Clinical and molecular basis of hepatocerebral mitochondrial DNA depletion syndrome in Japan: Evaluation of outcomes after liver transplantation

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Research

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Abstract

Background

Hepatocerebral mitochondrial DNA depletion syndrome (MTDPS) is a disease caused by defects in mitochondrial DNA maintenance and leads to liver failure and neurological complications during infancy. Liver transplantation (LT) remains controversial due to poor outcomes associated with extrahepatic symptoms. The purposes of this study were to clarify the current clinical and molecular features of hepatocerebral MTDPS and to evaluate outcomes LT in MTDPS patients in Japan.

Results

We retrospectively assessed the clinical and genetic findings, as well as the clinical courses, of 23 hepatocerebral MTDPS patients from a pool of 999 patients who were diagnosed with mitochondrial diseases between 2007 and 2019. Causative genes were identified in 20 of 23 patients: *MPV17* (n=13), *DGUOK* (n=4), *POLG* (n=1), *MICOS13* (n=1), and *TWNK* (n=1). Eight MPV17-deficient patients harbored c.451dupC and all four DGUOK-deficient patients harbored c.143-307_170del335. The most common initial manifestation was failure to thrive (n=13, 56.5%). The most frequent liver symptom was cholestasis (n=21, 91.3%). LT was performed on 11 patients, including eight MPV17-deficient and two DGUOK-deficient patients. Four patients, including one with mild intellectual disability, survived; seven who had remarkable neurological symptoms before LT died. Five of the MPV17-deficient survivors had either c.149G>A or c.293C>T.

Conclusions

MPV17 was the most common genetic cause of hepatocerebral MTDPS. The outcome of LT for MTDPS was not favorable, as previously reported, but patients who had *MPV17* mutations associated with mild phenotypes such as c.149G>A or c.293C>T and no marked neurologic manifestations before LT, had moderately better outcomes.

Background

Mitochondrial diseases are clinically and genetically heterogeneous disorders that affect multiple organs and are characterized by impaired energy production. Mitochondrial diseases can present at any age. Neurological symptoms are the most common clinical presentation and liver involvements are observed in approximately 10–20% of cases, particularly in patients that present as neonates or during early infancy[1].

Mitochondrial DNA depletion syndrome (MTDPS) is caused by defects in any of the proteins involved in mtDNA maintenance, leading to quantitative and qualitative defects in mtDNA, and currently has been classified as mtDNA maintenance defects[2, 3]. MTDPS has three clinical phenotypes; myopathic,

encephalomyopathic, and hepatocerebral. Hepatocerebral MTDPS is known to cause acute liver failure in infancy and is associated with mutations in *DGUOK*, *MPV17*, *POLG*, *SUCLG1*, and *TWNK*[4].

Liver transplantation (LT) is considered as a definitive treatment option for pediatric patients with liver failure, and the survival rate for pediatric LT recipients in Japan is more than 85% at 5 years[5]. Contrarily, previous studies have reported that the overall survival rate of LT performed for mitochondrial hepatopathies was only 30%, due to post-LT deterioration of neurologic and extrahepatic symptoms[6]. LT for mitochondrial diseases may be considered in patients with isolated liver disease, but it is difficult to exclude the development or deterioration of extrahepatic manifestation before LT in a clinical setting.

In 2013, we reported the clinical and molecular characteristics of MTDPS in Japan[7], identifying 13 patients with hepatocerebral MTDPS. Among those patients, mutations in *DGUOK* were the most frequently observed followed by *MPV17* and *POLG*. Since that earlier report, we have diagnosed 10 additional patients with hepatocerebral MTDPS and have performed LT on some patients with mitochondrial hepatopathies[8–10]. The purposes of this study were to clarify the current clinical and molecular features of hepatocerebral MTDPS and to evaluate outcomes LT in MTDPS patients in Japan.

Methods

We performed a retrospective review of patients who were diagnosed with hepatocerebral MTDPS from 2007 to 2019. Patients were enzymatically and/or genetically diagnosed and diagnosis of MTDPS was confirmed by quantitative polymerase chain reaction (qPCR). This study was approved by the ethics boards of Chiba Children's Hospital and Saitama Medical University.

