946						
	"C" allele is the WT	Additive	C/C	REF		REF	
	C/C = 0, C/T = 3, T/T = 52		C/T	NA		NA[a]	
			T/T	NA		NA[a]	

Table 7. (*continued*)

	SNPs, dominant allele, frequencies of the allele	Model	Genotype	Any NAFLD		Moderate to severe NAFLD	
				Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
		Recessive	C/T+C/C	REF		REF	
			T/T	NA		NA[a]	
		Dominant	C/C	REF		REF	
			C/T+T/T	NA		NA[a]	
	Donor PEMT rs7946						
	"C" allele is the WT	Additive	C/C	REF		REF	
	C/C = 0, C/T = 0, T/T = 48		C/T	NA		NA[a]	
			T/T	NA		NA[a]	
		Recessive	T/T	REF		REF	
			C/T+C/C	NA		NA[a]	
		Dominant	C/C	REF		REF	
			C/T+T/T	NA		NA[a]	
14	Recipient ENPP1 rs1044498						
	"A" allele is the WT	Additive	A/A	REF		REF	
	A/A = 42, A/C = 10, C/C = 1		A/C	0.37 (0.09–1.52)	0.964	0.5 (0.09–2.68)	0.966
			C/C	NA		NA[a]	
		Recessive	A/C+A/A	REF		RAF	
			C/C	NA		NA[a]	
		Dominant	A/A	REF		REF	
			A/C+C/C	0.46(0.12–1.78)	0.262	0.75 (0.17–3.28)	0.70
	Donor ENPP1 rs1044498						
	"A" allele is the WT	Additive	A/A	REF		REF	
	A/A = 31, A/C = 9, C/C = 6		A/C	0.44 (0.10–1.99)	0.289	1.68 (0.37–7.64)	0.547
			C/C	1.10 (0.17–6.99)	0.594	1.05 (1.16–6.72)	0.824
		Recessive	A/C+A/A	REF		REF	
			C/C	1.33 (0.22–8.16)	0.756	0.93 (0.15–5.72)	0.936
		Dominant	A/A	REF		REF	
			A/C+C/C	0.63 (0.18–2.20)	0.468	1.40 (0.39–5.03)	0.610
15	Recipient PPARG rs1805192						
	"C" allele is the WT	Additive	C/C	REF		REF	
	C/C = 55, C/G = 0, G/G = 0		C/G	NA		NA	
			G/G	NA		NA	
		Recessive	C/G+C/C	REF		REF	
			G/G	NA		NA	
		Dominant	C/C	REF		REF	
			C/G+G/G	NA		C/G	
	Donor PPARG rs1805192						
	"C" allele is the WT	Additive	C/C	REF		REF	
	C/C = 52, C/G = 0, G/G = 0		C/G	NA		NA	
			G/G	NA		NA	
		Recessive	G/G	REF		REF	
			C/G+C/C	NA		NA	

Table 7. (*continued*)

	SNPs, dominant allele, frequencies of the allele	Model	Genotype	Any NAFLD		Moderate to severe NAFLD	
				Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
		Dominant	C/C	REF		REF	
			C/G+G/G	NA		C/G	
16	Recipient CD14_rs2569190						
	"A" allele is the WT	Additive	A/A	REF		REF	
	A/A = 15, A/G = 31, G/G = 9		A/G	0.39 (0.10–1.49)	0.081	0.61 (0.17–2.23)	0.319
			G/G	1.27 (0.18–8.89)	0.412	1.20 (0.23–6.39)	0.568
		Recessive	A/G+A/A	REF		REF	
			G/G	2.46 (0.46–13.18)	0.292	1.65 (0.39–7.06)	0.497
		Dominant	A/A	REF		REF	
			A/G+G/G	0.49 (0.13–1.81)	0.287	0.72 (0.21–2.46)	0.603
	Donor CD14_rs2569190						
	"A" allele is the WT	Additive	A/A	REF		REF	
	A/A = 9, A/G = 30, G/G = 8		A/G	0.57 (0.10–3.27)	0.919	0.96 (0.21–4.28)	0.542
			G/G	0.29 (0.04–2.32)	0.244	0.42 (0.05–3.31)	0.344
		Recessive	A/G+A/A	REF		REF	
			G/G	0.44 (0.10–2.08)	0.303	0.43 (0.08–2.41)	0.338
		Dominant	A/A	REF		REF	
			A/G+G/G	0.49 (0.09–2.69)	0.412	0.82 (0.19–3.64)	3.54
17	Recipient NR1I2 rs2461823						
	"T" allele is the WT	Additive	T/T	REF		REF	
	C/C = 15, C/T = 31, T/T = 9		C/T	1.68 (0.37–7.64)	0.324	1.27 (0.18–8.89)	0.761
			C/C	0.91 (0.17–4.81)	0.589	2.53 (0.45–14.20)	0.190
		Recessive	C/T+T/T	REF		REF	
			C/C	0.62 (0.18–2.05)	0.430	0.61 (0.16–2.25)	0.454
		Dominant	T/T	REF		REF	
			C/T+C/C	1.37 (0.32–5.79)	0.673	2.05 (0.38–11.03)	0.402
	Donor NR1I2 rs2461823						
	"T" allele is the WT	Additive	T/T	REF		REF	
	C/C = 11, C/T = 21, T/T = 12		C/T	3.50 (0.79–15.49)	0.213	3.08 (0.53–17.80)	0.538
			C/C	2.45 (0.79–15.49)	0.213	4.17 (0.61–28.62)	0.251
		Recessive	C/T+T/T	REF		REF	
			C/C	1.14 (0.28–4.67)	0.858	1.92 (0.47–7.77)	0.362
		Dominant	T/T	REF		REF	
			C/T+C/C	3.08 (0.78–12.11)	0.108	3.42 (0.64–18.25)	0.150
18	Recipient IRS1 rs1801278						
	"C" allele is the WT	Additive	C/C	REF		REF	
	C/C = 46, C/T = 5, T/T = 0		C/T	0.12 (0.01–1.18)	0.069	0.47 (0.05–4.55)	0.514
			T/T	NA		NA	
		Recessive	C/T+C/C	REF		REF	
			T/T	NA		NA	
		Dominant	C/C	REF		REF	
			C/T+T/T	0.12 (0.01–1.18)	0.069	0.47 (0.05–4.55)	0.514

