Published in final edited form as:

Clin Transplant. 2016 April ; 30(4): 452–460. doi:10.1111/ctr.12710.

Impact of *EGF*, *IL28B*, and *PNPLA3* polymorphisms on the outcome of allograft hepatitis C: a multicenter study

Jessica L. Mueller^{a,b,*}, Lindsay Y. King^{a,b,*}, Kara B. Johnson^{a,b}, Tian Gao^c, Lauren D. Nephew^d, Darshan Kothari^{b,e}, Mary Ann Simpson^f, Hui Zheng^g, Lan Wei^h, Kathleen E. Corey^{a,b}, Joseph Misdrajiⁱ, Joon Hyoek Lee^j, M. Valerie Lin^{a,b}, Neliswa A. Gogela^{a,b}, Bryan C. Fuchs^{b,h}, Kenneth K. Tanabe^{b,h}, Fredric D. Gordon^{b,f}, Michael P. Curry^{b,e}, and Raymond T. Chung^{a,b}

^aDivision of Gastroenterology, Department of Medicine, Massachusetts General Hospital, Boston, MA

^bHarvard Medical School, Boston, MA

^cDivision of Gastroenterology, Department of Medicine, Boston Medical Center, Boston, MA

^dDivision of Gastroenterology, Department of Medicine, University of Pennsylvania Health System, Philadelphia, PA

^eDivision of Gastroenterology, Department of Medicine, Beth Israel Deaconess Medical Center, Boston

^fDivision of Gastroenterology, Department of Medicine, Lahey Hospital & Medical Center, Burlington

^gBiostatistics Center, Massachusetts General Hospital, Boston, MA, USA

^hDivision of Surgical Oncology, Department of Surgery, Massachusetts General Hospital, Boston, MA, USA

ⁱDepartment of Pathology, Massachusetts General Hospital, Boston, MA, USA

^jDepartment of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Corresponding author: Raymond T. Chung, MD, Division of Gastroenterology, Department of Medicine, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA. Tel.: +617 724 7562; fax: +617 643 0446; rtchung@partners.org.

*These authors contributed equally to the manuscript.

Conflict of interest: None.

Authors' contributions

Lindsay Y. King, Jessica L. Mueller: Participated in research design, participated in the writing of the manuscript, participated in the performance of the research, participated in data analysis; Kara B. Johnson: Participated in research design, participated in the performance of the research; Tian Gao, Lauren D. Nephew, Darshan Kothari, Mary Ann Simpson, M. Valerie Lin, Neliswa A. Gogela: Participated in the performance of the research; Hui Zheng: Participated in data analysis; Lan Wei: Participated in the performance of the research, contributed new reagents or analytic tools, participated in data analysis; Kathleen E. Corey, Joseph Misdraji: Participated in research design, participated in writing of the manuscript; Joon Hyoek Lee: Participated in research design. Bryan C. Fuchs: Participated in the performance of the research, contributed new reagents or analytic tools, participated in writing of the manuscript; Kenneth K. Tanabe: Participated in research design, contributed new reagents or analytic tools; Fredric D. Gordon, Michael P. Curry: Participated in research design, participated in performance of the research; Raymond T. Chung: Participated in research design, participated in the writing of the manuscript, participated in data analysis, participated in the performance of the research.

Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

Abstract

Hepatitis C virus (HCV) infection is accelerated following liver transplantation (LT). Single nucleotide polymorphisms (SNPs) near the epidermal growth factor (*EGF*) (rs4444903), *IL28B* (rs12979860), and *PNPLA3* (rs738409) loci are associated with treatment response, fibrosis, and hepatocellular carcinoma in non-transplant hepatitis C, but allograft population data are limited. We sought to determine the role of these SNPs in 264 patients with HCV who underwent LT between 1990 and 2008. Genotypes were determined from donor wedge/allograft biopsies and recipient explants. Cox proportional hazards model was used to assess time to cirrhosis, liver-related death, and retransplantation, adjusting for donor age and sustained virological response (SVR). Over a median follow-up of 6.3 yr, a trend toward increased progression to graft cirrhosis was observed among recipients of an *EGF* non-AA vs. AA donor liver (adjusted HR 2.01; 95% CI 0.93–4.34; $p = 0.08$). No other genotypes predicted cirrhosis development or graft survival. The CC *IL28B* variant in both recipients and donors was associated with increased rate of SVR (R-CC/D-CC 8/12[67%], R-non-CC/D-CC or R-CC/D-non-CC 23/52[44%], R-non-CC/D-non-CC 12/45[27%], p linear trend = 0.009). Recipient *EGF*, *IL28B*, and *PNPLA3*, and donor *IL28B* and *PNPLA3* genotypes do not predict adverse outcomes in HCV LT recipients. A potential association exists between donor *EGF* genotype and cirrhosis.