Patients

We have used biochemical and molecular genetic testing to diagnose mitochondrial diseases in Japan since 2007. A total of 999 patients were diagnosed with mitochondrial diseases, 101 (10.1%) of which were mitochondrial hepatopathies. Among these, 23 patients were diagnosed with hepatocerebral MTDPS.

Mitochondrial respiratory chain enzyme activity

We examined mitochondrial respiratory chain enzyme activity using skin fibroblasts, livers, or other samples as previously described[11]. Enzymatic diagnosis was confirmed according to the diagnostic criteria described by Bernier *et al*[12].

Quantitative polymerase chain reaction

Nuclear DNA and mtDNA enumerated by qPCR, according to the previously described methods[7, 13]. The mtDNA gene ND1 was compared against a nuclear reference gene, exon 24 of *CFTR*. A relative copy number of mtDNA to nuclear DNA of <35% was defined as mtDNA depletion.

Results

Clinical characteristics

Table 1 shows the clinical characteristics of the patients. The cohort comprised 23 patients (11 male and 12 female) with hepatocerebral MTDPS from 19 non-consanguineous families; 15 of the patients have been reported earlier[3, 7, 8, 10]. Twenty patients (87%) presented with initial manifestations during infancy, and six of those developed initial symptoms during the neonatal period. The most common initial manifestation was failure to thrive, seen in 13 patients (56.5%), followed by vomiting (8/23 patients), and jaundice (4/23 patients). Mitochondrial respiratory chain enzymes were analyzed in 22 of the patients, and multiple enzyme deficiencies in liver tissues were noted in 16. All affected patients tested for mtDNA content showed significant mtDNA depletion, ranging from 0.5 to 31.7%. Causative genes were identified in 20 of the 23 hepatocerebral MTDPS patients.

Liver manifestations are shown in Table 2. The most frequently observed liver symptom was cholestasis (21/23 patients). Hepatomegaly, fatty liver, and liver fibrosis were seen in 14 (60.9%), 16 (69.6%), and 17 (73.9%) of the 23 patients, respectively. Hepatocellular carcinoma (HCC) developed in two patients with MPV17 deficiency and α-fetoprotein showed various levels, ranging from 413 to 503,320 ng/mL.

Table 3 shows the breakdown of extrahepatic manifestations. Failure to thrive (16/23) was the most common extrahepatic involvement. Vomiting (10/23) and feeding difficulties (11/23), which developed during the neonatal period, were also frequent symptoms. Hypoglycemia and lactic acidosis were found in 15 and 16 patients, respectively. Pulmonary hypertension (PH) was observed in 5/23 patients (*MPV17*, 4 patients [Pt936, Pt1244, Pt1273, and Pt1943]; *DGUOK*, one patient [Pt66]). Hypothermia was seen in a patient with DGUOK deficiency.

Bodyweights at birth and at the time of follow-up are shown in Table 4. MPV17-deficient patients had normal birth weight (mean 0.3 ± 0.7 SD); whereas non-MPV17 patients showed significant prenatal growth restriction (mean -1.7 ± 0.9 SD). Postnatally, both MPV17 and non-MPV17 patients exhibited low body weight (MPV17, mean -2.6 ± 1.5 SD; non-MPV17, mean -3.0 ± 1.8 SD) equally. Postnatal growth impairment might be notable in MPV17 deficiency.

Molecular investigations

We identified causative genes in 20 of the 23 patients, including *MPV17* (13 patients), *DGUOK* (4 patients), and *POLG*, *MICOS13*, and *TWNK* (one patient each) mutations. The variants expected pathogenic are presented in Table 5. Homozygous or compound heterozygous c.451dupC (p.L151Pfs*39) with other mutations were detected in 8 of 13 MPV17 deficient patients. The c.143-307_170del335 mutation was found in all four patients with *DGUOK* deficiency. Pt94 had a homozygous variant of unknown significance (VUS) in *MICOS13*. Since the association of MTDPS and MICOS13 deficiency is unknown, a verification study is ongoing at the time of this writing. Pt1156 harbored a

heterozygous mutation c.953C>A and VUS in *TWNK*. RNA-sequencing of Pt1156 fibroblast cells indicated a splicing abnormality of the c.953C wild-type allele.

