Genotype-phenotype relationships of truncating mutations, p.E297G and p.D482G in bile salt export pump deficiency

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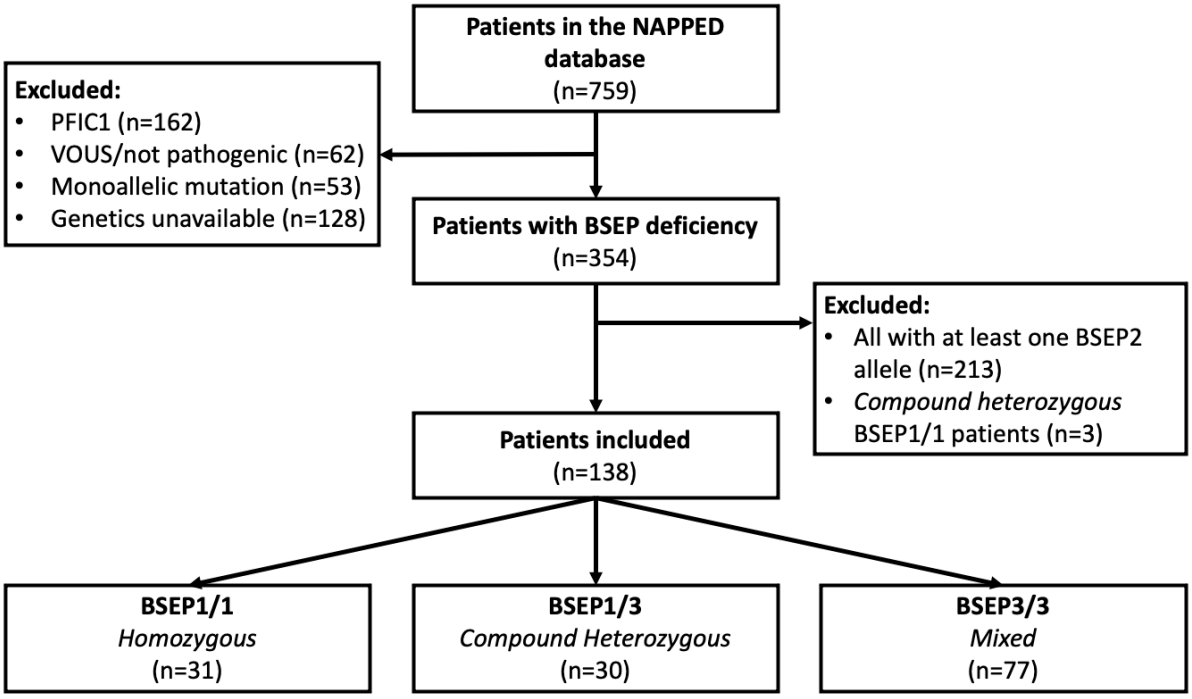

Fig. S1. Extensive flowchart of patient inclusion from the NAPPED database. Genotype category explained under methods section. *NAPPED: NAtural course and Prognosis of PFIC and Effect of biliary Diversion; PFIC1: Progressive Familial Intrahepatic Cholestasis Type 1 (FIC1 deficiency); VOUS (variant of unknown significance); BSEP (bile salt export pump).*