Keywords

Cirrhosis; hepatitis C virus; single nucleotide polymorphism; sustained virological response; transplantation

Chronic hepatitis C (CHC) infection is the most common indication for liver transplantation (LT) in the United States. In patients with preoperative viremia, hepatitis C virus (HCV) recurrence is universal. Following LT, the course of HCV infection is accelerated, with 10–30% of recipients progressing to cirrhosis within five yr (1–3). Recurrent HCV infection significantly reduces patient and allograft survival (4). Factors associated with disease progression are complex, but include clinical and genetic characteristics of both the donor and recipient, as well as viral factors. Understanding which patients are at risk for rapid disease progression following LT might enable providers to target specific patients for aggressive treatment and to optimize organ allocation.

In the non-transplant setting, single nucleotide polymorphisms (SNPs) in the epidermal growth factor (*EGF*) and the patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) genes, and near the interleukin-28B (*IL28B*) gene, have been linked to treatment response and disease course. The *EGF* A>G polymorphism rs4444903 has been associated with increased EGF levels (5), increased risk of hepatocellular carcinoma (HCC) (5, 6), increased fibrosis (7), and hepatic decompensation (8). The *PNPLA3* C>G polymorphism rs738409 is associated with steatosis, fibrosis (9, 10), and HCC (10, 11). The *IL28B* C>T polymorphism rs12979860 is strongly associated with spontaneous clearance of HCV and predicts interferon and ribavirin treatment response (12, 13), although data regarding the impact on disease course have been conflicting (14–16).

The study of these SNPs is more complicated in the setting of LT because both the recipient and the donor allograft have genetic contributions. Thus, the results from the non-transplant setting cannot be applied to the LT setting. Only the *IL28B* polymorphism has been studied extensively in the context of LT. The most consistent result among these studies has been the association of the *IL28B* genotype with antiviral therapy (AVT) response following LT, but results have varied according to donor and recipient genotype. In a large HCV cohort from the Mayo Clinic, the rate of sustained virological response (SVR) was significantly higher in patients with the CC genotype, regardless of whether it was the recipient or donor genotype (17). Other groups have found a significant association with donor but not recipient genotype (18) or recipient but not donor genotype (19). As in the non-transplant setting, data on the association between *IL28B* genotype and disease natural history post-transplant have been inconsistent (17, 18, 20, 21).

The *PNPLA3* polymorphism has recently been studied in a single cohort of patients with HCV who underwent LT. The time to Ishak stage 3 fibrosis or HCV-related mortality/graft loss differed by donor but not by recipient genotype (22). Whether this SNP contributes to fibrosis progression post-transplant has not been definitively established.

No study has evaluated the role of the donor and recipient *EGF* genotypes in the LT setting. Additionally, no study that we are aware of has evaluated *IL28B*, *EGF*, and *PNPLA3* polymorphisms in the same LT population. We therefore sought to evaluate the association between these three liver disease related SNPs and allograft hepatitis C in a multicenter cohort of patients who underwent LT for CHC.

Materials and methods

Study population

The study population consisted of adult (>17 yr of age) patients with CHC who underwent deceased donor LT between January 1, 1990 and December 31, 2008 at one of three medical centers (Massachusetts General Hospital, Beth Israel Deaconess Medical Center, or Lahey Hospital and Medical Center) in UNOS region 1. We excluded patients who achieved SVR before LT or had an undetectable viral load at the time of transplant (n = 15), patients coinfecting with human immunodeficiency virus (n = 4), patients undergoing retransplantation (n = 2), and patients for whom no follow-up data were available (n = 7). To avoid bias from operative complications, we also excluded patients who died or were retransplanted within the first 90 d after LT (n = 26) or developed hepatic arterial thrombosis following LT (n = 8) (Fig. 1). This study was approved by the Partners Human Research Committee.

