

Low frequency of cancer-predisposition gene mutations in liver transplant candidates with hepatocellular carcinoma

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Table S1: List of CZE CANCA consortium members

Institution	Members
Institute of Biochemistry and Experimental Oncology, First Faculty of Medicine, Charles University, Prague, Czech Republic	Zdenek Kleibl, Jana Soukupova, Marketa Janatova Petra Zemankova, Marianna Borecka
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Table S2: List of 226 genes included in the CZECA panel (and used transcription variants), divided into two groups based on their clinical significance.

Established high-to-moderate CPG (N = 48)	<p><i>APC</i> (NM_000038), <i>ATM</i> (NM_000051), <i>BAP1</i> (NM_004656), <i>BARD1</i> (NM_000465), <i>BMPRIA</i> (NM_004329), <i>BRCA1</i> (NM_007294), <i>BRCA2</i> (NM_000059), <i>BRIPI</i> (NM_032043), <i>CDHI</i> (NM_004360), <i>CDK4</i> (NM_000075), <i>CDKN2A</i> (NM_000077), <i>CHEK2</i> (NM_007194), <i>EPCAM</i> (NM_002354), <i>FH</i> (NM_000143), <i>FLCN</i> (NM_144997), <i>KIT</i> (NM_000222), <i>MEN1</i> (NM_000244), <i>MET</i> (NM_001127500), <i>MLH1</i> (NM_000249), <i>MSH2</i> (NM_000251), <i>MSH6</i> (NM_000179), <i>MUTYH</i>* (NM_001128425), <i>NBN</i> (NM_002485), <i>NFI</i> (NM_000267), <i>NF2</i> (NM_000268), <i>PALB2</i> (NM_024675), <i>PMS2</i> (NM_000535), <i>POLD1</i> (NM_002691), <i>POLE</i> (NM_006231), <i>PRKARIA</i> (NM_212471), <i>PTEN</i> (NM_000314), <i>PTCH1</i> (NM_000264), <i>RAD51C</i> (NM_058216), <i>RAD51D</i> (NM_002878), <i>RBI</i> (NM_000321), <i>RET</i> (NM_020975), <i>SDHB</i> (NM_003000), <i>SDHC</i> (NM_003001), <i>SDHD</i> (NM_003002), <i>SMAD4</i> (NM_005359), <i>SMARCB1</i> (NM_003073), <i>STK11</i> (NM_000455), <i>SUFU</i> (NM_016169), <i>TP53</i> (NM_000546), <i>TSC1</i> (NM_000368), <i>TSC2</i> (NM_000548), <i>VHL</i> (NM_000551), <i>WT1</i> (NM_024426)</p>
Candidate CPG (N = 178)	<p><i>AIP</i> (NM_003977), <i>ALK</i> (NM_004304), <i>APEXI</i> (NM_001641), <i>ATMIN</i> (NM_015251), <i>ATR</i> (NM_001184), <i>ATRIP</i> (NM_130384), <i>AURKA</i> (NM_198433), <i>AXINI</i> (NM_003502), <i>BABAMI</i> (NM_001033549), <i>BLM</i> (NM_000057), <i>BRAP</i> (NM_006768), <i>BRCC3</i> (NM_024332), <i>BRE</i> (NM_004899), <i>BUB1B</i> (NM_001211), <i>CASP8</i> (NM_001080125), <i>CCND1</i> (NM_053056), <i>CDC73</i> (NM_024529), <i>CDKN1B</i> (NM_004064), <i>CDKN1C</i> (NM_000076), <i>CEBPA</i> (NM_004364), <i>CEP57</i> (NM_014679), <i>CHEK1</i> (NM_001114122), <i>CLSPN</i> (NM_022111), <i>CSNK1D</i> (NM_001893), <i>CSNK1E</i> (NM_001894), <i>CWF19L2</i> (NM_152434), <i>CYLD</i> (NM_015247), <i>DCLRE1C</i> (NM_001033855), <i>DDB2</i> (NM_000107), <i>DHFR</i> (NM_000791), <i>DICER1</i> (NM_030621), <i>DIS3L2</i> (NM_152383), <i>DMBT1</i> (NM_007329), <i>DMC1</i> (NM_007068), <i>DNAJC21</i> (NM_194283), <i>DPYD</i> (NM_000110), <i>EGFR</i> (NM_005228), <i>EMSY</i> (NM_001300942), <i>EPHX1</i> (NM_000120), <i>ERCC1</i> (NM_001983), <i>ERCC2</i> (NM_000400), <i>ERCC3</i> (NM_000122), <i>ERCC4</i> (NM_005236), <i>ERCC5</i> (NM_000123), <i>ERCC6</i> (NM_000124), <i>ESR1</i> (NM_000125), <i>ESR2</i> (NM_001437), <i>EXO1</i> (NM_006027), <i>EXT1</i> (NM_000127), <i>EXT2</i> (NM_000401), <i>EYA2</i> (NM_005244), <i>EZH2</i> (NM_004456), <i>FAAP