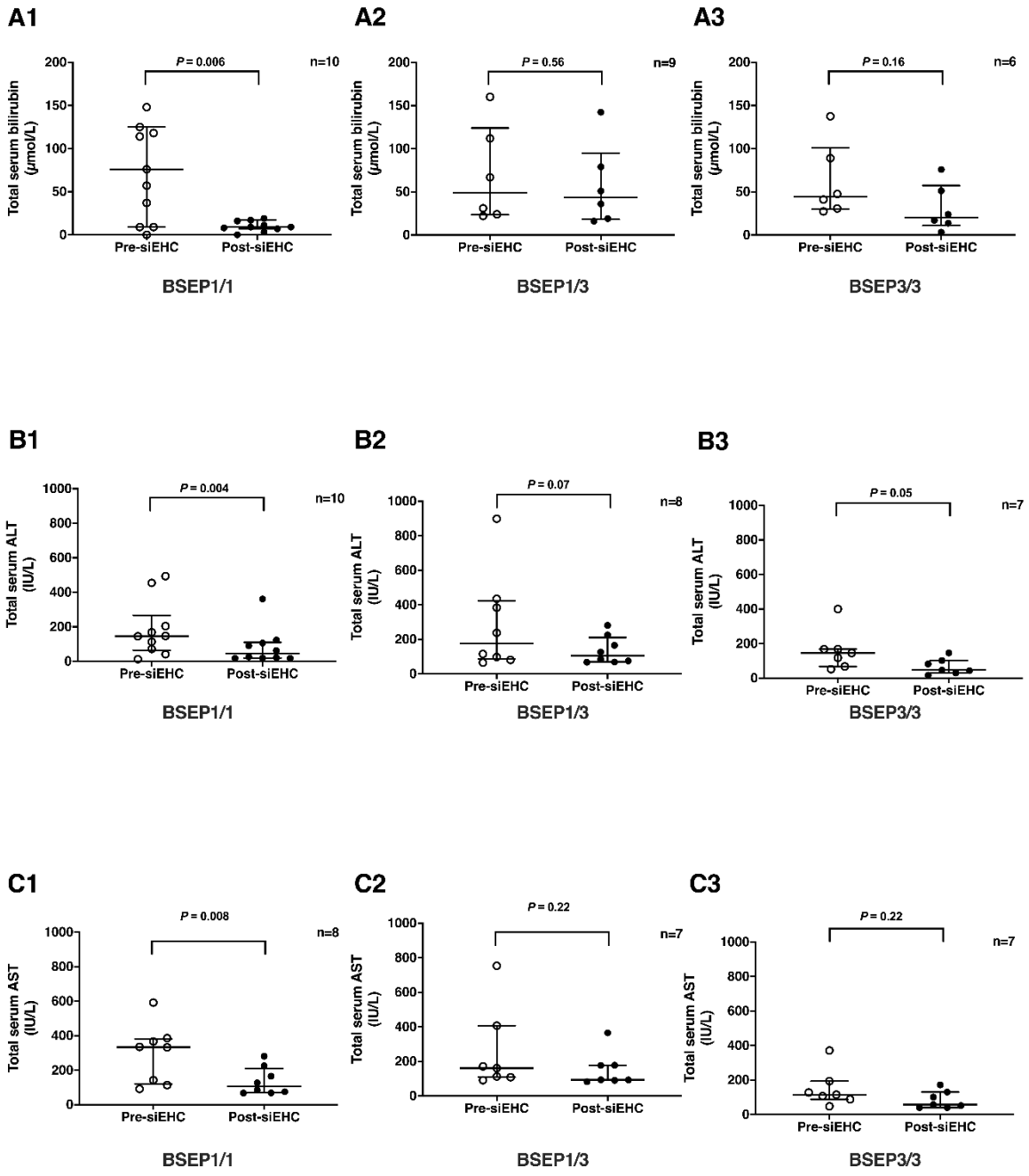

Fig. S2. Serum liver biochemistry prior to (open symbols) and after (closed symbols) surgical biliary diversion. In patients with a BSEP1/1, BSEP1/3 or BSEP3/3 genotype. Wilcoxon signed-rank test. Bars represent median and IQR. *BSEP (bile salt export pump); siEHC (surgical interruption of the enterohpatic circulation).*

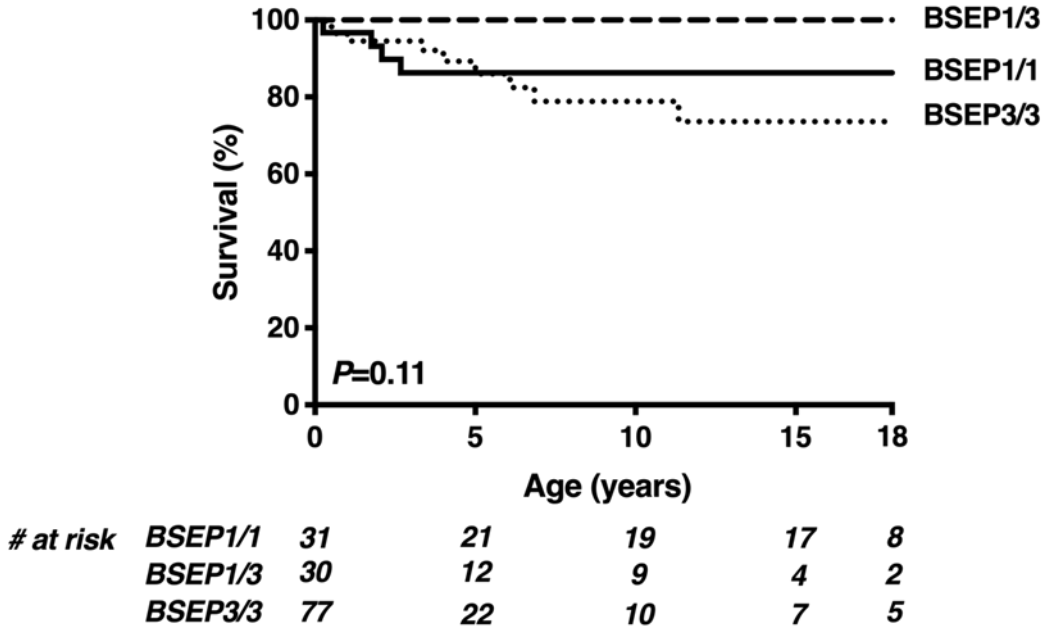

Fig. S3. Observed total survival over time. Genotypic categorization of BSEP1/1, BSEP1/3 and BSEP3/3 groups is defined in the methods section. Log-rank test. *BSEP (bile salt export pump).*