Liver transplantation and prognosis

LT from a living donor was performed on 11 patients, including eight with MPV17 deficiency and two with DGUOK deficiency. Two LT patients (Pt68YB and Pt2017ES) had HCC, one LT patient (Pt2017EB) had multiple hepatic masses and end-stage liver disease, and the remainder of the LT patients had liver failure. Neurological manifestations were observed before LT in eight patients other than Pt1702, Pt2017ES and Pt63. Four of the 11 LT patients survived, three of which were MPV17-deficient patients. On the other hand, 3 of the 12 patients who did not receive LT survived. Following LT, three MPV17-deficient patients (Pt936, Pt1244, and Pt1273) and one DGUOK-deficient patient (Pt66) developed PH, as did one MPV17-deficient patient (Pt1943) that did not undergo LT. All 5 patients suffering from PH showed poor prognosis. The causes of death after LT were respiratory failure due to sepsis in Pt936, PH in Pt1244 and heart failure in Pt1273. Tissue vulnerability following LT caused a ruptured suture in Pt68EB, who developed peritonitis and sepsis. Pt68YB died of sepsis and acute respiratory distress syndrome caused by pneumonia after LT. Among eight MPV17-deficient patients who harbored a frameshift mutation (c.451dupC) in at least one allele, only one patient (Pt1702) survived. All of the patients with *MPV17* mutations who survived had either c.149G>A : or c.293C>T in at least one allele. Pt339 and Pt1702, both with c.293C>T, developed some neurological symptoms, such as developmental delay, seizures, and psychiatric symptoms, while sibling patients with c.149G>A did not exhibit neurological manifestations, other than mild intellectual disability in Pt2017EB.

Discussion

Mutations in *MPV17* were the most common genetic cause of MTDPS in the patient cohort involved in this study, followed by mutations in *DGUOK*. The prevalence of these mutations in MTDPS patients observed in our study is different from previous studies. For example, a previous study reported that *POLG* mutations, followed by *MPV17* and *DGUOK* mutations were the most common in European countries[14]. Another study showed that *MPV17* and *DGUOK* were first and second most frequent genetic causes of MTDPS, respectively[15], although all the parents of the patients in that study were consanguineous.

Failure to thrive was the most common initial manifestation in hepatocerebral MTDPS. Interestingly, mean birth weight in MPV17-deficient patients was significantly higher than in non-MPV17 patients. However, no significant differences in body weight were noted between these two groups in the postnatal period, suggesting that MPV17-deficient patients had marked postnatal growth restrictions compared to non-MPV17 patients. Previous studies have reported that low birth weight was observed in 20–80% of patients with *DGUOK* mutations and also in patients with *POLG* mutations[15–21]. However, very few studies have reported MPV17-deficient patients exhibiting intrauterine growth restrictions (IUGR)[15, 21–23]. Studies in animal models have not observed significant differences in birth weight of *MPV17*$^{-/-}$ and

MPV17$^{+/+}$ mice[24]. It has been shown that mtDNA copy numbers were not decreased in proliferating cells in *MPV17*$^{-/-}$ mice but were decreased in quiescent cells[25]. Cell proliferation in the fetus continues until the gestational age of 32 weeks[26], therefore fetal growth might be relatively maintained in MPV17-deficient patients. Further studies are required to elucidate our findings of infrequent IUGR in MPV17 deficiency.

The frameshift mutation c.451dupC was seen in 8 of 13 patients (61.5%) in our cohort with MPV17 deficiency. A homozygous c.451dupC mutation was also identified in Korean sibling patients who died from liver failure at the age of 6 months[22], but has not reported elsewhere. Japanese patients with the homozygous c.451dupC also developed liver failure requiring LT during infancy and died within 2 years of LT. It is conceivable that the c.451dupC mutation might be more frequent in East Asian populations, and homozygosity at this locus is probably associated with poor outcomes regardless of whether LT is performed. The mortality rate of MPV17 deficiency was 61.5% (8/13 patients) in this study, which is lower than that reported previously (75%) [3], and 7 of 8 (87.5%) patients in this study with homozygous c.451dupC *MPV17* mutations or compound heterozygous mutations along with the c.451dupC mutations did not survive. In contrast, two patients with c.293C>T and sibling patients with c.149G>A, in which homozygosity is associated with a comparatively better prognosis, survived regardless of LT[3, 27]. Taken together, patients harboring c.149G>A or c.293C>T in at least one *MPV17* allele of might show milder phenotypes.