DNA extraction and genotyping

DNA was extracted from formalin-fixed, paraffin-embedded (FFPE) tissue using the QiaAMP FFPE Tissue Kit (Qiagen Inc, Valencia, CA, USA). Explants were used for determining recipient genotype, and lymph node, gallbladder, or allograft wedge or core biopsies were used for determining donor genotype. Genotyping was performed on 5 ng of DNA using the 7900HT Fast Real-Time PCR System with commercial TaqMan SNP

Genotyping Assays for *IL28B* rs12979860, *EGF* rs4444903, and *PNPLA3* rs738409 (Life Technologies, Grand Island, NY, USA). Primers and conditions are available upon request. Genotypes were assigned using Sequence Detection System (SDS 2.4; Applied Biosystems, Grand Island, NY, USA) software with manual review by two independent investigators, blinded to subject phenotype.

Assessment of covariates

Baseline variables extracted from review of electronic medical records included the following recipient characteristics: age at the time of LT, gender, race, and HCC status at time of LT. Donor baseline characteristics were obtained from the New England Organ Bank and included: age at time of LT, race, and gender. Additionally, information on the administration of antiviral therapy and steroid pulse therapy following LT was collected.

Clinical endpoints

Cirrhosis—Liver biopsies were performed when considered to be clinically warranted by the clinician. Histological examination of liver biopsies was performed by local pathologists according to Metavir or Ishak system according to local preference. As protocol liver biopsies were not performed on all patients, the outcome of cirrhosis was defined by either liver histology or, when no liver biopsy was available, documentation of cirrhosis by radiologic imaging or by a clinical provider with clinical signs and/or symptoms of cirrhosis present.

Sustained virological response—A subset of patients received antiviral therapy (AVT) with peginterferon ± ribavirin. In these patients, SVR was assessed and defined as undetectable HCV RNA at 24 wk after the cessation of any duration of therapy.

Survival—The primary endpoint analyzed was a composite endpoint consisting of liver-related death or allograft failure (retransplantation or progression to cirrhosis). All outcomes were identified by manual review of the electronic medical records performed by two independent reviewers.

Statistical analysis

Continuous variables are summarized as mean (standard deviation [SD]) or median (interquartile range [IQR]). Time to cirrhosis and time to the composite endpoint of cirrhosis, liver-related death, or retransplantation were analyzed using the Cox proportional hazards model to calculate adjusted hazard ratios (HR) and 95% confidence intervals (CI). The final multivariable model included the donor or recipient genotype for each SNP as well as covariates showing $p < 0.1$ in the univariate analysis (donor age and achievement of SVR). SVR was modeled as a time-dependent covariate. Kaplan–Meier survival curves were generated and compared using the log-rank tests. Logistic regression was used to assess SVR in patients receiving antiviral therapy. A two-tailed p -value < 0.05 was considered statistically significant. SAS (Cary, NC, USA) version 9.3 was used for statistical analyses.

Results

The final cohort consisted of 264 patients who underwent LT for CHC. Of the 264 patients, 229 had donor tissue available and 228 had recipient tissue available for genotyping, leaving a total of 193 patients with both donor and recipient tissue available (Fig. 1). Baseline demographic and clinical characteristics as well as the distribution of *EGF*, *IL28B*, and *PNPLA3* genotypes among the recipients and donors are outlined in Table 1. The mean age of the cohort was 52.0 ± 6.7 yr. The cohort was predominantly Caucasian (84%) and male (84%). HCC was present at the time of LT in 119 (45%) of patients. Tables S1–S3 show donor and recipient characteristics stratified by the donor *EGF*, *IL28B*, and *PNPLA3* genotypes, respectively.