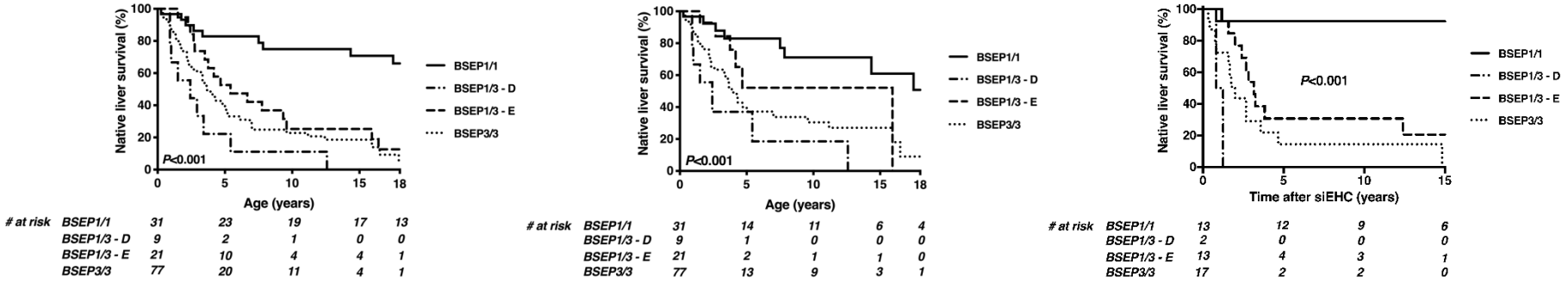

Fig. S4. Observed native liver survival over time, specific for type of BSEP1 mutation in BSEP1/3 (p.E297G and p.D482G).

Left panel: all patients; *middle panel*: patients without siEHC during follow up, patients with siEHC are censored at time of siEHC; *right panel*: patients after siEHC. Genotypic categorization of BSEP1/1, BSEP1/3 and BSEP3/3 groups is defined in the methods section; BSEP1/3-D: patients in the BSEP1/3 group with a p.D482G-PPTM combination; BSEP1/3-E: patients in the BSEP1/3 group with a p.E297G-PPTM combination. BSEP (*bile salt export pump); siEHC (surgical interruption of the enterohepatic circulation).*

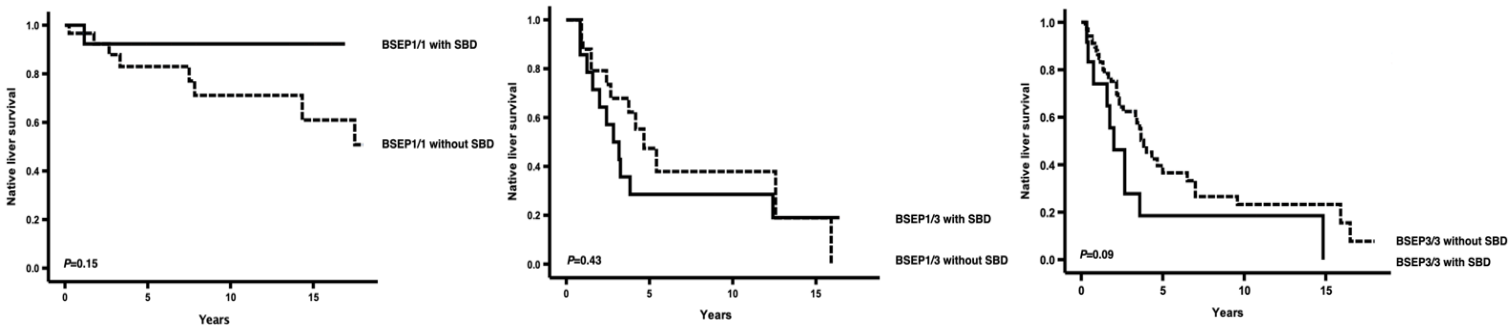

Fig. S5. Observed native liver survival over time with clock reset approach. *Left panel*: patients with a BSEP1/1 genotype; *middle panel*: patients with a BSEP1/3 genotype; *right panel*: patients with a BSEP3/3 genotype. Genotypic categorization of BSEP1/1, BSEP1/3 and BSEP3/3 groups is defined in the methods section. For patients without siEHC**/SBD** the x-axis is defined as age in years and patients with siEHC**/SBD** are censored in the plot. For patients with siEHC**/SBD** the x-axis is defined as time from diversion in years. *BSEP (bile salt export pump); SBD (surgical biliary diversion*); *siEHC (surgical interruption of the enterohepatic circulation).*Clock reset and competing risk approach.