24</i> (NM_152266), <i>FAM175A</i> (NM_139076), <i>FAM175B</i> (NM_032182), <i>FAN1</i> (NM_014967), <i>FANCA</i> (NM_000135), <i>FANCB</i> (NM_001018113), <i>FANCC</i> (NM_000136), <i>FANCD2</i> (NM_033084), <i>FANCE</i> (NM_021922), <i>FANCF</i> (NM_022725), <i>FANCG</i> (NM_004629), <i>FANCI</i> (NM_001113378), <i>FANCL</i> (NM_001114636), <i>FANCM</i> (NM_020937), <i>FBXW7</i> (NM_033632), <i>GADD45A</i> (NM_001924), <i>GATA2</i> (NM_001145661), <i>GPC3</i> (NM_004484), <i>GRB7</i> (NM_001242442), <i>HELQ</i> (NM_133636), <i>HNF1A</i> (NM_001306179), <i>HOXB13</i> (NM_006361), <i>HRAS</i> (NM_005343), <i>HUS1</i> (NM_004507), <i>KAT5</i> (NM_182710), <i>KCNJ5</i> (NM_000890), <i>LIG1</i> (NM_000234), <i>LIG3</i> (NM_013975), <i>LIG4</i> (NM_002312), <i>LMO1</i> (NM_002315), <i>LRIG1</i> (NM_015541), <i>MAX</i> (NM_002382), <i>MCPHI</i> (NM_024596), <i>MDC1</i> (NM_014641), <i>MDM2</i> (NM_002392), <i>MDM4</i> (NM_002393), <i>MGMT</i> (NM_002412), <i>MLH3</i> (NM_001040108), <i>MMP8</i> (NM_002424), <i>MPL</i> (NM_005373), <i>MRE11A</i> (NM_005591), <i>MSH3</i> (NM_002439), <i>MSH5</i> (NM_002441), <i>MSR1</i> (NM_138715), <i>MUS81</i> (NM_025128), <i>NATI</i> (NM_000662), <i>NCAM1</i> (NM_001242607), <i>NELFB</i> (NM_015456), <i>NFKBIZ</i> (NM_031419), <i>NHEJ1</i> (NM_024782), <i>NSD1</i> (NM_022455), <i>OGG1</i> (NM_002542), <i>PARP1</i> (NM_001618), <i>PCNA</i> (NM_002592), <i>PHB</i> (NM_002634), <i>PHOX2B</i> (NM_003924), <i>PIK3CG</i> (NM_002649), <i>PLA2G2A</i> (NM_000300), <i>PMS1</i> (NM_000534), <i>POLB</i> (NM_002690), <i>PPM1D</i> (NM_003620), <i>PREX2</i> (NM_024870), <i>PRF1</i> (NM_001083116), <i>PRKDC</i> (NM_006904), <i>PTTG2</i> (NM_006607), <i>RAD1</i> (NM_002853), <i>RAD17</i> (NM_133338), <i>RAD18</i> (NM_020165), <i>RAD23B</i> (NM_002874), <i>RAD50</i> (NM_005732), <i>RAD51</i> (NM_133487), <i>RAD51API</i> (NM_001130862), <i>RAD51B</i> (NM_133509), <i>RAD52</i> (NM_134424), <i>RAD54B</i> (NM_012415), <i>RAD54L</i> (NM_003579), <i>RAD9A</i> (NM_004584), <i>RBBP8</i> (NM_002894), <i>RECQL</i> (NM_002907), <i>RECQL4</i> (NM_004260), <i>RECQL5</i> (NM_004259), <i>RFC1</i> (NM_002913), <i>RFC2</i> (NM_181471), <i>RFC4</i> (NM_181573), <i>RHBDP2</i> (NM_024599), <i>RNF146</i> (NM_001242844), <i>RNF168</i> (NM_152617), <i>RNF8</i> (NM_003958), <i>RPA1</i> (NM_002945), <i>RUNX1</i> (NM_001754), <i>SBDS</i> (NM_016038), <i>SDHA</i> (NM_004168), <i>SDHAF2</i> (NM_017841), <i>SETBP1</i> (NM_015559), <i>SETX</i> (NM_015046), <i>SHPRH</i> (NM_001042683), <i>SLX4</i> (NM_032444), <i>SMARCA4</i> (NM_001128849), <i>SMARCE1</i> (NM_003079), <i>TCL1A</i> (NM_021966), <i>TELO2</i> (NM_016111), <i>TERF2</i> (NM_005652), <i>TERT</i> (NM_198253), <i>TLR2</i> (NM_003264), <i>TLR4</i> (NM_138554), <i>TMEM127</i> (NM_017849), <i>TOPBP1</i> (NM_007027), <i>TP53BP1</i> (NM_001141980), <i>TSHR</i> (NM_000369), <i>UBE2A</i> (NM_003336), <i>UBE2B</i> (NM_003337), <i>UBE2I</i> (NM_003345), <i>UBE2V2</i> (NM_003350), <i>UBE4B</i> (NM_001105562), <i>UIMC1</i> (NM_001199297), <i>WRN</i> (NM_000553), <i>XPA</i> (NM_000380), <i>XPC</i> (NM_004628), <i>XRCC1</i> (NM_006297), <i>XRCC2</i> (NM_005431), <i>XRCC3</i> (NM_005432), <i>XRCC4</i> (NM_022406), <i>XRCC5</i> (NM_021141), <i>XRCC6</i> (NM_001469), <i>ZNF350</i> (NM_021632), <i>ZNF365</i> (NM_014951)</p>