LT in patients with mitochondrial diseases remains controversial due to the potential for extrahepatic manifestations. In guidelines for pediatric patients, LT for patients with mitochondrial diseases involving severe and life-threatening extrahepatic multi organ manifestations is contraindicated due to the high possibility of neurological deterioration[28]. In such patients, limited data are available regarding the efficacy of LT and long-term prognosis, and outcomes are known to be heterogenous[1, 29-31]. It has been reported that 5 of 14 patients with *DGUOK* mutations survived for more than 5 years after LT without severe neurological symptoms, even though some patients presented with muscle hypotonia and psychomotor retardation before transplantation[29]. In that study, all survivors harbored at least one mutation that predicted a DGUOK protein with some potential residual activity. Table 6 summarizes 19 patients with *MPV17* mutations and who received LT[23, 27, 32–37], including eight patients from our cohort; 8 of these 19 patients (42.1%) survived after LT. Patients with the homozygous c.149G>A or compound heterozygous c.149G>A or c.293C>T with other mutations tended to show better outcomes after LT, although of 11 deceased patients in our cohort, eight (72.7%) presented with neurological involvements before LT. Mild neurological symptoms were observed before LT in just one of the eight patients that survived, but seven patients (87.5%) manifested with neurological abnormalities after LT. Collectively, patients harboring c.149G>A or c.293C>T in at least one allele without marked neurological manifestations might have a better prognosis and higher quality of life after LT.

A previous study found that 3 of 14 patients with *DGUOK* mutations developed PH after LT[29]. In the current study, PH was seen in five patients including four with MPV17 deficiency and one with DGUOK deficiency. Four of these developed PH after LT. Although PH can be caused by chronic liver disease and

portal hypertension, PH after LT is infrequent; PH has also been reported in patients with primary mitochondrial diseases (e.g. m.3243A>G, *NFU1*, *BOLA3*)[38, 39], though the mechanism underlying this remains unknown. In addition to the two patients who initially presented with HCC in this study, three MPV17-deficient patients developed HCC[27, 35, 37]. HCC was also observed in DGUOK-deficient patients[19, 29]. It is presumed that dNTP imbalance is associated tumorigenesis but much remains to be clarified about the association between carcinoma and MTDPS[40]. Our results recommend that physicians should monitor patients with *MPV17* and *DGUOK* mutations for the development of HCC during follow-up visits.

In summary, this study revealed that *MPV17* is the most common genetic cause of hepatocerebral MTDPS in Japan. The c.451dupC mutation in *MPV17* was the most frequent in the cohort, and homozygosity for this mutation was associated with poor outcomes. As previously reported, the survival rate for MTDPS patients after LT in our cohort was lower than that for other diseases. Our results suggest that a better life prognosis after LT might be expected in MTDPS patients who have *MPV17* mutations, such as c.149G>A or c.293C>T, that are associated with milder phenotypes and do not have marked clinical manifestations before LT, although there is a possibility that neurological symptoms may develop following LT.

Abbreviations

MTDPS, mitochondrial DNA depletion syndrome; LT, liver transplantation; qPCR, quantitative polymerase chain reaction; HCC, hepatocellular carcinoma; PH, pulmonary hypertension; VUS, variant of unknown significance; IUGR, intrauterine growth restriction

Declarations

Ethics approval and consent to participate

All procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

Consent for publication

Written informed consent was obtained from the parents of all subjects included in the study.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors declare that they have no conflict of interest.

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Author's contributions

M.S., N.K., and S.K. designed the study. M.S., N.K., K.I., and A.M. drafted the manuscript. N.A., Y.S., T.E., S.U., A.I., T.F., R.I., A.F., M.K., and J.M. collected and provided the patient data. M.O.T and T.T. performed enzyme and qPCR analyses. The whole scheme was planned and supervised by Y.O., A.O., and K.M. Professional advice on the draft was given by T.F., Y.K., K.T., and K.S. K.M. critically revised the manuscript.