The distribution of *IL28B* genotypes differed between recipients and donors (CC: 25% vs. 45%; CT: 55% vs. 43%; and TT: 20% vs. 12%, respectively; $p < 0.0001$ for CC vs. non-CC). The distribution of *PNPLA3* genotypes was also significantly different between recipients and donors (CC: 50% vs. 60%; CG: 39% vs. 35%; and GG: 11% vs. 5%, respectively; $p = 0.04$ for CC vs. non-CC). The distribution of *EGF* genotypes was virtually identical between recipients and donors (AA: 27% vs. 26%; AG 49% vs. 50%; and GG: 24% vs. 24%, respectively).

Graft cirrhosis

Over a median follow-up of 6.3 yr (IQR 3.3–9.3 yr), allograft cirrhosis developed in 54 (20%) patients. A trend toward an increased risk of progression to cirrhosis was observed among recipients who received a liver from an *EGF* non-AA vs. AA genotype donor (unadjusted HR 2.01; 95% CI 0.94–4.30; $p = 0.07$) (Fig. 2). This trend persisted after adjusting for donor age and SVR as a time-dependent covariate (multivariable HR 2.01; 95% CI 0.93–4.34; $p = 0.08$). When analyzed under the additive genetic model, each donor G allele was associated with a HR of 1.38 (95% CI 0.92–2.07). When each donor genotype was analyzed separately, the HR point estimates of the AG genotype (HR 1.99, 95% CI 0.91–4.39) and GG genotype (HR 2.03, 95% CI 0.83–4.99) were similar. No associations were observed between recipient *EGF*, *IL28B*, and *PNPLA3* or donor *IL28B* and *PNPLA3* genotypes and cirrhosis (Table 2).

Mortality and graft failure

During the study follow-up period, there were 97 deaths (37%), 59 of which were liver-related (61%) and 10 retransplantations (4%). There was not a statistically significant difference in overall graft survival (deaths and retransplantations) according to either recipient or donor *EGF*, *IL28B*, or *PNPLA3* genotypes (all $p > 0.20$; data not shown). Additionally, an analysis of the association between the SNPs and the composite endpoint of graft cirrhosis, liver-related death, and retransplantation was performed. Again, there was not a statistically significant association between any of the recipient or donor genotypes and the composite outcome. The multivariable-adjusted HR for the composite outcome in recipients with *EGF* non-AA genotype donors livers compared to AA donor livers was 1.29; 95% CI 0.76–2.19; $p = 0.35$ (Table S4).

SVR and *IL28B* genotype

One hundred and sixty-two LT recipients received some duration of AVT (peginterferon ± ribavirin) following LT. Of these, 56 (36%) achieved SVR, 85 (52%) did not achieve SVR, and 21 (13%) were unable to be evaluated for SVR because they either died or were lost to follow up while on treatment or before they reached 24 weeks post-therapy. Rates of SVR were affected by both recipient and donor genotype. The rate of SVR according to recipient *IL28B* genotype was 54% for CC vs. 36% for non-CC, $p = 0.10$ (Fig. 3A), and the rate of SVR according to donor *IL28B* genotype was 50% for CC vs. 30% for non-CC, $p = 0.03$ (Fig. 3B). To understand if there is an additive effect of both recipient and donor *IL28B* genotypes, SVR was assessed based on each possible recipient and donor genotype combination. When recipients and donors were grouped together in pairs, the rate of SVR was highest among CC recipients (R-CC) of a CC donor (D-CC) and lowest among non-CC recipients (R-non-CC) of a non-CC donor (D-non-CC) (R-CC/D-CC 8/12 [67%], R-non-CC/D-CC 19/42 [45%] or R-CC/D-non-CC 4/10 [40%], R-non-CC/D-non-CC 12/45 [27%], p linear trend = 0.009; Fig. 3C).

