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Long-term outcomes of living-donor liver transplantation for Progressive familial intrahepatic cholestasis type 1

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Abbreviations

ATP8B1: ATPase class I type 8B member 1; EBD: external biliary diversion; IQR: interquartile range; LDLT: living donor liver transplantation; LT: liver transplantation; PFIC-1: progressive familial intrahepatic cholestasis type 1; POD: postoperative day.

Abstract

Objectives: Progressive familial intrahepatic cholestasis type 1 (PFIC-1), an autosomal recessive disorder, is characterized by cholestasis, jaundice, and refractory pruritus. In some patients with PFIC-1, liver cirrhosis and end-stage liver disease develop and lead to liver transplantation (LT). In this observational study, we sought to clarify the long-term outcomes of LT for PFIC-1 and predictors of favorable outcomes.

Methods: The study cohort comprised 12 patients with PFIC-1 who had undergone living donor liver transplantation (LDLT) during the previous three decades (1990–2019). We compared the clinical manifestations and type of *ATP8B1* mutations between patients in whom LDLT had been successful and those in whom it had been unsuccessful.

Results: LDLT failed in 5 of the 12 patients and the 25-year survival rate was 58%. Comparison of physical growth after LDLT revealed significant retardation of stature in patients in whom LDLT had been unsuccessful; these patients developed severe and persistent diarrhea. *ATP8B1* genotypic analysis revealed that frameshifting, splicing, and large deletion mutations occurred more commonly in successful cases, whereas missense mutations occurred more frequently in unsuccessful cases. No mutations were identical in the two groups.

Conclusions: These results suggest an association between post-LT outcomes and extrahepatic manifestations, especially intestinal function. Further investigation of correlations between *ATP8B1* genotypes and intestinal function could help to identify patients with PFIC-1 who will achieve favorable post-LT outcomes.

An infographic is available for this article at: *http://links.lww.com/MPG/C44*.

Key words: Progressive familial intrahepatic cholestasis type 1(PFIC-1), ATP8B1, Liver transplantation, Long-term follow up.

What is known

- Progressive familial intrahepatic cholestasis type 1(PFIC-1) is an important cause of liver cirrhosis -related end-stage liver disease in pediatric patients.
- Although some patients require liver transplantation (LT), its indications and long-term outcomes are poorly defined.
- Success of LT in patients with PFIC-1 depends mainly on the extrahepatic manifestations.

What is new

- We report a case series of patients with PFIC-1 who had undergone LT during the previous three decades (1990–2019).
- Mutation types or locations in the ATP8B1 coding sequence may correlate with post-LT intestinal manifestations and long term outcomes.

Introduction

Progressive familial intrahepatic cholestasis type 1 (PFIC-1), previously known as Byler's disease, is an autosomal recessive disorder characterized by neonatal or infantile onset cholestasis, jaundice, and refractory pruritus [1]. It is exceptionally rare, its incidence being approximately 1 in 50,000–100,000 live births [1,2]. Previous studies have revealed that the *ATPase class I type 8B member 1* (*ATP8B1*) gene on chromosome 18q21 is responsible for PFIC-1 [3]. *ATP8B1* encodes an aminophospholipid flippase that is involved in the biliary excretion of bile salts by hepatocytes. *ATP8B1* mutations therefore lead to impaired bile salt secretion [1,4,5]. *ATP8B1* mutations also affect intracellular transport in multiple organs, including the small bowel, kidney, and pancreas, thus causing extrahepatic manifestations of PFIC-1, which include malabsorption, protein-loss, enteropathy, intractable diarrhea, and subsequent growth failure [1,2].

Despite medical and surgical treatments, including ursodeoxycholic acid therapy, resin therapy, and partial biliary diversion, liver cirrhosis and end-stage liver disease develop in some patients with PFIC-1, which necessitates liver transplantation (LT). However, the indications for LT for PFIC-1, especially in patients with extrahepatic features, and its long-term outcomes remain unclear. Over the last 3 decades, 12 patients with PFIC-1 were referred to our institution from multiple centers in Japan for living donor liver transplantation (LDLT). Here, we describe our LDLT outcomes in patients with PFIC-1 and revisit the clinical manifestations and types of *ATP8B1* mutations between patients in whom LDLT was successful and those in whom it was unsuccessful with the aim of clarifying predictors of favorable outcomes of LT in these patients.