Table 7. (*continued*)

	SNPs, dominant allele, frequencies of the allele	Model	Genotype	Any NAFLD		Moderate to severe NAFLD	
				Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
	Donor IRS1 rs1801278						
	"C" allele is the WT	Additive	C/C	REF		REF	
	C/C = 36, C/T = 7, T/T = 1		C/T	0.85 (0.17–4.37)	0.968	1.50 (0.29–7.81)	0.969
			T/T	NA		NA	
		Recessive	C/T+C/C	REF		REF	
			T/T	NA		NA	
		Dominant	C/C	REF		REF	
			C/T+T/T	1.06 (0.22–5.15)	0.942	2.00 (0.43–9.42)	0.381
19	Recipient LCP1_rs7324845						
	"G" allele is the WT	Additive	G/G	REF		REF	
	G/G = 0, A/G = 4, A/A = 50		A/G	NA		NA	
			A/A	NA		NA	
		Recessive	A/G+G/G	REF		REF	
			A/A	1.78 (0.23–13.72)		NA	
		Dominant	G/G	REF		REF	
			A/G+A/A	NA		NA	
	Donor LCP1_rs7324845						
	"G" allele is the WT	Additive	G/G	REF		REF	
	G/G = 1, A/G = 14, A/A = 31		A/G	NA		NA	
			A/A	NA		NA	
		Recessive	A/G+G/G	REF		REF	
			A/A	1.63 (0.45–5.93)	0.459	1.99 (0.52–7.65)	0.319
		Dominant	G/G	REF		REF	
			A/G+A/A	NA		NA	
20	Recipient LPPR4 rs12743824						
	"C" allele is the WT	Additive	C/C	REF		REF	
	A/A = 11, A/C = 19, C/C = 15		A/C	0.23 (0.05–1.06)	0.049	0.16 (0.03–0.81)	0.027
			A/A	0.67 (0.11–4.17)	0.664	0.73 (0.15–3.47)	0.421
		Recessive	A/C+C/C	REF		REF	
			A/A	1.65 (0.37–7.37)	0.512	1.74 (0.44–6.98)	0.433
		Dominant	C/C	REF		REF	
			A/C+A/A	0.33 (0.08–1.40)	0.133	0.32 (0.09–1.17)	0.084
	Donor LPPR4 rs12743824						
	"C" allele is the WT	Additive	C/C	REF		REF	
	A/A = 6, A/C = 19, C/C = 7		A/C	0.55 (0.08–3.59)	0.852	0.48 (0.08–2.92)	0.488
			A/A	0.40 (0.04–3.96)	0.514	0.67 (0.07–6.41)	0.972
		Recessive	A/C+C/C	REF		REF	
			A/A	0.63 (0.11–3.72)	0.606	1.13 (0.17–7.45)	0.903
		Dominant	C/C	REF		REF	
			A/C+A/A	0.51 (0.08–3.14)	0.467	0.52 (0.09–2.93)	0.458
21	Recipient ABCC2 rs8187710						
	"G" allele is the WT	Additive	G/G	REF		REF	

Table 7. (*continued*)

	SNPs, dominant allele, frequencies of the allele	Model	Genotype	Any NAFLD		Moderate to severe NAFLD	
				Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
	A/A = 1, A/G = 6, G/G = 48		A/G	1.20 (0.20–7.22)	0.966	2.00 (0.36–11.05)	0.967
			A/A	NA		NA	
		Recessive	A/G+G/G	REF		REF	
			A/A	NA		NA	
		Dominant	G/G	REF		REF	
			A/G+A/A	0.80 (0.16–3.99)	0.786	1.50 (0.29–7.52)	0.622
	Donor ABCC2 rs8187710						
	"G" allele is the WT	Additive	G/G	REF		REF	
	A/A = 0, A/G = 6, G/G = 42		A/G	3.08 (0.33–28.77)	0.324	1.80 (0.32–10.06)	0.503
			A/A	NA		NA	
		Recessive	A/G+G/G	REF		REF	
			A/A	NA		NA	
		Dominant	G/G	REF		REF	
			A/G+A/A	3.08 (0.33–28.77)	0.324	1.80 (0.32–10.06)	0.503
22	Recipient TM6SF2 rs58542926						
	"C" allele is the WT	Additive	C/C	REF		REF	
	C/C = 44, C/T = 8, T/T = 3		C/T	1.89 (0.34–10.46)	0.240	1.93 (0.42–8.84)	0.962
			T/T	0.32 (0.03–3.74)	0.257	NA	
		Recessive	C/T+C/C	REF		REF	
			T/T	0.29 (0.02–3.39)	0.322	NA	
		Dominant	C/C	REF		REF	
			C/T+T/T	1.10 (0.28–4.34)	0.890	1.11 (0.28–4.38)	0.887
	Donor TM6SF2 rs58542926						
	"C" allele is the WT	Additive	C/C	REF		REF	
	C/C = 42, C/T = 5, T/T = 0		C/T	0.83 (0.13–5.57)	0.851	1.08 (0.16–7.20)	0.934
			T/T	NA		NA	
		Recessive	C/T+C/C	REF		REF	
			T/T	NA		NA	
		Dominant	C/C	REF		REF	
			C/T+T/T	0.83 (0.13–5.57)	0.851	1.08 (0.16–7.20)	0.934
23	Recipient TCF7L2 rs7903146						
	"C" allele is the WT	Additive	C/C	REF		REF	
	C/C = 27, C/T = 22, T/T = 5		C/T	3.73 (0.83–16.71)	0.216	3.73 (0.83–16.71)	0.216
			T/T	2.00 (0.16–24.33)	0.977	2.00 (0.16–24.33)	0.977
		Recessive	C/T+C/C	REF		REF	
			T/T	2.76 (0.29–26.55)	0.380	0.47 (0.05–4.55)	0.515
		Dominant	C/C	REF		REF	
			C/T+T/T	1.60 (0.53–4.82)	0.404	1.40 (0.45–4.36)	0.564
	Donor TCF7L2 rs7903146						
	"C" allele is the WT	Additive	C/C	REF		REF	
	C/C = 28, C/T = 19, T/T = 1		C/T	0.56 (0.13–2.52)	0.968	0.56 (0.13–2.52)	0.968
			T/T	NA		NA	