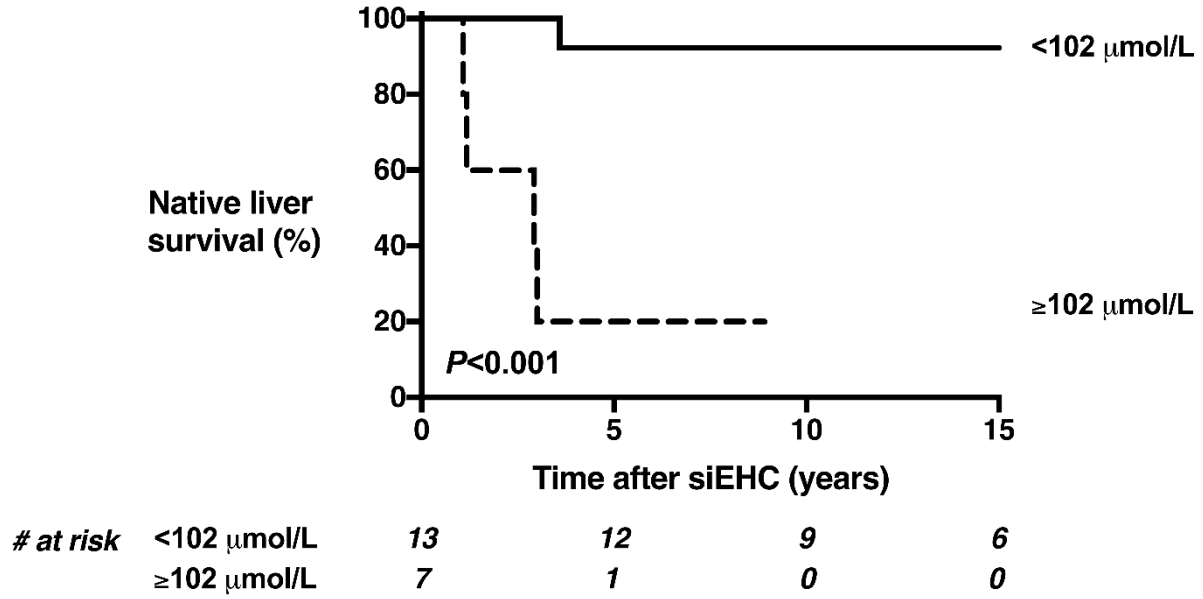

Fig. S6. Native liver survival according to 102umol cutoff after siEHC. In patients with a post-surgical serum bile acid level lower than, or equal to or higher than 102μmol/L. Log-rank test. *siEHC (surgical interruption of the enterohepatic circulation).*

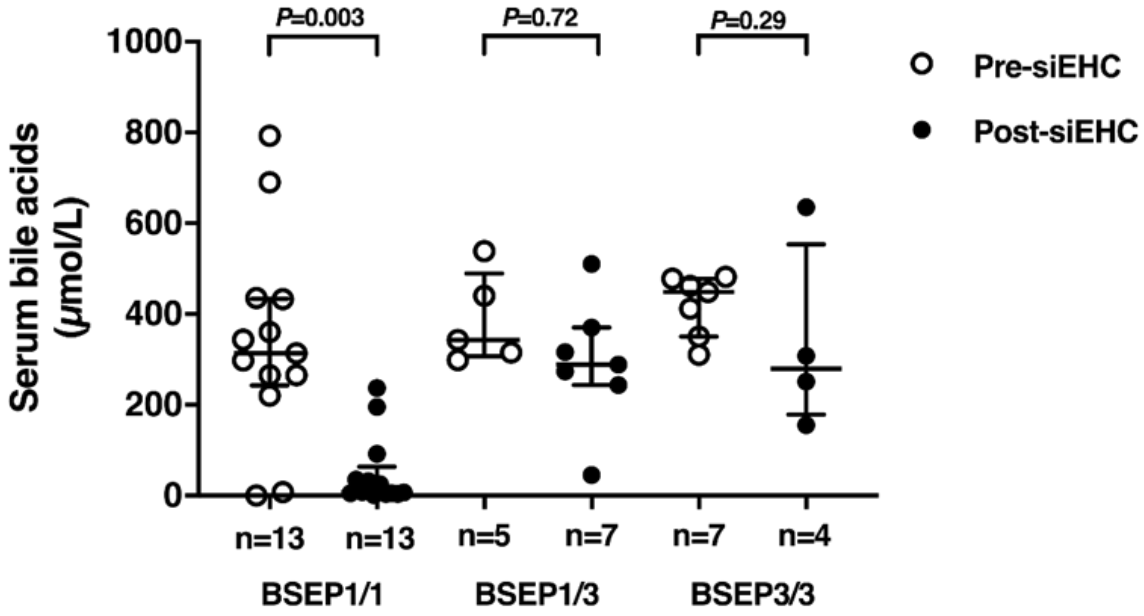

Fig. S7. Serum bile acids prior to (open symbols) and after (closed symbols) surgical biliary diversion. In (unpaired) patients with a BSEP1/1, BSEP1/3 or BSEP3/3 genotype. Wilcoxon signed-rank test. Bars represent median and IQR. *BSEP (bile salt export pump); siEHC (surgical interruption of the enterohepatic circulation).*

Table S1. Overview of genetic BSEP categories

BSEP category	BSEP subgroup	Genetic definition
BSEP1	BSEP1/1	p.D482G or p.E297G on both alleles
	BSEP1/2	p.D482G or p.E297G on one allele; missense mutation other than p.D482G or p.E297G on second allele
	BSEP1/3	p.D482G or p.E297G on one allele; predicted protein truncating mutation on second allele
BSEP2	BSEP2/2	missense mutation other than p.D482G or p.E297G on both alleles
	BSEP2/3	missense mutation other than p.D482G or p.E297G on one allele; predicted protein truncating mutation on second allele
BSEP3	BSEP3/3	predicted protein truncating mutation on both alleles

BSEP (bile salt export pump).