Methods

Patients

This was a retrospective study of patients with PFIC-1 who had undergone LDLT in Kyoto University Hospital, Department of Surgery, between January 1990 and July 2019. Twelve consecutive patients were included in this study; no patients were excluded. Additionally, no patients with PFIC-1 underwent deceased-donor LT in our institute during the study period because there were very few donations from deceased donors in Japan after enforcement of a new law on organ transplantation in 2010. Diagnoses of PFIC-1 were made on the basis of physical, radiologic, and histopathological findings and identification of *ATP8B1* genetic mutations [6]. All study patients underwent LDLT in our hospital. The surgical procedures

and post-operative immunosuppression protocols have previously been reported [7-9]. All biliary reconstructions, except one, were achieved via Roux-en-Y hepaticojejunostomy, the remaining biliary reconstruction being achieved by duct to duct anastomosis. One patient underwent total external biliary diversion (EBD) during the initial LDLT and an ileocolic anastomosis 14 months later.

Data regarding sex, age at the time of LDLT, pre-and post-transplant physical findings, clinical laboratory findings at the pretransplant assessment, ABO compatibility, graft-to-recipient weight ratio, most recent graft liver histology findings, post-transplant survival of patient (time from first transplant to death or the date of the end of the study), and cause of death were obtained retrospectively from medical records.

Molecular genetic analysis of *ATP8B1*

ATP8B1-complementary DNA sequencing was performed after reverse-transcription polymerase chain reaction of lymphocyte RNA, and mutations were confirmed using genomic lymphocyte DNA [6]. Otherwise, mutations were identified by previously developed methods for variant detection and analysis using targeted next-generation sequencing and bioinformatics [10]. Patient sequences were compared with the normal *ATP8B1*-complementary DNA sequence (GenBank accession number AF038007 and NM_005603) and genomic sequence (Ensembl, ENSG00000081923, Gene ID 5205) [6]. No donors underwent *ATP8B1* gene analysis.

Statistical analysis

Statistical software (SPSS, version 25.0; SPSS, Chicago, IL) was used for statistical analysis. A p-value < 0.05 was considered to denote a statistically significant difference. Data are presented as number/percentages and median (interquartile range, IQR) for categorical and continuous variables, respectively. Fischer's exact, the χ^2 test and Mann–Whitney U tests were used to evaluate differences between groups. The log-rank test was used to compare patient mortality, whereas Kaplan–Meier curves were used to plot the probabilities of patient survival.

This study was approved by the Institutional Review Board of Kyoto University Hospital, Japan (R-2308).

Results

Complete data were available for final analysis for 12 patients with PFIC-1 (five male and seven female patients). These patients' diagnoses of PFIC-1 were based on clinical manifestations, liver pathology, and *ATP8B1* genetic findings. The baseline characteristics of the study patients on presentation to our institution for LT are shown in Supplemental Table 1, http://links.lww.com/MPG/C40. Their LT profiles and other results are summarized in Supplemental Table 2, *http://links.lww.com/MPG/C41*. Serum total bile acid concentrations tended to be relatively high in the patients who died; however, none of the studied baseline characteristics differed significantly between those who survived post-LT and those that did not. There were no cases of ABO incompatible LDLT in the living or deceased patient group. Kaplan–Meier analyses of patient and first graft survival are shown in Figure 1. Three of twelve patients underwent retransplantation from a living donor (Re-LDLT) because of graft liver failure due to steatohepatitis following refractory diarrhea, pancreatitis, and protracted parenteral nutrition. The 1-, 5-, 10-, 15-, and 25-year patient survival rates were 100%, 100%, 91%, 58%, and 58%, respectively. The 1-, 5-, 10-, 15-, and 25-year graft survival rates in these patients were 100%, 91%, 82%, 58%, and 58%, respectively, which indicates that Re-LDLT did not contribute significantly to their survival. Five patients died, one following splenic artery aneurism rupture associated with graft liver cirrhosis caused by steatohepatitis (POD 5032), one of cardiac failure after Re-LDLT associated with graft liver failure with steatohepatitis due to refractory diarrhea and pancreatitis (POD4671), one of graft liver failure associated with steatohepatitis and refractory diarrhea (POD4889), one of chronic renal failure after Re-LDLT because of graft liver failure due to severe steatohepatitis with chronic rejection (POD4694), and the remaining one of rupture of esophageal varices after Re-Re-LDLT owing to graft liver failure caused by chronic rejection (POD2006). There was no morbidity from significant thrombosis in the hepatic artery and portal vein, or biliary anastomotic stricture associated with LT.