Table 7. (*continued*)

	SNPs, dominant allele, frequencies of the allele	Model	Genotype	Any NAFLD		Moderate to severe NAFLD	
				Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
		Recessive	C/T+C/C	REF		REF	
			T/T	NA		NA	
		Dominant	C/C	REF		REF	
			C/T+T/T	0.68 (0.21–2.19)	0.517	1.14 (0.34–3.83)	0.836
24	Recipient UCP3 rs11235972						
	"G" allele is the WT	Additive	G/G	REF		REF	
	A/A = 1, A/G = 18, G/G = 33		A/G	0.81 (0.25–2.60)	0.968	1.00 (0.30–3.38)	0.971
			A/A	NA		NA	
		Recessive	A/G+G/G	REF		REF	
			A/A	NA		NA	
		Dominant	G/G	REF		REF	
			A/G+A/A	NA		0.92 (0.28–3.09)	0.897
	Donor UCP3 rs11235972						
	"G" allele is the WT	Additive	G/G	REF		REF	
	A/A = 1, A/G = 11, G/G = 35		A/G	0.55 (0.14–2.20)	0.968	0.24 (0.04–1.25)	0.976
			A/A	NA		NA	
		Recessive	A/G+G/G	REF		REF	
			A/A	NA		NA	
		Dominant	G/G	REF		REF	
			A/G+A/A	0.64 (0.17–2.48)	0.520	0.21 (0.04–1.11)	0.066
25	Recipient ADIPOQ rs1501299						
	"G" allele is the WT	Additive	G/G	REF		REF	
	G/G = 32, G/T = 20, T/T = 3		G/T	0.56 (0.18–1.76)	0.845	0.71 (0.22–2.36)	0.760
			T/T	0.23 (0.02–2.81)	0.346	0.83 (0.07–10.20)	0.991
		Recessive	T/T	REF		REF	
			G/T+G/G	0.29 (0.02–3.39)	0.322	0.95 (0.08–11.14)	0.964
		Dominant	G/G	REF		REF	
			G/T+T/T	0.50 (0.16–1.50)	0.215	0.73 (0.23–2.28)	0.587
	Donor ADIPOQ rs1501299						
	"G" allele is the WT	Additive	G/G	REF		REF	
	G/G = 24, G/T = 15, T/T = 5		G/T	1.20 (0.31–4.65)	0.753	2.13 (0.56–8.14)	0.480
			T/T	2.40 (0.23–29.96)	0.503	1.62 (0.22–11.89)	0.914
		Recessive	G/T+G/G	REF		REF	
			T/T	2.24 (0.23–22.05)	0.489	1.19 (0.18–8.00)	0.858
		Dominant	G/G	REF		REF	
			G/T+T/T	1.40 (0.40–4.96)	0.602	1.99 (0.57–6.90)	0.280
26	Recipient EFCAB4B rs887304						
	"T" allele is the WT	Additive	T/T	REF		REF	
	C/C = 31, C/T = 22, T/T = 2		C/T	NA		NA	
			C/C	NA		NA	
		Recessive	C/T+T/T	REF		REF	
			C/C	0.95 (0.32–2.85)	0.927	1.75 (0.57–5.37)	0.331

Table 7. (*continued*)

	SNPs, dominant allele, frequencies of the allele	Model	Genotype	Any NAFLD		Moderate to severe NAFLD	
				Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
		Dominant	T/T	REF		REF	
			C/T+C/C	NA		NA	
	Donor EFCAB4B rs887304						
	"T" allele is the WT	Additive	T/T	REF		REF	
	C/C = 35, C/T = 12, T/T = 2		C/T	NA		NA	
			C/C	NA		NA	
		Recessive	C/T+T/T	REF		REF	
			C/C	0.83 (0.23–3.01)	0.781	NA	
		Dominant	T/T	REF		REF	
			C/T+C/C	NA		NA	
27	Recipient TNF rs361525						
	"G" allele is the WT	Additive	G/G	REF		REF	
	A/A = 31, A/G = 22, G/G = 2		A/G	1.33 (0.30–6.03)	0.971	1.00 (0.22–4.56)	0.968
			A/A	NA		NA	
		Recessive	A/G+G/G	REF		REF	
			A/A	NA		NA	
		Dominant	G/G	REF		REF	
			A/G+A/A	1.56 (0.36–6.82)	0.558	1.33 (0.33–5.46)	0.698
	Donor TNF rs361525						
	"G" allele is the WT	Additive	G/G	REF		REF	
	A/A = 0, A/G = 2, G/G = 44		A/G	0.57 (0.03–9.77)	0.699	1.93 (0.11–33.12)	0.649
			A/A	NA		NA	
		Recessive	A/G+G/G	REF		REF	
			A/A	NA		NA	
		Dominant	G/G	REF		REF	
			A/G+A/A	0.57 (0.03–9.77)	0.699	1.93 (0.11–33.12)	0.649
28	Recipient APOE rs7412						
	"C" allele is the WT	Additive	C/C	REF		REF	
	C/C = 49, C/T = 5, T/T = 1		C/T	2.53 (0.26–24.41)	0.962	0.43 (0.04–4.16)	0.975
			T/T	NA		NA	
		Recessive	C/T+C/C	REF		REF	
			T/T	NA		NA	
		Dominant	C/C	REF		REF	
			C/T+TT	1.27 (0.21–7.60)	0.796	0.34 (0.04–3.19)	0.348
	Donor APOE rs7412						
	"C" allele is the WT	Additive	C/C	REF		REF	
	C/C = 29, C/T = 20, T/T = 5		C/T	1.83 (0.42–7.91)		1.17 (0.31–4.42)	0.813
			T/T	NA		NA	
		Recessive	C/T+C/C	REF		REF	
			T/T	NA		NA	
		Dominant	C/C	REF		REF	
			C/T+TT	1.83 (0.42–7.91)	0.421	1.17 (0.31–4.42)	0.813