Discussion

Our results demonstrate a potential novel association between donor *EGF* genotype and the development of graft cirrhosis. In contrast, recipient *EGF*, *IL28B*, and *PNPLA3* and donor *IL28B* and *PNPLA3* genotypes do not predict adverse clinical outcomes in LT recipients with HCV. We suspect that the borderline significance of the association between *EGF* genotype and graft cirrhosis is related to the limited power to detect this association in our cohort. Although our cohort consisted of 264 patients with HCV undergoing LT, only 229 patients had donor tissue available for genotyping, thus limiting our power to detect a true association. Our finding of an increased risk of development of graft cirrhosis in patients with the *EGF* non-AA compared to AA genotype is consistent with prior data regarding the *EGF* locus and clinical outcome in the non-transplant setting. In a cross-sectional study, the G allele of *EGF*rs4444903 was associated with higher degrees of liver fibrosis in younger subjects with CHC (7). Additionally, we previously found an association between *EGF* non-AA genotype and increased risk of clinical deterioration among HCV cirrhotics (8). Moreover, *EGF* expression, as assessed in a liver-based gene expression signature, was associated with progression to advanced cirrhosis, HCC development, and poor survival in HCV-related early-stage cirrhosis (23, 24). Our findings extend the results of these studies by identifying a potential contribution of the *EGF* locus to disease progression in the post-transplant setting.

The functional nature of the *EGF*rs4444903 polymorphism also lends biological plausibility to our findings. As all patients with pretransplant SVR were excluded, all patients had detectable viral loads following transplant, and therefore, liver grafts were uniformly reinfected. However, rate of reinfection and quantity of reinfected cells may differ between individuals. Hepatitis C virus cellular entry is a complicated, multistep process that involves multiple attachment and entry factors (25). The process originates with binding of HCV envelope glycoproteins to glycosaminoglycans on the cell surface (26) with subsequent clathrin-dependent endocytosis, a process requiring many different host factors (27). The

EGF receptor (EGFR) (28) and its HRas signaling pathway have been identified as host factors for HCV cellular entry (29), and HCV infection induces EGFR signaling in cell culture models (30) and increases EGFR expression in HCV-infected patients (29). In fact, binding of EGF to EGFR markedly enhanced entry of HCV pseudoparticles into several different cell lines and primary human hepatocytes (28).

Additionally, we have previously reported increased stability of EGF 61*G allele transcripts compared to EGF 61*A allele transcripts in human hepatoma cell lines and primary human hepatocytes as well as increased levels of serum and liver EGF in subjects with cirrhosis who have the *EGF*GG vs. AA genotype (5). Thus, it is plausible that an individual with the *EGF*GG vs. AA genotype would have increased expression of EGF, and thus enhanced entry of HCV into allograft hepatocytes.

Although we found a trend toward an association between donor *EGF* genotype and graft cirrhosis, we did not find an association between donor *EGF* genotype and graft survival. We tried to exclude mechanical complications of transplantation by excluding patients who died or were retransplanted within 90 d or who developed hepatic arterial thrombosis, but allograft failure is complex and multifactorial. It is difficult to capture death specifically related to recurrent HCV, as AVT can lead to rejection which can ultimately lead to allograft failure.

Our findings confirm the favorable association of the *IL28B* 12979860 CC genotype with response to AVT and SVR, but we did not find an association between the recipient or donor *IL28B* genotype and adverse clinical outcomes. While one group found an association between the donor *IL28B* CC genotype and the composite outcome of progression to cirrhosis, liver-related death, and retransplantation (17), and another group found an association between the donor CC genotype and severe recurrent HCV in a case-control study (21), data on the association of *IL28B* genotype and the clinical course of post-transplant HCV have been inconsistent. The association between donor *IL28B* CC genotype and the composite outcome of progression to cirrhosis, liver-related death, or retransplantation was only observed after censoring treated patients on the day AVT was initiated (17). As the decision to initiate treatment for HCV is not random, censoring at the time of AVT could introduce bias. In addition, another group found no significant association of either the donor or recipient *IL28B* genotype with the occurrence of allograft cirrhosis, three- and five-yr graft survival, three- and five-yr overall survival, or time to hepatic decompensation (18).

We did not observe an association between *PNPLA3* recipient or donor genotype and adverse clinical outcomes. One group reported an association between donor *PNPLA3* non-CC genotype and the composite outcome of progression to Ishak stage 3 fibrosis, liver-related death, and retransplantation (22). Because we did not have protocol biopsies available for all patients, our composite endpoint included cirrhosis rather than bridging fibrosis. Additionally, our study occurred over a longer time period, with a median follow-up of 6.3 yr compared to 1.7 yr of follow-up.