The most recent or last body weight and height after LDLT differed significantly between living and deceased patients (Z score for weight; −1.70 [IQR, 1.20] vs. −3.2 [IQR, 1.20], p = 0.030, Z score for height; −2.0 [IQR, 2.4] vs. −5.3 [IQR, 3.3], p = 0.010) (Figure 2A, B). Additionally, Z scores for height were significantly greater after LDLT than pre LDLT in the patients who survived (−4.5 [IQR, 2.1] vs. −2.0 [IQR, 2.4], p = 0.01).

Mutations of *ATP8B1* in all patients are listed in Supplemental Table 3, *http://links.lww.com/MPG/C42* and their positions in the *ATP8B1* coding sequence (1251

amino acids) are summarized in Figure 3. Fifteen different *ATP8B1* mutations were identified in our 12 patients. These included seven missense mutations, four splicing mutations, two frameshift mutations, a large insertion causing frameshift mutation, and a large deletion mutation. Missense mutations occurred more frequently in patients who did not survive, whereas frameshifting, splicing, and large deletion mutations occurred more commonly in those who did survive. Missense mutations were present significantly more frequently in patients who did not survive than in those who did (8 of 10 loci in deceased patients vs. 3 of 14 loci in living patients; $p = 0.01$). Some mutations overlapped within each group; however, there was no overlap of mutations between the surviving and deceased patient groups.

The present graft liver histology and social activity of surviving patients is summarized in Table 1 and representative liver histology is shown in Supplemental Figure 1, *http://links.lww.com/MPG/C43*. Steatosis and fibrosis were present to varying degrees in all patients and steatohepatitis was present in four. Rejection was relatively well controlled in all cases. Five patients are able to participate in social activity, including work and school, whereas the remaining two are home-bound because of extrahepatic symptoms, including malabsorption, protein-losing enteropathy, intractable diarrhea, and subsequent growth failure. After the first LDLT, 11 patients developed severe and persistent diarrhea while receiving conventional medications for diarrhea, whereas one patient (Living Pt No. 2) did not develop diarrhea. The diarrhea of three of the living patients (Pts. No 3,5,6) improved spontaneously after several years, however, all other patients, including the deceased patients, had persistent watery diarrhea and were administered antidiarrheal medications such as cholestyramine, loperamide, and antiflatulent agents. The two home-bound patients (Pts No.1 and No7) have persistent diarrhea and the same homozygous *ATP8B1* deletion mutation (F529del).

Discussion

We reviewed the outcomes of LT performed on 12 patients to treat PFIC-1 during a 30-year period in a single tertiary care hospital in Japan. This is one of the largest cohorts with the longest follow-up of patients with PFIC-1 who have undergone LT. Part of this series was reported in a 20-year LDLT outcome analysis from our institute approximately ten years ago [6–9]. This previously reported study showed that while LT is the only definitive treatment available for PFIC-1, an undesired effect of this treatment is the potential worsening of extrahepatic PFIC-1 manifestations, including malabsorption, protein-loss, enteropathy, and intractable diarrhea. These extrahepatic PFIC-1 manifestations are almost always associated with steatosis of the liver. Those findings led to us adopting extremely cautious indications

for LDLT for patients with PFIC-1 over the last decade. Therefore, in this study, we assessed these patients' long-term follow data, focusing on comparing clinical manifestations and *ATP8B1* mutations between living and deceased patients with the aim of clarifying predictors of favorable outcomes of LT in these patients.

The survival curves shown in Figure 1 show that there was no perioperative LDLT mortality and that the10-year survival rate was favorable compared with that following LT for other pediatric liver diseases. However, the survival rate beyond the first 10 years rapidly declined and re-LDLT was not effective in these patients. Physical growth comparisons revealed that patients with failed LDLT had significant stature retardation. These results suggest that the post-transplant outcomes of PFIC-1 patients differ from those of other LT-treated pediatric liver disorders, such as biliary atresia. Post-transplant mortality is usually highest perioperatively because of surgical complications and uncontrolled rejection and decreases gradually thereafter. In our series, there were no surgical complications associated with the first LDLT and few cases of uncontrolled rejection. Some post-LDLT patients remained in good condition for many years, manifesting only mild growth retardation and extrahepatic symptoms such as refractory diarrhea. These findings prompted us to revisit our LDLT results from the perspective of *ATP8B1* mutation type, which may be associated with impairment of membrane transportation in intestinal tissues.