Table 7. (*continued*)

	SNPs, dominant allele, frequencies of the allele	Model	Genotype	Any NAFLD		Moderate to severe NAFLD	
				Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
29	Recipient FABP2 rs1799883						
	"T" allele is the WT	Additive	T/T	REF		REF	
	C/C = 29, C/T = 20, T/T = 5		C/T	1.24 (0.17–9.25)	0.722	2.15 (0.20–23.18)	0.671
			C/C	0.94 (0.14–6.55)	0.797	2.44 (0.24–24.78)	0.476
		Recessive	C/T+T/T	REF		REF	
			C/C	0.95 (0.15–6.20)	0.957	0.43 (0.05–4.16)	0.466
		Dominant	T/T	REF		REF	
			C/T+C/C	1.26 (0.42–3.78)	0.686	0.77 (0.25–2.38)	0.649
	Donor FABP2 rs1799883						
	"T" allele is the WT	Additive	T/T	REF		REF	
	C/C = 29, C/T = 12, T/T = 4		C/T	NA		0.03 (0.00–0.64)	0.025
			C/C	NA		0.20 (0.02–2.21)	0.856
		Recessive	C/T+T/T	REF		REF	
			C/C	NA		7.25 (0.68–76.87)	0.100
		Dominant	T/T	REF		REF	
			C/T+C/C	0.91 (0.26–3.12)		0.55 (0.14–2.12)	0.382
30	Recipient LIPC rs1800588						
	"C" allele is the WT	Additive	C/C	REF		REF	
	C/C = 35, C/T = 17, T/T = 3		C/T	0.84 (0.26–2.76)	0.753	1.53 (0.46–5.08)	0.638
			T/T	1.18 (0.10–14.35)	0.842	1.09 (0.09–13.35)	0.921
		Recessive	C/T+C/C	REF		REF	
			T/T	1.25 (0.11–14.70)	0.859	0.95 (0.08–11.14)	0.964
		Dominant	C/C	REF		REF	
			C/T+CT/T	0.87 (0.29–2.74)	0.834	1.46 (0.46–4.57)	0.521
	Donor LIPC rs1800588						
	"C" allele is the WT	Additive	C/C	REF		REF	
	C/C = 27, C/T = 14, T/T = 5		C/T	0.47 (0.12–1.83)	0.572	0.94 (0.25–3.62)	0.649
			T/T	0.09 (0.01–0.92)	0.079	0.43 (0.04–4.35)	0.479
		Recessive	C/T+C/C	REF		REF	
			T/T	0.12 (0.01–1.44)	0.065	0.43 (0.04–4.24)	0.473
		Dominant	C/C	REF		REF	
			C/T+CT/T	0.32 (0.09–1.10)	0.069	0.79 (0.23–2.72)	0.702
31	Recipient ADRB2 rs1042714						
	"G" allele is the WT	Additive	G/G	REF		REF	
	C/C = 13, C/G = 29, G/G = 13		C/G	1.02 (0.27–3.93)	0.968	0.61 (0.15–2.43)	0.257
			C/C	1.00 (0.21–4.87)	0.987	1.37 (0.29–6.54)	0.392
		Recessive	C/G+C/G	REF		REF	
			C/C	0.98 (0.26–3.76)	0.974	2.25 (0.58–8.78)	0.734
		Dominant	G/G	REF		REF	
			C/G+C/C	1.02 (0.28–3.65)	0.981	0.80 (0.22–2.90)	0.734
	Donor ADRB2 rs1042714						
	"G" allele is the WT	Additive	G/G	REF		REF	

Table 7. (*continued*)