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Tables

Table 1. Clinical characteristics of 23 hepatocerebral MTDPS patients.

ID	Gene	Sex	Age at onset	Initial manifestations	Affected complex	%mtDNA in Liver
Pt68EB	*MPV17*	M	3 m	failure to thrive, hypotonia, jaundice	CI+III+IV (liver)	7.8
Pt68YB	*MPV17*	M	8 m	failure to thrive, jaundice	CI+III+IV (liver)	6.6
Pt292	*MPV17*	F	1 m	failure to thrive, vomiting	CI+III (liver)	9.8
Pt339	*MPV17*	F	8 m	failure to thrive	CI+III (liver)	20.5
Pt936	*MPV17*	M	1 m	failure to thrive	CI+III+IV (liver)	8.0
Pt1244	*MPV17*	M	1 m	failure to thrive	CI+III+IV (liver)	1.2
Pt1273	*MPV17*	F	1 m	failure to thrive, vomiting	CI+III+IV (liver)	3.4
Pt1702	*MPV17*	M	neonate	failure to thrive, vomiting	NA	NA
Pt1943	*MPV17*	M	neonate	tachypnea, jaundice	CI+III (liver)	0.5
Pt2017EB	*MPV17*	M	7 m	liver failure	CI+III (liver)	0.7
Pt2017YS	*MPV17*	F	1 y	vomiting, lethargy	normal (Fb)	NA
Pt2017ES	*MPV17*	F	4y5m	vomiting, lethargy	CI+II+IV (liver)	0.6
Pt2170	*MPV17*	F	7m	failure to thrive, cholestasis, liver dysfunction	CI+II+III (liver)	15.3
Pt50YS	*DGUOK*	F	neonate	tachypnea, hypothermia, hypoglycemia	CI+III+IV (liver)	6.0
Pt50ES	*DGUOK*	F	3 m	failure to thrive, incomplete head control	CI+III+IV (liver)	3.0
Pt66	*DGUOK*	F	neonate	feeding difficulty	CI+III+IV (liver)	2.3
Pt92	*DGUOK*	M	1 m	failure to thrive, jaundice	CI+II+III (liver)	18.4
Pt74	*POLG*	F	4 m	failure to thrive, lethargy, hypotonia, vomiting	CI+III+IV (liver)	3.3
Pt94	*MICOS13*	F	3 m	breath holding	CI (liver)	11.5
Pt1156	*TWNK*	M	neonate	hypoglycemia, lactic acidosis	CI+IV (liver)	6.3
Pt63	ND	M	2 m	failure to thrive, vomiting	CI (liver)	23.7
Pt148	ND	F	neonate	vomiting	CI (liver)	31.7
Pt1589	ND	M	4y3m	elevated transaminases	CI+III+IV (liver)	10.6

EB, elder brother; YB, younger brother; YS, younger sister; ES, elder sister; ND, not detected; C, complex; NA, not available; Fb, fibroblast

Table 2. Liver manifestations in 23 hepatocerebral MTDPS patients.

ID	Gene	Cholestasis	Hepatomegaly	Fatty liver	Fibrosis	Liver failure	Tumor	AFP (ng/mL)
Pt68EB	*MPV17*	+	+	+	+	+	-	NA
Pt68YB	*MPV17*	+	-	+	+	-	HCC	24,000
Pt292	*MPV17*	+	+	+	-	+	-	219,980
Pt339	*MPV17*	+	-	+	+	-	-	NA
Pt936	*MPV17*	+	+	+	+	+	-	315,521
Pt1244	*MPV17*	+	+	+	+	+	-	503,320
Pt1273	*MPV17*	+	+	+	+	+	-	93,619
Pt1702	*MPV17*	+	-	+	+	+	-	NA
Pt1943	*MPV17*	+	+	-	-	+	-	NA
Pt2017EB	*MPV17*	+	+	+	+	+	Multiple hepatic nodules	413
Pt2017YS	*MPV17*	+	-	+	-	+	Multiple hepatic nodules	3,078
Pt2017ES	*MPV17*	+	-	+	+	-	HCC	1,332
Pt2170	*MPV17*	+	+	+	+	+	-	60,500
Pt50YS	*DGUOK*	+	+	-	-	+	-	NA
Pt50ES	*DGUOK*	-	-	-	-	+	-	NA
Pt66	*DGUOK*	+	-	+	+	+	-	NA
Pt92	*DGUOK*	+	+	-	+	+	-	>50,000
Pt74	*POLG*	+	+	+	+	+	-	NA
Pt94	*MICOS13*	+	+	+	+	+	-	NA
Pt1156	*TWNK*	+	+	+	+	+	-	NA
Pt63	ND	+	+	-	+	+	-	200,000
Pt148	ND	+	-	-	+	+	-	8,400
Pt1589	ND	-	NA	NA	NA	-	-	NA