In our series, preoperative baseline serum total bile acid concentrations tended to be lower in living than in subsequently deceased patients; this difference was not statistically significant. This may be clinically significant in that lower serum total bile acid concentrations could reflect inferior enterohepatic bile acid circulation ability in the patients who died. However, steatohepatitis was the main cause of graft liver failure in four of those five patients. Even all the living patients showed varying degrees of liver fibrotic changes with steatosis and steatohepatitis despite the rejection process being adequately controlled. These findings may also reflect an important role of ATP8B1 in the intestine and suggest that the success of LT in patients with PFIC-1 may depend on its extrahepatic manifestations, particularly the severity of intestinal malabsorption and intractable diarrhea.

As to the present status of living patients, diarrhea is well controlled in four of them; all four have been able to engage well in social activities since the first LDLT. It has been shown that, even after correction of hepatic bile-salt-secretion impairment following LT, there is insufficient intestinal bile salt absorption [7]. Findings of a recent *in vitro* study suggest a correlation between cell surface expression of SLC10A2, the ileal sodium/bile acid

cotransporter, and ATP8B1 flippase activity in Caco-2 cells [11]. *In vivo*, SLC10A2 is most strongly expressed in the ileum and is responsible for the absorption of bile acids. Therefore, downregulation of intestinal epithelial surface expression of SLC10A2 together with incomplete ATP8B1 activity following LT causes a large increase in bile acid secretion relative to the amount previously secreted. Increased bile acids in the stools then cause high volume osmotic diarrhea that significantly affects physical growth and overall post-LT survival results.

Previous reports have shown that external biliary diversion (EBD) is effective in reducing the symptoms of PFIC-1 patients after LT [12]. In our series, Case 7, a surviving patient, underwent EBD during the initial LDLT. However, serum electrolyte imbalance and hypolipidemia were prolonged and growth continued to be retarded. Although subsequent ileocolic anastomosis ameliorated serum electrolyte imbalances, growth retardation did not improve. Oya et al. reported that EBD was ineffective in their series of PFIC-1 cases who underwent LDLT [13]. It would be worth revisiting the indication for this procedure on the basis of individual patient's intestinal function.

Genotype–phenotype correlations have not been elucidated in PFIC-1 patients. Klomp et al. reported that small mutations such as missense mutations are more common in patients with benign, recurrent intrahepatic cholestasis, and that nonsense, frameshifting, and large deletion mutations are more common in those with PFIC-1 [14]. However, this was not the case in this or another study [15]. In our long-term observational series, missense mutations were more common in patients who died, whereas frameshifting, splicing, and large insertion and deletion mutations were more common in those who survived. We also observed no overlapping of mutations between the living and deceased patient groups. Taken together, these results, along with those of the survival curve analysis and physical growth Z-score, suggest that ATP8B1 genomic organization and mutations are associated with intestinal function and physical growth post-LT. This association may be augmented by the correlation between *ATP8B1* mutation and the ability of living patients to engage in social activities. Two patients with the same homozygous *ATP8B1* mutation (F529del) have followed similar clinical courses characterized by malabsorption, protein loss, enteropathy, intractable diarrhea, protracted steatohepatitis, and subsequent growth failure. These results suggest that, especially with regard to extrahepatic manifestations of PFIC-1, some missense mutations of ATP8B1 may be just as, or more, damaging than frameshift mutations or deletions.

In conclusion, our results suggest that certain *ATP8B1* mutations are associated with

post-LT extrahepatic manifestations, including intestinal absorption dysfunction, and subsequent growth, ability to engage in social activity, and overall survival. Meanwhile, our study has inevitable limitations in that it was a small, retrospective, single center study and we did not investigate objective markers of intestinal function and histological findings. Some unmeasured variables may have contributed to poorer outcomes in this group of patients. Correlations between *ATP8B1* genotypes and intestinal function or intestinal transporter expression in patients with PFIC-1 remain unclear. In the future, these correlations should be explored to aid in the identification of patients with PFIC-1 who are likely to benefit from LT.