	SNPs, dominant allele, frequencies of the allele	Model	Genotype	Any NAFLD		Moderate to severe NAFLD	
				Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
	C/C = 28, C/G = 20, G/G = 2		C/G	2.33 (0.12–43.79)	0.475	NA	
			C/C	1.56 (0.09–27.36)	0.989	NA	
		Recessive	C/G+G/G	REF		REF	
			C/C	0.72 (0.22–2.34)	0.587	1.13 (0.36–3.59)	0.833
		Dominant	G/G	REF		REF	
			C/G+C/C	1.82 (0.11–31.03)	0.679	NA	
32	Recipient GCLC rs17883901						
	"G" allele is the WT	Additive	G/G	REF		REF	
	A/A = 1, A/G = 12, G/G = 42		A/G	0.86 (0.23–3.18)	0.968	0.90 (0.23–3.49)	0.971
			A/A	NA		NA	
		Recessive	A/G+G/G	REF		REF	
			A/A	NA		NA	
		Dominant	G/G	REF		REF	
			A/G+A/A	0.99 (0.27–3.54)	0.981	0.80 (0.21–3.04)	0.743
	Donor GCLC rs17883901						
	"G" allele is the WT	Additive	G/G	REF		REF	
	A/A = 0, A/G = 6, G/G = 44		A/G	0.26 (0.04–1.58)	0.143	0.79 (0.13–4.82)	0.802
			A/A	NA		NA	
		Recessive	A/G+G/G	REF		REF	
			A/A	NA		NA	
		Dominant	G/G	REF		REF	
			A/G+A/A	0.26 (0.04–1.58)	0.143	0.79 (0.13–4.82)	0.802
33	Recipient LOC157273 rs4240624						
	"G" allele is the WT	Additive	G/G	REF		REF	
	A/A = 41, A/G = 13, G/G = 0		A/G	NA		NA	
			A/A	NA		NA	
		Recessive	A/G+G/G	REF		REF	
			A/A	0.98 (0.27–3.52)	0.971	2.13 (0.51–8.96)	0.301
		Dominant	G/G	REF		REF	
			A/G+A/A	NA		NA	
	Donor LOC157273 rs4240624						
	"G" allele is the WT	Additive	G/G	REF		REF	
	A/A = 41, A/G = 13, G/G = 0		A/G	NA		0.68 (0.03–14.03)	0.972
			A/A	NA		0.48 (0.03–8.42)	0.534
		Recessive	A/G+G/G	REF		REF	
			A/A	0.46(0.10–2.05)		0.67 (0.17–2.63)	0.563
		Dominant	G/G	REF		REF	
			A/G+A/A	NA		0.52 (0.03–8.93)	0.651
34	Recipient PNPLA3 rs738408						
	"C" allele is the WT	Additive	C/C	REF		REF	
	C/C = 16, C/T = 31, T/T = 6		C/T	2.04 (0.37–11.22)	0.491	2.04 (0.37–11.22)	0.491
			T/T	1.40 (0.10–19.01)	0.986	1.40 (0.10–19.01)	0.986

Table 7. (*continued*)

	SNPs, dominant allele, frequencies of the allele	Model	Genotype	Any NAFLD		Moderate to severe NAFLD	
				Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
		Recessive	C/T+C/C	REF		REF	
			T/T	1.24 (0.21–7.48)	0.814	2.13 (0.38–11.84)	0.386
		Dominant	C/C	REF			
			C/T+T/T	0.99 (0.29–3.31)	0.981	1.19 (0.34–4.12)	0.784
	Donor PNPLA3 rs738408						
	"C" allele is the WT	Additive	C/C	REF		REF	
	C/C = 34, C/T = 12, T/T = 0		C/T	2.33 (0.53–10.35)	0.265	2.09 (0.55–7.99)	0.281
			T/T	NA		NA	
		Recessive	C/T+C/C	REF		REF	
			T/T	NA		NA	
		Dominant	C/C	REF		REF	
			C/T+T/T	1.24 (0.31–4.95)	0.763	2.09 (0.55–7.99)	0.281
35	Recipient HFE rs1800562						
	"G" allele is the WT	Additive	G/G	REF		REF	
	A/A = 0, G/A = 8, G/G = 47		G/A	1.03 (0.22–4.86)	0.966	2.13 (0.47–9.71)	0.327
			A/A	NA		NA	
		Recessive	G/A+G/G	REF		REF	
			A/A	NA		NA	
		Dominant	G/G	REF		REF	
			G/G+A/A	1.03 (0.22–4.86)	0.966	2.13 (0.47–9.71)	0.327
	Donor HFE rs1800562						
	"G" allele is the WT	Additive	G/G	REF		REF	
	A/A = 0, G/A = 2, G/G = 48		G/A	0.60 (0.04–10.20)	0.724	NA	
			A/A	NA		NA	
		Recessive	G/A+G/G	REF		REF	
			A/A	NA		NA	
		Dominant	G/G	REF		REF	
			G/G+A/A	0.60 (0.04–10.20)	0.724	NA	
36	Recipient ADIPOQ RS2241766						
	"T" allele is the WT	Additive	T/T	REF		REF	
	G/G = 14, G/T = 0, T/T = 40		G/T	NA		NA	
			G/G	1.20 (0.34–4.24)	0.777	0.74 (0.20–2.81)	0.661
		Recessive	G/T+T/T	REF		REF	
			G/G	1.20 (0.34–4.24)	0.777	0.74 (0.20–2.81)	0.661
		Dominant	T/T	REF		REF	
			G/T+G/G	1.20 (0.34–4.24)	0.777	0.74 (0.20–2.81)	0.661
	Donor ADIPOQ RS2241766						
	"T" allele is the WT	Additive	T/T	REF		REF	
	G/G = 9, G/T = 10, T/T = 25		G/T	5.06 (0.50–46.68)	0.167	2.13 (0.48–9.50)	0.513
			G/G	1.13 (0.23–5.62)	0.444	1.70 (0.36–8.09)	0.842
		Recessive	G/T+T/T	REF		REF	
			G/G	0.80 (0.17–3.84)	0.780	1.35 (0.31–5.96)	0.689

Table 7. (*continued*)