Table S2. Genetic profile (i.e. mutations in *ABCB11* on first and second allele) and corresponding genotype severity allocation of the 138 included patients.

	First allele	Previous reports	Second allele	n	Previous reports
BSEP1/1	**BSEP1**		**BSEP1**	**31**	
	c.890A>G; p.Glu297Gly	Van Wessel et al. J Hepatol 2020, Varma et al. Hepatology 2015, Davit-Spraul et al. Hepatology 2010, Pawlikowska et al. J Hepatol 2010, Strautnieks et al. Gastroenterology 2008	c.890A>G; p.Glu297Gly	**19**	Van Wessel et al. J Hepatol 2020, Varma et al. Hepatology 2015, Davit-Spraul et al. Hepatology 2010, Pawlikowska et al. J Hepatol 2010, Strautnieks et al. Gastroenterology 2008
	c.1445A>G; p.Asp482Gly	Van Wessel et al. J Hepatol 2020, Jankowska et al. J Pediatr Gastroenterol Nutr. 2016, Czubkowski et al. Ann Hepatol. 2015, Jankowska et al. J Pediatr Gastroenterol Nutr. 2014, Pawlikowska et al. J Hepatol 2010, Pawlikowska et al. J Hepatol 2010, Strautnieks et al. Gastroenterology 2008, Strautnieks et al. Gastroenterology 2008	c.1445A>G; p.Asp482Gly	**12**	Van Wessel et al. J Hepatol 2020, Jankowska et al. J Pediatr Gastroenterol Nutr. 2016, Czubkowski et al. Ann Hepatol. 2015, Jankowska et al. J Pediatr Gastroenterol Nutr. 2014, Pawlikowska et al. J Hepatol 2010, Pawlikowska et al. J Hepatol 2010, Strautnieks et al. Gastroenterology 2008, Strautnieks et al. Gastroenterology 2008
BSEP1/3	BSEP1		BSEP3	**30**	
	c.890A>G; p.Glu297Gly		c.2906_17del; p.Lys969_Lys972del	**2**	Van Wessel et al. J Hepatol 2020, Strautnieks et al.

					Gastroenterology 2008
	c.890A_G; p.Glu297Gly		c.1583_1584delTA; p.Ile528SerfsTer21	**2**	Van Wessel et al. J Hepatol 2020, Strautnieks et al. Gastroenterology 2008
	c.890A_G; p.Glu297Gly		c.611+1G>A; Splice site 3' intron 7	**2**	Van Wessel et al. J Hepatol 2020, Strautnieks et al. Gastroenterology 2008
	c.890A>G; p.Glu297Gly		c.2012-8T>G; Splice site 3' Intron 16	**1**	Van Wessel et al. J Hepatol 2020, Grammatikopoulos et al. J Pediatr Gastroenterol Nutr 2015, Strautnieks et al. Gastroenterology 2008
	c.890A_G; p.Glu297Gly		c.1826-1827dup; p.lle610Gln fsX45 (p.lle610GlnfsTer45)	**1**	Van Wessel et al. J Hepatol 2020, Davit-Spraul et al. Hepatology 2010
	c.890A_G; p.Glu297Gly		c.1435-17_1450dup33bp; p.His484ArgfsX5 (p.His484ArgfsTer5)	**1**	Van Wessel et al. J Hepatol 2020, Davit-Spraul et al. Hepatology 2010
	c.890A>G; p.Glu297Gly		c.3904G>T; p.Glu1302X	**1**	Van Wessel et al. J Hepatol 2020, Strautnieks et al. Gastroenterology 2008
	c.890A>G; p.Glu297Gly		c.2343+1G>T; Splice site 5' intron 19	**1**	Van Wessel et al. J Hepatol 2020, Strautnieks et al. Gastroenterology 2008
	c.890A_G; p.Glu297Gly		c.3268C>T, p.R1090X (p.Arg1090Ter)	**1**	Van Wessel et al. J Hepatol 2020, Davit-Spraul et al. Hepatology 2010, Strautnieks et al. Gastroenterology 2008