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Figure legends

Figure 1. Kaplan–Meier analyses of survival of patients with PFIC-1 following liver transplantation at Kyoto University Hospital from 1990 to 2019. The 1-, 5-, 10-, 15-, and 25-year patient survival rates were 100%, 100%, 91%, 58%, and 58%, respectively. The 1-, 5-, 10-, 15-, and 25-year graft survival rates for patients with PFIC-1 were 100%, 91%, 82%, 58%, and 58%, respectively. Retransplantation from a living donor did not contribute significantly to survival of these patients.

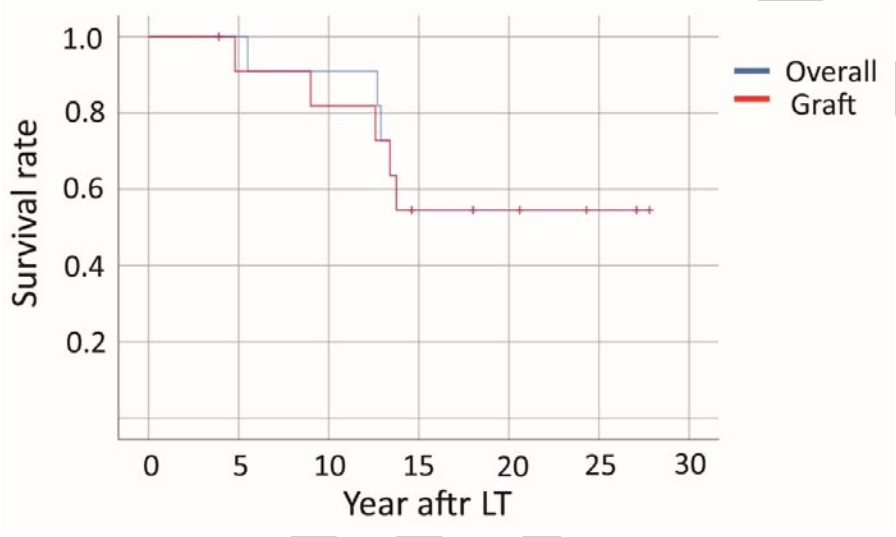

Figure 2. Comparisons of body weight and height between living and deceased patients after live donor liver transplant (LDLT) showing that they differed significantly (A: Z score of weight; −1.70 [IQR, 1.20] vs. −3.2 [IQR, 1.20], p = 0.030, B: Z score of height; −2.0 [IQR, 2.4] vs. −5.3 [IQR, 3.3], p = 0.010). B: Body height Z scores were significantly greater after LDLT in the living patient group (−4.5 [IQR,2.1] vs. −2.0 [IQR, 2.4], p = 0.01).

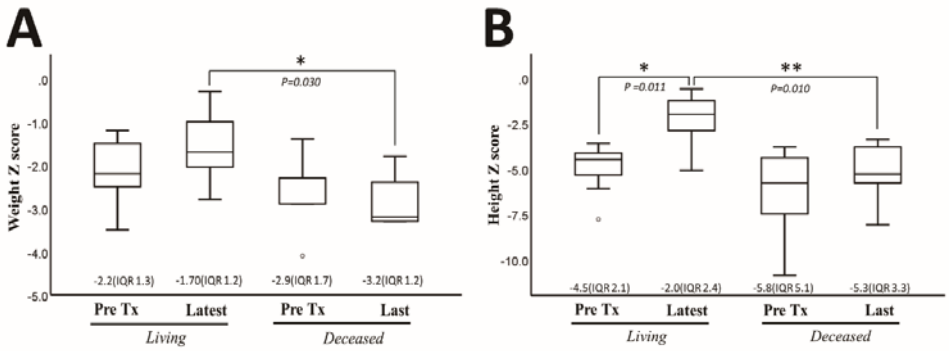

Figure 3. Summary of the positions of mutations in the protein sequence. Black bars represent the transmembrane domain. The mutations identified in posttransplant living (n = 7) and deceased patients are shown above and below the protein schematic, respectively.