	SNPs, dominant allele, frequencies of the allele	Model	Genotype	Any NAFLD		Moderate to severe NAFLD	
				Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
		Dominant	T/T	REF		REF	
			G/T+G/G	2.11 (0.54–8.32)	0.286	1.91 (0.56–6.55)	0.302
37	Recipient LPIN1 rs13412852						
	"C" allele is the WT	Additive	C/C	REF		REF	
	C/C = 22, C/T = 27, T/T = 6		C/T	1.64 (0.50–5.38)	0.110	1.47 (0.45–4.80)	0.254
			T/T	0.35 (0.05–2.31)	0.154	0.43 (0.04–4.39)	0.360
		Recessive	C/T+C/C	REF		REF	
			T/T	0.27 (0.04–1.60)	0.148	0.34 (0.04–3.19)	0.348
		Dominant	C/C	REF		REF	
			C/T+T/T	1.21 (0.40–3.66)	0.734	1.22 (0.39–3.84)	0.729
	Donor LPIN1 rs13412852						
	"C" allele is the WT	Additive	C/C	REF		REF	
	C/C = 22, C/T = 22, T/T = 1		C/T	1.85 (0.52–6.55)	0.973	1.00 (0.30–3.33)	0.969
			T/T	NA		NA	
		Recessive	C/T+C/C	REF		REF	
			T/T	NA		NA	
		Dominant	C/C	REF		REF	
			C/T+T/T	1.96 (0.57–6.92)	0.295	0.93 (0.28–3.06)	0.903
38	Recipient NR1I2 rs2461823						
	"T" allele is the WT	Additive	T/T	REF		REF	
	C/C = 15, C/T = 31, T/T = 9		C/T	1.68 (0.37–7.64)	0.324	2.53 (0.45–14.20)	0.189
			C/C	0.91 (0.17–4.81)	0.589	1.27 (0.18–8.89)	0.761
		Recessive	C/T+T/T	REF		REF	
			C/C	0.73 (0.17–3.11)	0.673	0.49 (0.09–2.62)	0.402
		Dominant	T/T	REF		REF	
			C/T+C/C	1.63 (0.49–5.42)	0.430	1.65 (0.45–6.12)	0.454
	Donor NR1I2 rs2461823						
	"T" allele is the WT	Additive	T/T	REF		REF	
	C/C = 11, C/T = 21, T/T = 12		C/T	3.50 (0.79–15.49)	0.213	3.08 (0.53–17.80)	0.538
			C/C	2.45 (0.47–13.16)	0.713	4.18 (0.61–28.62)	0.251
		Recessive	C/C	REF		REF	
			C/T+T/T	0.33 (0.08–1.28)	0.108	0.29 (0.06–1.56)	0.150
		Dominant	T/T	REF		REF	
			C/T+C/C	0.88 (0.21–3.61)	0.858	0.52 (0.13–2.12)	0.362
39	Recipient ADRB3 rs4994						
	"A" allele is the WT	Additive	A/A	REF		REF	
	A/A = 42, A/G = 10, G/G = 2		A/G	7.44 (0.86–64.05)	0.100	0.86 (0.19–3.83)	0.617
			G/G	0.83 (0.05–14.11)	0.431	2.00 (0.12–34.41)	0.599
		Recessive	G/G	REF		REF	
			A/G+A/A	0.63 (0.04–10.57)	0.745	2.06 (0.12–34.95)	0.617
		Dominant	A/G+G/G	REF		REF	
			A/A	4.13 (0.81–21.19)	0.089	1.00 (0.26–3.90)	1.000

Table 7. (*continued*)

	SNPs, dominant allele, frequencies of the allele	Model	Genotype	Any NAFLD		Moderate to severe NAFLD	
				Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
	Donor ADRB3 rs4994						
	"A" allele is the WT	Additive	A/A	REF		REF	
	A/A = 40, A/G = 4, G/G = 0		A/G	0.67 (0.09–5.23)	0.700	0.56 (0.05–5.84)	0.625
			G/G	NA		NA	
		Recessive	G/G	REF		REF	
			A/G+A/A	NA		NA	
		Dominant	A/A	REF		REF	
			A/G+G/G	0.67 (0.09–5.23)	0.700	0.56 (0.05–5.84)	0.625
40	Recipient PPARA rs1800234						
	"T" allele is the WT T/T = 55		NA			NA	
	Donor PPARA rs1800234						
	"T" allele is the WT T/T = 51		NA			NA	
41	Recipient ADIPOR1 rs10920533						
	"G" allele is the WT	Additive	G/G	REF		REF	
	A/A = 9, A/G = 26, G/G = 19		A/G	1.23 (0.37–4.03)	0.265	3.91 (0.91–16.81)	0.494
			A/A	7.20 (0.75–69.38)	0.090	6.67 (1.10–40.43)	0.113
		Recessive	A/G+G/G	REF		REF	
			A/A	6.40 (0.74–55.52)	0.092	2.77 (0.64–11.89)	0.171
		Dominant	G/G	REF		REF	
			A/G+A/A	1.7 3(0.55–5.39)	0.348	4.49 (1.11–18.23)	0.036
	Donor ADIPOR1 rs10920533						
	"G" allele is the WT	Additive	G/G	REF		REF	
	A/A = 3, A/G = 18, G/G = 26		A/G	1.15 (0.34–3.93)	0.965	1.36 (0.37–5.02)	0.946
			A/A	NA		NA	
		Recessive	A/G+G/G	REF		REF	
			A/A	NA		NA	
		Dominant	G/G	REF		REF	
			A/G+A/A	1.47 (0.44–4.85)	0.530	2.04 (0.60–6.92)	0.255
42	Recipient ADIPOR2 rs767870						
	"G" allele is the WT	Additive	G/G	REF		REF	
	A/A = 39, A/G = 15, G/G = 0		A/G	NA		NA	
			A/A	NA		NA	
		Recessive	A/G+G/G	REF		REF	
			A/A	1.07 (0.32–3.61)	0.917	0.34 (0.10–1.18)	0.089
		Dominant	G/G	REF		REF	
			A/G+A/A	NA		NA	
	Donor ADIPOR2 rs767870						
	"G" allele is the WT	Additive	G/G	REF		REF	
	A/A = 27, A/G = 16, G/G = 5		A/G			0.52 (0.07–4.00)	0.976
			A/A	1.33 (0.19–9.47)	0.724	0.28 (0.04–2.02)	0.160

Table 7. (*continued*)