EB, elder brother; YB, younger brother; YS, younger sister; ES, elder sister; ND, not detected; HCC, hepatocellular carcinoma; NA, not available; AFP, α-fetoprotein

Table 3. Extrahepatic manifestations in hepatocerebral MTDPS patients (n=23).

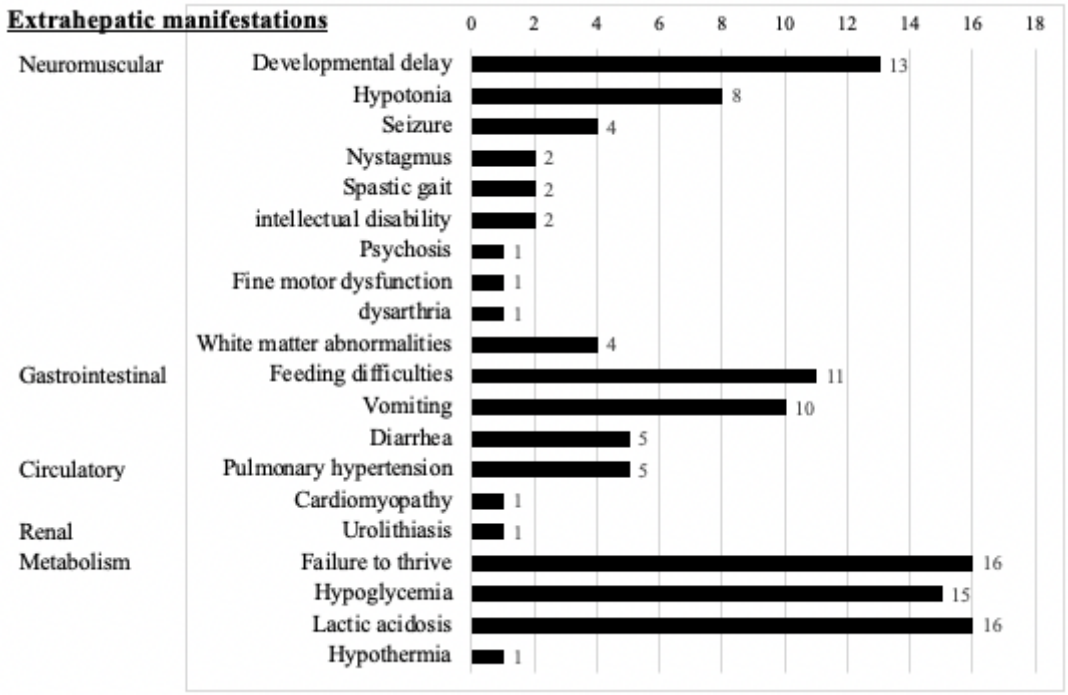

Table 4. Body weight at birth and at follow-up.