	c.890A_G; p.Glu297Gly		c.1723C>T; p.Arg575X (p.Arg575Ter)	**1**	Van Wessel et al. J Hepatol 2020, Strautnieks et al. Nature Genetics 1998, Strautnieks et al. Gastroenterology 2008
	c.890A_G; p.Glu297Gly		c.2343+1G>T; Splice site 5' intron 19	**1**	Van Wessel et al. J Hepatol 2020, Strautnieks et al. Gastroenterology 2008
	c.890A_G; p.Glu297Gly		c.3491delT;p.Val1164Glyfs*7 (p.Val1164GlyfsTer7)	**1**	Van Wessel et al. J Hepatol 2020, Strautnieks et al. Gastroenterology 2008
	c.890A_G; p.Glu297Gly		c.3169C>T; p.Arg1057* (p.Arg1057Ter or R575X)	**1**	Van Wessel et al. J Hepatol 2020, Liu et al. Liver Int. 2018, Strautnieks et al. Nature Genetics 1998
	c.890A_G; p.Glu297Gly		c.541-546delAAAATC, K208-I209del (p.Arg181_Ile182del)	**1**	Van Wessel et al. J Hepatol 2020
	c.890A_G; p.Glu297Gly		c.1146_1166del; p.Phe383_Ala389del	**1**	Van Wessel et al. J Hepatol 2020
	c.890A_G; p.Glu297Gly		c.390G>T; p.G130G	**1**	-
	c.890A_G; p.Glu297Gly		c.3945delC	**1**	-
	c.890A_G; p.Glu297Gly		c.1966_1967delTT	**1**	-
	c.1445A>G; p.Asp482Gly		c.1558 A>T; p.Arg520X (p.Arg520Ter)	**2**	Van Wessel et al. J Hepatol 2020, Strautnieks et al. Gastroenterology 2008
	c.1445A>G; p.Asp482Gly		c.2343+1G>A; Splice site 5' intron 19	**2**	Van Wessel et al. J Hepatol 2020, Strautnieks et al. Gastroenterology 2008
	c.1445A>G; p.Asp482Gly		c.1198-1G>C; p.? Splice site	**1**	Van Wessel et al. J Hepatol 2020, Varma et al. Hepatology 2015
	c.1445A>G; p.Asp482Gly		c.2178+1G>A; Splice site 5' Intron 18	**1**	Van Wessel et al. J Hepatol 2020,

					Strautnieks et al. Gastroenterology 2008
	c.1445A>G; p.Asp482Gly		c.908 +1 G>T; p.? Splice site	**1**	Van Wessel et al. J Hepatol 2020, Strautnieks et al. Gastroenterology 2008
	c.1445A>G; p.Asp482Gly		c.1081 C>T p.Gln361	**1**	-
	c.1445A>G; p.Asp482Gly		c.3804delG	**1**	-
BSEP3/3	BSEP3		BSEP3	**77**	Missing 1
	c.1062T>A;p.Tyr354X	Van Wessel et al. J Hepatol 2020, Van Wessel et al. J Hepatol 2020, Davit-Spraul et al. Hepatology 2010	c.1062T>A;p.Tyr354X	**7**	Van Wessel et al. J Hepatol 2020, Davit-Spraul et al. Hepatology 2010
	c.379delA; p.Thr127HisfsX6	Van Wessel et al. J Hepatol 2020, Shagrani et al. Clin Genet 2017, Strautnieks et al. Gastroenterology 2008	c.379delA; p.Thr127HisfsX6	**7**	Van Wessel et al. J Hepatol 2020, Shagrani et al. Clin Genet 2017, Strautnieks et al. Gastroenterology 2008
	c.3904G>T; p.Glu1302Ter (p.E1302*)	Van Wessel et al. J Hepatol 2020, Strautnieks et al. Gastroenterology 2008	c.3904G>T; p.Glu1302Ter (p.E1302*)	**5**	Van Wessel et al. J Hepatol 2020, Strautnieks et al. Gastroenterology 2008
	c.1243C>T; p.Arg415X (R415X)	Van Wessel et al. J Hepatol 2020, Liu et al. Liver Int. 2018, Davit-Spraul et al. Hepatology 2010	c.1243C>T; p.Arg415X (R415X)	**2**	Van Wessel et al. J Hepatol 2020, Liu et al. Liver Int. 2018, Davit-Spraul et al. Hepatology 2010
	c.3268C>T; p.R1090X	Van Wessel et al. J Hepatol 2020, Davit-Spraul et al. Hepatology 2010, Strautnieks et al. Gastroenterology 2008	c.3268C>T; p.R1090X	**2**	Van Wessel et al. J Hepatol 2020, Davit-Spraul et al. Hepatology 2010, Strautnieks et al. Gastroenterology 2008
	c.3213+1delG; p.Asp1072ThrfsX25	Van Wessel et al. J Hepatol 2020, Strautnieks et al.	c.3213+1delG; p.Asp1072ThrfsX25	**2**	Van Wessel et al. J Hepatol 2020, Strautnieks et al.