	SNPs, dominant allele, frequencies of the allele	Model	Genotype	Any NAFLD		Moderate to severe NAFLD	
				Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
		Recessive	A/G+G/G	REF		REF	
			A/A	1.23 (0.37–4.05)	0.732	0.46 (0.14–1.52)	0.205
		Dominant	G/G	REF		REF	
			A/G+A/A	1.24 (0.19–8.29)	0.821	0.36 (0.05–2.38)	0.287
43	Recipient SLC38A8r s11864146						
	"A" allele is the WT	Additive	A/A	REF		REF	
	A/A = 48, A/G = 7, G/G = 0		A/G	1.64 (0.29–9.32)	0.578	2/93 (0.58–14.77)	0.192
			G/G	NA		NA	
		Recessive	A/G+A/A	REF		REF	
			G/G	NA		NA	
		Dominant	A/A	REF		REF	
			A/G+G/G	1.64 (0.29–9.32)	0.578	2.93 (0.58–14.77)	0.192
	Donor SLC38A8r s11864146						
	"A" allele is the WT	Additive	A/A	REF		REF	
	A/A = 40, A/G = 6, G/G = 0		A/G	3.00 (0.32–28.19)	0.337	1.67 (0.30–9.34)	0.561
			G/G	NA		NA	
		Recessive	A/G+A/A	REF		REF	
			G/G	NA		NA	
		Dominant	A/A	REF		REF	
			A/G+G/G	3.00 (0.32–28.19)	0.337	1.67 (0.30–9.34)	0.561
44	Recipient NR1I2 rs7643645						
	"A" allele is the WT	Additive	A/A	REF		REF	
	A/A = 17, A/G = 29, G/G = 7		A/G	2.14 (0.63–7.26)	0.696	2.85 (0.67–12.22)	0.831
			G/G	2.81 (0.42–18.73)	0.464	6.22 (0.89–43.66)	0.125
		Recessive	A/G+A/A	REF		REF	
			G/G	0.73 (0.17–3.11)	0.673	0.49 (0.09–2.62)	0.454
		Dominant	A/A	REF		REF	
			A/G+G/G	1.63 (0.49–5.42)	0.430	2.05 (0.38–11.03)	0.402
	Donor NR1I2 rs7643645						
	"A" allele is the WT	Additive	A/A	REF		REF	
	A/A = 16, A/G = 24, G/G = 4		A/G	0.84 (0.21–3.43)	0.682	1.62 (0.38–6.94)	0.925
			G/G	1.36 (0.11–16.57)	0.744	2.99 (0.31–28.83)	0.421
		Recessive	A/G+A/A	REF		REF	
			G/G	0.33 (0.08–1.23)	0.108	0.29 (0.06–1.56)	0.362
		Dominant	A/A	REF		REF	
			A/G+G/G	0.88 (0.21–3.61)	0.858	3.42 (0.64–18.25)	0.150
45	Recipient MTTP rs1800591						
	"G" allele is the WT	Additive	G/G	REF		REF	
	G/G = 36, G/T = 14, T/T = 4		G/T	1.02 (0.28–3.69)	0.694	0.98 (0.27–3.56)	0.764
			T/T	0.57 (0.07–4.50)	0.582	0.59 (0.06–6.27)	0.666
		Recessive	G/T+G/G	REF		REF	
			T/T	0.56 (0.07–4.34)	0.581	0.59 (0.06–6.13)	0.483

Table 7. (*continued*)

	SNPs, dominant allele, frequencies of the allele	Model	Genotype	Any NAFLD		Moderate to severe NAFLD	
				Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
		Dominant	G/G	REF		REF	
			G/T+T/T	0.89 (0.28–2.85)	0.842	0.92 (0.28–3.03)	0.895
	Donor MTTP rs1800591						
	"G" allele is the WT	Additive	G/G	REF		REF	
	G/G = 36, G/T = 14, T/T = 4		G/T	0.78 (0.19–3.18)		0.34 (0.06–1.90)	0.221
			T/T	NA		NA	
		Recessive	G/T+G/G	REF		REF	
			T/T	NA		1.07 (0.09–12.80)	0.957
		Dominant	G/G	REF		RE0.725F	
			G/T+T/T	0.78 (0.19–3.18)	0.725	0.88 (0.26–2.95)	0.829
46	Recipient APOE rs429358						
	"T" allele is the WT	Additive	T/T	REF		REF	
	C/C = 0, C/T = 8, T/T = 46		C/T	2.11 (0.38–11.61)	0.390	2.07 (0.45–9.42)	0.348
			C/C	NA		NA	
		Recessive	C/T+T/T	RFE		REF	
			C/C	NA		NA	
		Dominant	T/T	REF		REF	
			C/T+C/C	2.11 (0.38–11.61)	0.390	2.07 (0.45–9.42)	0.348
	Donor APOE rs429358						
	"T" allele is the WT	Additive	T/T	REF		REF	
	C/C = 1, C/T = 11, T/T = 35		C/T	0.91 (0.22–3.75)	0.970	1.60 (0.40–6.33)	0.969
			C/C	NA		NA	
		Recessive	C/T+T/T	REF		REF	
			C/C	NA		NA	
		Dominant	T/T	REF		REF	
			C/T+C/C	1.04 (0.26–4.18)	0.952	1.92 (0.51–7.24)	0.338

CI, confidence interval; NA, not applicable; NAFLD, non-alcoholic fatty liver disease; SNP, single nucleotide polymorphism.

Additional protective effect was also noted for donor HSD17B13 (A > G; rs6834314) polymorphism.