			Birth			Postnatal		
ID	Gene	Sex	Gestational age	Body weight (g)	SD	Age at exam	Body weight (kg)	SD
Pt68EB	*MPV17*	M	37w0d	3060	1	3m	4.6	-2.7
Pt68YB	*MPV17*	M	40w0d	3260	0.1	8m	5.5	-3.1
Pt292	*MPV17*	F	40w5d	3428	1	7m	4.8	-3.5
Pt339	*MPV17*	F	NA	NA	NA	2y7m	10.2	-2
Pt936	*MPV17*	M	38w0d	3240	1.3	4m	4.5	-3
Pt1244	*MPV17*	M	40w0d	2909	-0.9	4m	3.7	-4
Pt1273	*MPV17*	F	39w0d	3010	0.1	1y	5	-4.7
Pt1702	*MPV17*	M	NA	NA	NA	NA	NA	NA
Pt1943	*MPV17*	M	37w5d	2692	-0.5	6m	4.28	-4.1
Pt2017EB	*MPV17*	M	38w0d	2950	0.5	7y	20.05	-0.7
Pt2017YS	*MPV17*	F	37w6d	2830	0.1	4y	14.85	-0.2
Pt2017ES	*MPV17*	F	38w0d	2728	0.1	7y	22.1	-0.1
Pt2170	*MPV17*	F	36w2d	2428	0	1y1m	6.54	-2.8
Pt50YS	*DGUOK*	F	40w2d	2750	-1.2	NA	NA	NA
Pt50ES	*DGUOK*	F	40w0d	2510	-1.5	NA	NA	NA
Pt66	*DGUOK*	F	37w3d	1688	-3.2	8m	3.2	-5.5
Pt92	*DGUOK*	M	40w0d	3120	-0.3	6m	7.2	-0.9
Pt74	*POLG*	F	40w0d	normal	NA	4m	5.6	-2.3
Pt94	*MICOS13*	F	40w3d	2780	-0.8	NA	NA	NA
Pt1156	*TWNK*	M	37w3d	1992	-2.1	2m	2.7	-4.2
Pt63	ND	M	37w0d	1884	-2.5	7m	5.4	-3.7
Pt148	ND	F	38w4d	2254	-1.7	15d	2.4	-1.5
Pt1589	ND	M	23w5d	624	0	NA	NA	NA

	MPV17 (Mean±SD)	non-MPV17 (Mean±SD)	*P* value
Birth	0.3±0.7 (n=11)	-1.7±0.9 (n=8)	<0.01
Postnatal	-2.6±1.5 (n=12)	-3.0±1.8 (n=6)	0.59

EB, elder brother; YB, younger brother; ES, elder sister; ND, not detected; LT, liver transplantation; NA, not available

Table 5. Identified gene mutations in patients, liver transplantation status, and clinical outcomes.

ID	Gene	Allele 1	Allele 2	LT (age)	Outcome
Pt68EB	*MPV17*	c.451dupC : p.L151Pfs*39	c.509C >T : p.S170F	+ (1y5mo)	died (1y10m)
Pt68YB	*MPV17*	c.451dupC : p.L151Pfs*39	c.509C >T : p.S170F	+ (6y)	died (6y)
Pt292	*MPV17*	c.451dupC : p.L151Pfs*39	c.148C>T : p.R50W	-	died (1y2m)
Pt339	*MPV17*	c.293C>T : p.P98L	c.376-1G>A	-	alive (11y)
Pt936	*MPV17*	c.451dupC : p.L151Pfs*39	c.451dupC : p.L151Pfs*39	+ (4m)	died (1y9m)
Pt1244	*MPV17*	c.451dupC : p.L151Pfs*39	c.451dupC : p.L151Pfs*39	+ (11m)	died (2y6m)
Pt1273	*MPV17*	c.451dupC : p.L151Pfs*39	c.71-2_79del11ins4	+ (1y)	died (3y)
Pt1702	*MPV17*	c.451dupC : p.L151Pfs*39	c.293C>T : p.P98L	+ (8m)	alive (23y)
Pt1943	*MPV17*	c.451dupC : p.L151Pfs*39	c.308_310del : p.C103del	-	died (10m)
Pt2017EB	*MPV17*	c.148C>T : p.R50W	c.149G>A : p.R50Q	+ (7y)	alive (8y)
Pt2017YS	*MPV17*	c.148C>T : p.R50W	c.149G>A : p.R50Q	-	alive (5y)
Pt2017ES	*MPV17*	c.148C>T : p.R50W	c.149G>A : p.R50Q	+ (7y)	alive (8y)
Pt2170	*MPV17*	c.148C>T : p.R50W	c.271_273del : p.L91del	-	died (1y11m)
Pt50YS	*DGUOK*	c.143-307_170del335	c.143-307_170del335	-	died (9mo)
Pt50ES	*DGUOK*	c.143-307_170del335	c.143-307_170del335	+ (1y6m)	died (1y7m)
Pt66	*DGUOK*	c.143-307_170del335	c.743T>C : p.L248P	+ (8m)	died (1y6m)
Pt92	*DGUOK*	c.143-307_170del335	c.143-307_170del335	-	died (7m)
Pt74	*POLG*	c.3554T>C : p.I1185T	c.2870C>T : p.A957V	-	died (8m)
Pt94	*MICOS13*VUS		VUS	-	died (8m)
Pt1156	*TWNK*	c.953C>A : p.A318D	VUS	-	died (7m)
Pt63	ND	-	-	+ (9m)	alive (16y)
Pt148	ND	-	-	-	died (1m)
Pt1589	ND	-	-	-	alive (6y)