		Gastroenterology 2008			Gastroenterology 2008
	c.1062T>A; p.Tyr354X	Van Wessel et al. J Hepatol 2020	c.2931delA;p.Ala978Profs*9	**2**	Van Wessel et al. J Hepatol 2020
	c.3400>T; p.Gln1134Ter (exon 25)	Van Wessel et al. J Hepatol 2020	c.3400>T; p.Gln1134Ter (exon 25)	**2**	Van Wessel et al. J Hepatol 2020
	c.1385T>C; pJ420T + ivs19 rearr	-	c.1457T>C; p.V444A + c.3307del ATCA; p.I1061fs1095X	**2**	Dröge et al. J Hepatol. 2017
	c.1639-2A>C	-	c.1639-2A>C	**2**	-
	c.145C>T; p.Gln49X	Van Wessel et al. J Hepatol 2020, Liu et al. Liver Int. 2018	c.908+5G>A	**1**	Van Wessel et al. J Hepatol 2020, Wang et al. Pediat Res 2019, Liu et al. Liver Int 2018, Wang et al. Hepatol Res 2018
	c.2012-8T>G splice site 3' Intron 16	Van Wessel et al. J Hepatol 2020, Grammatikopoulos et al. J Pediatr Gastroenterol Nutr 2015, Strautnieks et al. Gastroenterology 2008	c.1941delA; p.Gly648ValfsX6	**1**	Van Wessel et al. J Hepatol 2020, Strautnieks et al. Gastroenterology 2008
	c.2012-8T>G splice site 3' Intron 16	Van Wessel et al. J Hepatol 2020, Grammatikopoulos et al. J Pediatr Gastroenterol Nutr 2015, Strautnieks et al. Gastroenterology 2008	c.1146_1166del;p.Phe383_Ala389del	**1**	Van Wessel et al. J Hepatol 2020
	c.2012-8T>G splice site 3' Intron 16	Van Wessel et al. J Hepatol 2020, Grammatikopoulos et al. J Pediatr Gastroenterol Nutr 2015, Strautnieks et al. Gastroenterology 2008	c.1142_1162 del	**1**	Van Wessel et al. J Hepatol 2020, Grammatikopoulos et al. J Pediatr Gastroenterol Nutr 2015
	c.1408C>T; p.Arg470Ter (p.R470*)	Van Wessel et al. J Hepatol 2020, Davit-Spraul et a. JIMD Rep 2014	c.1941delA; p.Gly648Valfs*6	**1**	Van Wessel et al. J Hepatol 2020, Strautnieks et al. Gastroenterology 2008

	c.1308+2T>A; Splicing	Van Wessel et al. J Hepatol 2020	c.1408C>T; p.Arg470Ter (p.R470*)	**1**	Van Wessel et al. J Hepatol 2020, Davit-Spraul et a. JIMD Rep 2014
	c.3213+5G>A	Van Wessel et al. J Hepatol 2020	c.3575delC; p.Ala1192GlufsTer51 (p.Ala1192GlufsX51)	**1**	Van Wessel et al. J Hepatol 2020, Davit-Spraul et al. Hepatology 2010
	IVS17 + 1T>A; Splicing	Van Wessel et al. J Hepatol 2020, Jara et al. N Engl J Med 2009	IVS17 + 1T>A; Splicing	**1**	Van Wessel et al. J Hepatol 2020, Jara et al. N Engl J Med 2009
	c.2611-2 A>T; Splice site 3' intron 22	Van Wessel et al. J Hepatol 2020, Strautnieks et al. Gastroenterology 2008	c.2611-2 A>T; Splice site 3' intron 22	**1**	Van Wessel et al. J Hepatol 2020, Strautnieks et al. Gastroenterology 2008
	c.3904G>T; p.Glu1302X	Van Wessel et al. J Hepatol 2020, Strautnieks et al. Gastroenterology 2008	c.2178+1G>A; Splice site 5' Intron 18	**1**	Van Wessel et al. J Hepatol 2020, Strautnieks et al. Gastroenterology 2008
	c.3169C>T; p.Arg1057X	Van Wessel et al. J Hepatol 2020, Liu et al. Liver Int. 2018, Strautnieks et al. Nature Genetics 1998	c.3169C>T; p.Arg1057X	**1**	Van Wessel et al. J Hepatol 2020, Liu et al. Liver Int. 2018, Strautnieks et al. Nature Genetics 1998
	c.2178+1G>A; Splice site 5' Intron 18	Van Wessel et al. J Hepatol 2020, Strautnieks et al. Gastroenterology 2008	c.2178+1G>A; Splice site 5' Intron 18	**1**	Van Wessel et al. J Hepatol 2020, Strautnieks et al. Gastroenterology 2008
	c.1792C>T; p.Gln598Ter (p.Q598*)	Van Wessel et al. J Hepatol 2020	c.1792C>T; p.Gln598Ter (p.Q598*)	**1**	Van Wessel et al. J Hepatol 2020
	c.150+3A>G; Splice site 3' intron 4	Van Wessel et al. J Hepatol 2020	c.150+3A>G; Splice site 3' intron 4	**1**	Van Wessel et al. J Hepatol 2020
	c.1489C>T; p.Qln497X	Van Wessel et al. J Hepatol 2020, Liu et al. Liver Int. 2018	c.2197C>T; p.Qln733X	**1**	Van Wessel et al. J Hepatol 2020, Liu et al. Liver Int. 2018
	c.145C>T; p.Gln49X	Van Wessel et al. J Hepatol 2020	c.3169C?T; p.Arg1057X	**1**	Van Wessel et al. J Hepatol 2020, Liu et al. Liver Int. 2018, Strautnieks et al. Nature Genetics 1998
	c.1416T>C; p.Y472* (p.Tyr472Ter)	Van Wessel et al. J Hepatol. 2020,	c.1416T>C; p.Y472* (p.Tyr472Ter)	**1**	Van Wessel et al. J Hepatol 2020,