There are several limitations to our study. First, our study design is retrospective. While post-transplant patients are followed closely by multiple specialists including transplant surgeons and hepatologists, some patients transferred to other institutions or were lost to follow up prior to the end of our study and were thus censored at the time of loss to follow-up. Second, while we had a relatively large number of potential patients, the availability of archival tissue limited the size of the cohort. However, our cohort is similar in size to prior studies of SNPs in the post-transplant setting. Third, the post-transplant course is complex with AVT, immunosuppressant changes, and episodic rejection, and it is therefore difficult to attribute outcomes specifically to HCV recurrence. Finally, although 92% of our cohort had at least one post-transplant biopsy, these were not uniform protocol biopsies, making it difficult to identify outcomes such as fibrosis progression and histological cirrhosis, and thus, our definition of cirrhosis was based on histology, radiology, and clinical documentation. In the absence of protocol biopsies, we believe that clinical cirrhosis is likely underreported. This could potentially bias our study toward the null, making our reported association ($p = 0.08$) even more likely to be a true association.

Despite these limitations, our study has several strengths and makes several important observations. Our cohort includes patients from multiple centers and is similar in size to prior studies of SNPs in the post-transplant setting. Additionally, our study is the first to investigate three SNPs in a single population and to explore the association between *EGF* genotype and allograft hepatitis C. While high rates of SVR with direct-acting antiviral therapies against HCV are anticipated, these findings still provide important biological insights into the pathogenesis of allograft HCV recurrence. Additionally, these results may have implications for disease progression in allografts in persons who are not treated, fail therapy, or have contraindications to therapy. In these patients, obtaining an *EGF* donor genotype could help us stratify patients into high- and low-risk progressors and adjust the timing of treatment or immunosuppression accordingly.

In conclusion, we found a trend toward an association between the donor *EGF* non-AA genotype and increased risk of graft cirrhosis in patients with HCV even after adjusting for known predictors of outcome including donor age and SVR. The functional nature of the *EGF* rs4444903 polymorphism and role of the EGFR in HCV viral entry and replication lend biological plausibility to our findings. With a plausible biochemical causal link between *EGF* genotype and HCV recurrence, our results suggest a potential association between *EGF* genotype and fibrosis progression and should be validated in a larger cohort.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

None.