Supplemental Figure 1. A,B. Photomicrographs of the most recent liver biopsy of living Patient 1 showing steatohepatitis with 50% of macrovesicular steatosis and bridging fibrosis. There is no evidence of acute or chronic rejection. (Hematoxylin–eosin staining; original magnification, ×10). C. The most recent liver biopsy of living Patient 7 showing steatohepatitis with mild activity and 15% steatosis and no evidence of acute or chronic rejection. (Hematoxylin–eosin staining; original magnification, ×10).

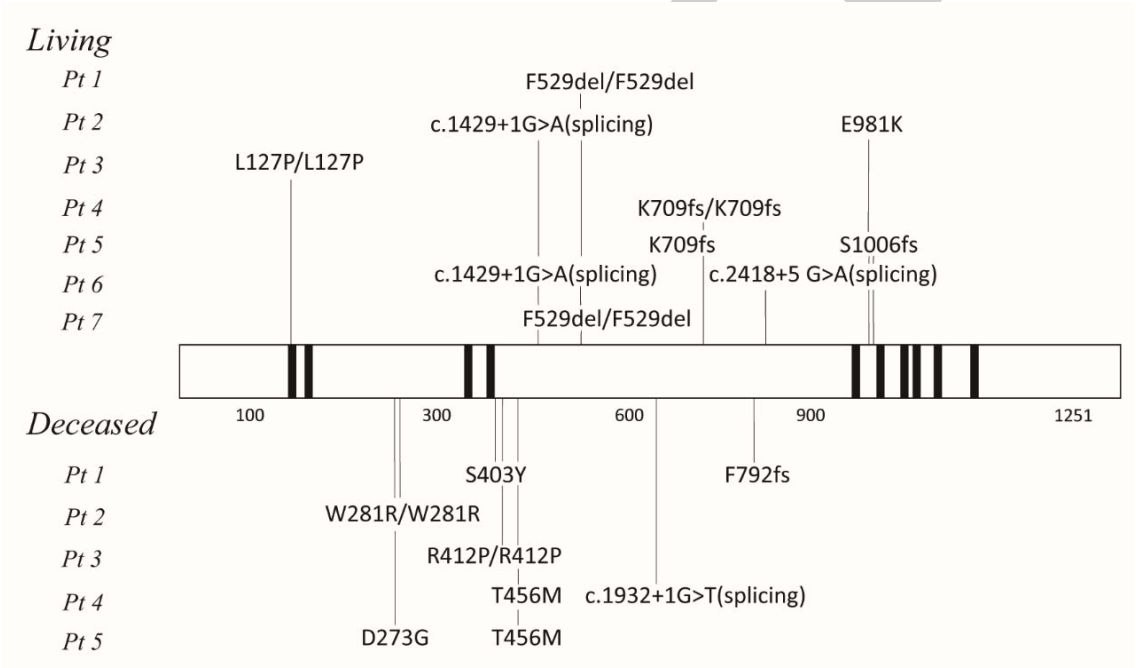

Table 1. The present graft liver histology and social activity of living patients

Patient No	Age(Year)	BH (SD)	BW (SD)	Gene mutations	Graft liver histology*	Present status
Pt 1	31.5	-2.8	-3.2	F529del/F529del	Steatohepatitis, Macro steatosis 50%, A1F4, RAI 0	At home
Pt 2	31	-0.3	-0.8	c.1429+1G>A/E981K		Full-time work
Pt 3	38.5	-1.1	-1.7		Macro steatosis 10%, A1F1, RAI 0	Full-time work
Pt 4	26.9	-2.1	-2.0	L127P/L127P		Short-time work
Pt 5	22.3	-0.9	-0.6	K709fs/K709fs	Macro steatosis 10%, A0F1, RAI 0	Full-time work
Pt 6	15.6	-1.7	-2.6	K709fs/S1006fs	Steatohepatitis, Macro steatosis 50%,A0F3, RAI 1	High-school student
Pt 7	11.8	-2.0	-5.1	c.1429+1G>A/c.2418+5 G>A	Steatohepatitis, Macro steatosis 40%, A0F2, RAI 0	At home (Primary school)
				F529del/F529del	Mixed steatosis 50%, A0F2, RAI 0	
					Steatohepatitis, Mixed steatosis 15%, A1F1, RAI 0	

*Fibrosis stages are shown by METAVIR scoring system, RAI; Rejection activity index.