		Strautnieks et al. Gastroenterology 2008			Strautnieks et al. Gastroenterology 2008
	c.1723C>T; p.R575X	Van Wessel et al. J Hepatol 2020, Strautnieks et al. Gastroenterology 2008, Strautnieks et al. Nature Genetics 1998	c.2178+1G>T; Splice site 5' Intron 18	**1**	Van Wessel et al. J Hepatol 2020, Strautnieks et al. Gastroenterology 2008
	c.1723C>T; P.Arg575X	Van Wessel et al. J Hepatol 2020, Strautnieks et al. Nature Genetics 1998, Strautnieks et al. Gastroenterology 2008	c.1723C>T; P.Arg575X	**1**	Van Wessel et al. J Hepatol 2020, Strautnieks et al. Gastroenterology 2008, Strautnieks et al. Nature Genetics 1998
	c.2787_2788insGAGAT; p.k930EfsX79 + c.3457C>T; p.R1153C	Liu et al. Liver Int. 2018, Strautnieks et al. Gastroenterology 2008, Strautnieks et al. Nature Genetics 1998	c.2787_2788insGAGAT; p.k930EfsX79 + c.3457C>T; p.R1153C	**1**	Liu et al. Liver Int. 2018, Strautnieks et al. Gastroenterology 2008, Strautnieks et al. Nature Genetics 1998
	c.1197+1G>T; Splicing	Van Wessel et al. J Hepatol 2020	c.1197+1G>T; Splicing	**1**	Van Wessel et al. J Hepatol 2020
	743-745 delTTA; p.Ile206del (I206del)	Van Wessel et al. J Hepatol 2020	743-745 delTTA; p.Ile206del (I206del)	**1**	Van Wessel et al. J Hepatol 2020
	c.1826_1827dupCA;p.IleGlnfs*45	Van Wessel et al. J Hepatol 2020	c.1826_1827dupCA;p.IleGlnfs*45	**1**	Van Wessel et al. J Hepatol 2020
	Duplication exons 14-28	Van Wessel et al. J Hepatol 2020	c.2177_2178+1delAGGinsGT	**1**	Van Wessel et al. J Hepatol 2020
	Deletion exons 6-9	Van Wessel et al. J Hepatol 2020	Deletion exons 6-9	**1**	Van Wessel et al. J Hepatol 2020
	c.2T>A; p.Met1?	Van Wessel et al. J Hepatol 2020	c.2T>A; p.Met1?	**1**	Van Wessel et al. J Hepatol 2020
	c.2692del; p.Trp898Gly	Van Wessel et al. J Hepatol 2020	c.2692del; p.Trp898Gly	**1**	Van Wessel et al. J Hepatol 2020
	c.3945delC	-	c.1408C>T; p.Arg470Ter (p.R470*)	**1**	Van Wessel et al. J Hepatol 2020, Davit-Spraul et a. JIMD Rep 2014
	c.2319dupC	-	c.1146_1166del;p.Phe383_Ala389del	**1**	Van Wessel et al. J Hepatol 2020
	c.2178+1G>A; Splice site 5' Intron 18	Van Wessel et al. J Hepatol 2020,	c.389+8G>A	**1**	-

		Strautnieks et al. Gastroenterology 2008			
	c.611 + 1G>A; Splice site 3' intron 7	Van Wessel et al. J Hepatol 2020, Strautnieks et al. Gastroenterology 2008	c.1881 dupT, p.splice, G628*	**1**	-
	c.409G>T	Liu et al. Liver Int. 2018	c.2542delG	**1**	-
	c.2327delT; p.Leu776Stop	-	c.2327delT; p.Leu776Stop	**1**	-
	c.3174delA; p.Gln1058fsX (p.Gln1058Hlsfs´39)	-	c.3174delA; p.Gln1058fsX (p.Gln1058Hlsfs´39)	**1**	-
	c.2380C>T; p.Q794X	-	c.2380C>T; p.Q794X	**1**	-
	c.989G>A; p.Trp330Ter	-	c.989G>A; p.Trp330Ter	**1**	-
	c.2115C>A; p.Tyr705Ter	-	c.2115C>A; p.Tyr705Ter	**1**	-
	c.1810-3C>G	-	c.1810-3C>G	**1**	-
	c.3586C>T	-	c.3586C>T	**1**	-
	c.1271delA	-	c.22C>T	**1**	-
	c.1827insCA; p.Ile610Glnfs*45	-	c.1827insCA; p.Ile610Glnfs*45	**1**	-
	g.24774-42062del	-	g.24774-42062del	**1**	-
	Deletion of exon 9	-	Deletion of exon 9	**1**	-
	Deletion of exons 15-17	-	Deletion of exons 15-17	**1**	-
BSEP (bile salt export pump). *Adapted from van Wessel et. al. J Hepatol. 2020.*					

Table S3. Indication for liver transplantation per BSEP category

	BSEP1/1 (n=7/31)	BSEP1/3 (n=20/30)	BSEP3/3 (n=39/77)
Pruritus	2	12	10
End-stage liver disease	4	8	23
HCC	1	0	4
Other	0	0	2

BSEP (bile salt export pump); HCC (hepatocellular carcinoma); n (number).