References

1. Berenguer M, Ferrell L, Watson J, et al. HCV-related fibrosis progression following liver transplantation: increase in recent years. *J Hepatol.* 2000; 32:673. [PubMed: 10782918]
2. Gane EJ, Portmann BC, Naoumov NV, et al. Long-term outcome of hepatitis C infection after liver transplantation. *N Engl J Med.* 1996; 334:815. [PubMed: 8596547]
3. Sanchez-Fueyo A, Restrepo JC, Quinto L, et al. Impact of the recurrence of hepatitis C virus infection after liver transplantation on the long-term viability of the graft. *Transplantation.* 2002; 73:56. [PubMed: 11792978]
4. Forman LM, Lewis JD, Berlin JA, Feldman HI, LUCEY MR. The association between hepatitis C infection and survival after orthotopic liver transplantation. *Gastroenterology.* 2002; 122:889. [PubMed: 11910340]
5. Tanabe KK, Lemoine A, Finkelstein DM, et al. Epidermal growth factor gene functional polymorphism and the risk of hepatocellular carcinoma in patients with cirrhosis. *JAMA.* 2008; 299:53. [PubMed: 18167406]
6. Abu Dayyeh BK, Yang M, Fuchs BC, et al. A functional polymorphism in the epidermal growth factor gene is associated with risk for hepatocellular carcinoma. *Gastroenterology.* 2011; 141:141. [PubMed: 21440548]
7. Falletti E, Cmet S, Fabris C, et al. Association between the epidermal growth factor rs4444903G/G genotype and advanced fibrosis at a young age in chronic hepatitis C. *Cytokine.* 2012; 57:68. [PubMed: 22122913]
8. King LY, Johnson KB, Zheng H, et al. Host genetics predict clinical deterioration in HCV-related cirrhosis. *PLoS One.* 2014; 9:e114747. [PubMed: 25504078]
9. Trepo E, Pradat P, Potthoff A, et al. Impact of patatin-like phospholipase-3 (rs738409 C>G) polymorphism on fibrosis progression and steatosis in chronic hepatitis C. *Hepatology.* 2011; 54:60. [PubMed: 21488075]
10. Valenti L, Rumi M, Galmozzi E, et al. Patatin-like phospholipase domain-containing 3 I148M polymorphism, steatosis, and liver damage in chronic hepatitis C. *Hepatology.* 2011; 53:791. [PubMed: 21319195]
11. Trepo E, Nahon P, Bontempi G, et al. Association between the PNPLA3 (rs738409 C>G) variant and hepatocellular carcinoma: evidence from a meta-analysis of individual participant data. *Hepatology.* 2014; 59:2170. [PubMed: 24114809]
12. Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature.* 2009; 461:399. [PubMed: 19684573]
13. Thomas DL, Thio CL, Martin MP, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature.* 2009; 461:798. [PubMed: 19759533]
14. Noureddin M, Wright EC, Alter H, et al. Association of IL28B genotype with fibrosis progression and clinical outcomes in patients with chronic hepatitis C: a longitudinal analysis. *Hepatology.* 2013; 58:1548. [PubMed: 23703931]
15. Fabris C, Falletti E, Cussigh A, et al. IL-28B rs12979860 C/T allele distribution in patients with liver cirrhosis: role in the course of chronic viral hepatitis and the development of HCC. *J Hepatol.* 2011; 54:716. [PubMed: 21146242]
16. Falletti E, Bitetto D, Fabris C, et al. Role of interleukin 28B rs12979860 C/T polymorphism on the histological outcome of chronic hepatitis C: relationship with gender and viral genotype. *J Clin Immunol.* 2011; 31:891. [PubMed: 21647799]
17. Duarte-Rojo A, Veldt BJ, Goldstein DD, et al. The course of posttransplant hepatitis C infection: comparative impact of donor and recipient source of the favorable IL28B genotype and other variables. *Transplantation.* 2012; 94:197. [PubMed: 22766768]
18. Lange CM, Moradpour D, Doehring A, et al. Impact of donor and recipient IL28B rs12979860 genotypes on hepatitis C virus liver graft reinfection. *J Hepatol.* 2011; 55:322. [PubMed: 21147186]
19. Coto-Llerena M, Perez-Del-Pulgar S, Crespo G, et al. Donor and recipient IL28B polymorphisms in HCV-infected patients undergoing antiviral therapy before and after liver transplantation. *Am J Transplant.* 2011; 11:1051. [PubMed: 21466653]

20. Eurich D, Boas-Knoop S, Bahra M, et al. Role of IL28B polymorphism in the development of hepatitis C virus-induced hepatocellular carcinoma, graft fibrosis, and posttransplant antiviral therapy. *Transplantation*. 2012; 93:644. [PubMed: 22411462]
21. Biggins SW, Trotter J, Gralla J, et al. Differential effects of donor and recipient IL28B and DDX58 SNPs on severity of HCV after liver transplantation. *J Hepatol*. 2013; 58:969. [PubMed: 23333445]
22. Dunn W, O'neil M, Zhao J, et al. Donor PNPLA3 rs738409 genotype affects fibrosis progression in liver transplantation for hepatitis C. *Hepatology*. 2014; 59:453. [PubMed: 24123231]
23. Hoshida Y, Villanueva A, Kobayashi M, et al. Gene expression in fixed tissues and outcome in hepatocellular carcinoma. *N Engl J Med*. 2008; 359:1995. [PubMed: 18923165]
24. Hoshida Y, Villanueva A, Sangiovanni A, et al. Prognostic gene expression signature for patients with hepatitis C-related early-stage cirrhosis. *Gastroenterology*. 2013; 144:1024. [PubMed: 23333348]
25. Von Hahn T, Rice CM. Hepatitis C virus entry. *J Biol Chem*. 2008; 283:3689. [PubMed: 17881349]
26. Barth H, Schnober EK, Zhang F, et al. Viral and cellular determinants of the hepatitis C virus envelope-heparan sulfate interaction. *J Virol*. 2006; 80:10579. [PubMed: 16928753]
27. Pileri P, Uematsu Y, Campagnoli S, et al. Binding of hepatitis C virus to CD81. *Science*. 1998; 282:938. [PubMed: 9794763]
28. Lupberger J, Zeisel MB, Xiao F, et al. EGFR and EphA2 are host factors for hepatitis C virus entry and possible targets for antiviral therapy. *Nat Med*. 2011; 17:589. [PubMed: 21516087]
29. Zona L, Lupberger J, Sidahmed-Adrar N, et al. HRas signal transduction promotes hepatitis C virus cell entry by triggering assembly of the host tetraspanin receptor complex. *Cell Host Microbe*. 2013; 13:302. [PubMed: 23498955]
30. Diao J, Pantua H, Ngu H, et al. Hepatitis C virus induces epidermal growth factor receptor activation via CD81 binding for viral internalization and entry. *J Virol*. 2012; 86:10935. [PubMed: 22855500]