Adiponectin is an adipocytokine produced by adipocytes and have an array of biological functions (34). Adiponectin acts by binding two 7-transmembrane domain proteins and its receptors ADIPOR1 (adiponectin receptor 1) and ADIPOR2 (35). Importantly, the binding of adiponectin to ADIPOR1 and ADIPOR2 leads to the phosphorylation and activation of adenosine monophosphate-activated protein kinase to modulate cellular energy utilization. Both ADIPOR1 and ADIPOR2 knockout mice exhibit mild insulin resistance (36). In ADIPOR1/R2 double knockout mice, the binding and actions of adiponectin are abolished, resulting in increased tissue triglyceride content, inflammation, and oxidative stress (36). ADIPOR2 knockout mice reported by Liu et al. (37) displayed reduced diet-induced insulin resistance but promoted type 2 DM. These data support the physiological roles of ADIPOR1 and ADIPOR2 as the predominant receptors for adiponectin in the regulation of glucose and lipid metabolism. Interestingly, in this analysis, we noted a strong positive association for NAFLD recurrence in the presence of the minor allele form of ADIPOR1 (A/G + A/A, rs10920533).

We identified ΔBMI (mean change in the BMI from the baseline pretransplant BMI) and post-LT DM as a significant factor associated with recurrent NAFLD and NASH at 1-year after LT. Considering that weight is a modifiable variable, much emphasis should be put on controlled weight gain and structured program for weight loss after liver transplant. A recent study including using protocol imaging study have identified weight gain as an important factor driving allograft steatosis after LT, further supporting our observation (8). An earlier study has noted that BMI increased significantly more and earlier among the NAFLD patients in comparison with non-NAFLD patients (38). These findings suggest the need for multidisciplinary, early, and close weight monitoring for transplant recipients with NASH. These patients could benefit from pretransplant counseling regarding weight gain and its consequences in the posttransplant period.

The primary strength of this study is the novel characterization of both clinical and genetic components influencing post-LT

NAFLD recurrence based on liver biopsy obtained around 1 year post-LT. In addition, being a single center study, the immunosuppression was fairly uniform (steroid free and predominantly tacrolimus based) across the cohort. Moreover, the liver biopsy was reread by a single experienced hepatopathologist with significant experience in this field, obviating any interobserver variations. There is an overall paucity of data comparing donor and recipient genotypes on NAFLD recurrence. To our knowledge, this study is the largest such attempt to study the association of genotyping including 46 known associated SNPs with NAFLD and characterize its association with recurrence after LT.

However, we acknowledge that this study also carries some limitations, particularly in its retrospective design that requires a reliance on the electronic medical record. This study relied solely on results from liver biopsy obtained around 1 year post-LT to predict recurrence of NAFLD, which may not be accurately reflect overall recurrence because more patients may have developed recurrent NAFLD on subsequent years of follow-up. However, our focus was to assess outcome based on early recurrence of NAFLD to characterize patient with aggressive recurrence of NAFLD to explore the most at-risk group so that potentially we can identify groups that can be targeted for early interventions. Unfortunately, we are unable to assess the association specifically with NASH recurrence due to relatively small number of patients developing NASH in our cohort, limiting our assessment of its association with SNPs. The analysis of SNPs themselves, particularly in the translational genotyping protocol, was somewhat limited given the raw amount of tissue from liver samples obtained. There are also inherent limitations of this being a single center experience because our study cohort may not accurately represent liver recipients from other centers across the country with differences in diversity and severity of illness before transplant.

In summary, recurrent NAFLD is increasingly common even at 1-year after liver transplant with recurrence as high as two-thirds of the NASH LT recipients. NASH recurrence is relatively infrequent, but advanced fibrosis including cirrhosis is possible even at 1 year with recurrent NASH. Recurrent NAFLD is tightly linked to ΔBMI and presence of post-LT DM. We have found a strong positive association for NAFLD recurrence in the presence of the minor allele form of ADIPOR1 (A/G + A/A, rs10920533) genotype. In addition donor/recipient *SOD2* rs4880 and donor HSD17B13 rs6834314 may be associated with reduced risk of NAFLD recurrence. Larger sample sizes with multicenter prospective study design and longer follow-up periods will be ideal for future studies to confirm these genetic associations.

CONFLICTS OF INTEREST

Guarantor of the article: Sanjaya K. Satapathy, MBBS, MD, DM, MS (Epi), FACG, FASGE, AGAF, FAASLD.

Specific author contributions: Sanjaya K. Satapathy, MBBS, MD, DM, MS (Epi), FACG, FASGE, AGAF, FAASLD, and Quynh Tran, PhD, contributed equally to this work. All authors made substantial contribution to the study design, acquisition and analysis of data, drafting of the manuscript, and critical review of the content.

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Potential competing interests: S.K.S. has served as a speaker for Intercept, Alexion, Dova, as an advisory board member for Gilead, Intercept, Bayer and has received research funding from Gilead, Biotest, Genfit, Conatus, Intercept, Shire, Exact Sciences, Eananta, Dova, Bayer. All other authors declare no conflicts of interest.

LIVER

Study Highlights

WHAT IS KNOWN

✓ Recurrence of nonalcoholic fatty liver disease (NAFLD) after liver transplantation (LT) is well recognized.

WHAT IS NEW HERE

✓ There is an overall paucity of data comparing donor and recipient genotypes on NAFLD recurrence. This study has evaluated the phenotypic and genotypic association of 46 known associated single nucleotide polymorphisms with NAFLD and characterized its potential association with recurrence after LT. Increased body mass index post-LT is strongly associated with NAFLD recurrence, whereas post-LT diabetes mellitus was associated with increased severity of NAFLD recurrence. Both donor and recipient *SOD2* rs4880 and donor HSD17B13 rs6834314 single nucleotide polymorphisms may be associated with reduced risk of early NAFLD recurrence, whereas presence of the minor allele form of ADIPOR1 rs10920533 in the recipient is associated with increased severity NAFLD recurrence.

TRANSLATIONAL IMPACT

✓ Identifying patients at risk of recurrence of NAFLD through genotypic and phenotypic characteristics at transplant will help early intervention directed toward prevention of recurrence of NAFLD.

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