MPV17: NM_002437, DGUOK: NM_080918, POLG: NM_002693, TWNK: NM_021830

EB, elder brother; YB, younger brother; YS, younger sister; ES, elder sister; ND, not detected; VUS, variant of unknown significance; LT, liver transplantation

Table 6. Molecular and neurological findings as well as outcomes in 19 MPV17-deficient patients who received LT.

	Sex	Allele 1	Allele 2	Age at onset	Neurological findings Before LT	After LT	LT age	Outcome
Pt68EB	M	c.451dupC : p.L151Pfs*39	c.509C >T : p.S170F	3 m	hypotonia	+	17mo	died (1y10m)
Pt68YB	M	c.451dupC : p.L151Pfs*39	c.509C >T : p.S170F	8 m	hypotonia	+	6y	died (6y)
Pt936	M	c.451dupC : p.L151Pfs*39	c.451dupC : p.L151Pfs*39	1 m	developmental delay, hypotonia	+	4m	died (1y9m)
Pt1244	M	c.451dupC : p.L151Pfs*39	c.451dupC : p.L151Pfs*39	1 m	developmental delay, hypotonia	+	11m	died (2y6m)
Pt1273	F	c.451dupC : p.L151Pfs*39	c.71-2_79del11ins4	1 m	developmental delay	+	1y	died (3y)
Pt1702	M	c.451dupC : p.L151Pfs*39	c.293C>T : p.P98L	neonate	-	psychosis, intellectual disability, fine motor dysfunction, dysarthria	8m	alive (23y)
Pt2017EB	M	c.148C>T : p.R50W	c.149G>A : p.R50Q	7 m	mild intellectual disability	+	7y	alive (8y)
Pt2017ES	F	c.148C>T : p.R50W	c.149G>A : p.R50Q	1 y	-	-	7y	alive (8y)
Parini 2009	M	c.149G>A : p.R50Q	c.149G>A : p.R50Q	1m	-	developmental delay, ataxia, severe motor-sensory axonal polyneuropathy	2y	alive (6y)
Karadimas 2006	F	c.149G>A : p.R50Q	c.149G>A : p.R50Q	6m	-	hypotonia, gross and fine motor delay, peripheral neuropathy	9m	alive (12y)
Karadimas 2006	F	c.149G>A : p.R50Q	c.149G>A : p.R50Q	1m	hypotonia, hyporeflexia	+	16m	died (2y)
Karadimas 2006	F	c.149G>A : p.R50Q	c.149G>A : p.R50Q	4m	-	peripheral neuropathy	11y	alive (21y)
Wong 2007	M	c.206G>A : p.W69*	c.206G>A : p.W69*	birth	-	-	5m	died (6m)
Navarro 2008	M	c.70+5G>A	c.70+5G>A	2m	hypotonia	+	1y	died (2y)
El-Hattab 2010	M	c.262A>G : p.K88E	c.262A>G : p.K88E	neonate	NA	developmental delay, muscle weakness	NA	died (2.5y)
El-Hattab 2010	M	c.485C>A : p.A162D	c.271_273del3 : p.L91del	infancy	NA	hypotonia	NA	alive (4y)
Mudd 2012	M	c.22_23insC	ND	infancy	hypotonia, mild motor delay	+	7y	died (9y)
Uusimaa 2014	M	c.191C>G : p.P64R	c.293C>T : p.P98L	5m	-	progressive demyelinating peripheral neuropathy	3y	alive (11.5y)
Vilarinho 2014	F	c.148C>T : p.R50W	c.148C>T : p.R50W	5y	-	dystonia, tremor, seizure	9y	died (10y)