Fig. 1.
Identification of the post-transplant hepatitis C cohort.

Fig. 2. Kaplan–Meier curves for time to development of allograft cirrhosis stratified by donor *EGF* genotype.

Fig. 3. Sustained virological response (SVR) rates according to recipient (A) and donor (B) *IL28B* genotypes, as well as combined recipient and donor *IL28B* genotype pairs (C).

Table 1

Baseline characteristics of the cohort at the time of liver transplantation (total n = 264)

Recipient characteristics	
Age, yr (mean, SD)	52.0 (6.7)
Male gender, n (%)	223 (84)
Race, n (%)	
White	221 (84)
Black	16 (6)
Hispanic	19 (7)
Asian	8 (3)
Hepatocellular carcinoma, n (%)	119 (45)
<i>EGF</i> genotype, n (%)	
AA	62 (27)
AG	112 (49)
GG	54 (24)
<i>IL28B</i> genotype, n (%)	
CC	56 (25)
CT	126 (55)
TT	46 (20)
<i>PNPLA3</i> genotype, n (%)	
CC	114 (50)
CG	90 (39)
GG	24 (11)
Donor characteristics	
Age, yr (median, IQR)	39 (23–49)
Male gender, n (%)	153 (60)
<i>EGF</i> genotype, n (%)	
AA	60 (26)
AG	114 (50)
GG	55 (24)
<i>IL28B</i> genotype, n (%)	
CC	103 (45)
CT	98 (43)
TT	28 (12)
<i>PNPLA3</i> genotype, n (%)	
CC	137 (60)
CG	81 (35)
GG	11 (5)

Thirty-six subjects missing recipient genotype, 35 subjects missing donor genotype, 13 subjects missing donor age, 11 subjects missing donor gender.

Table 2

Risk of cirrhosis after liver transplantation

Genotype	Unadjusted hazard ratio (95% CI)	p Value	Adjusted hazard ratio ^a (95% CI)	p Value
<i>EGF</i>				
Recipient (non-AA vs. AA)	0.96 (0.52–1.79)	0.90	1.10 (0.58–2.08)	0.78
Donor (non-AA vs. AA)	2.01 (0.94–4.30)	0.07	2.01 (0.93–4.34)	0.08
<i>IL28B</i>				
Recipient (non-CC vs. CC)	1.10 (0.58–2.07)	0.77	1.17 (0.61–2.22)	0.64
Donor (non-CC vs. CC)	1.06 (0.60–1.89)	0.83	0.85 (0.47–1.54)	0.60
<i>PNPLA3</i>				
Recipient (non-CC vs. CC)	1.14 (0.65–2.01)	0.64	1.41 (0.78–2.55)	0.26
Donor (non-CC vs. CC)	0.80 (0.44–1.45)	0.47	1.00 (0.53–1.86)	0.99

^a Adjusted for donor age and sustained virological response as a time-dependent covariate.