* only in case of homozygote or compound heterozygote.

Table S3: Clinicopathological characteristics in 334 HCC patients' subgroups of carriers PV in cancer-predisposition genes (any CPG) and non-carriers (None). The characteristics in all patients and in PV carrier subgroups did not differ from that in non-carriers except for those denoted by an asterisk (* <0.05).

	Any CPG N=47	Established CPG (N=7)	Candidate CPG (N=40)	None N=287
Age [years]; median (range)	65 (40-77)	69 (53-72)	64 (40-77)	63 (26-76)
Cirrhosis ; N= (%)	45 (95.7)	7 (100)	38 (95)	284 (99)
Alcoholic	12 (25.5)	3 (42.9)	9 (22.5)	117 (40.8)
Viral	18 (38.3)	3 (42.9)	15 (37.5)	102 (35.5)
Cholestatic & autoimmune	10 (21.3)	1 (14.3)	9 (22.5)	38 (13.2)
NASH (non-alcoholic steatohepatitis)	5 (10.6)	0	5 (12.5)	24 (8.4)
Metabolic	0	0	0	3 (1.0)
None	2 (4.3)	0	2 (5.0)	3 (1.0)
Treatment ; N= (%)				
Liver transplantation	42 (89.4)	5 (71.4)	37 (92.5)	257 (89.5)
Other	5 (10.6)	2 (28.6)	3 (7.5)	30 (10.4)
HCC characteristics				
AFP [ng/mL]; median (range)	8 (2-1210)	9.6 (2-1210)	6.5 (2-699)	
Milan criteria; N= (% of known)	30 (63.8)	4 (57.1)	26 (65.0)	190 (66.2)
Microangioinvasion; N= (% of known)	21 (55.3)	3 (60.0)	18 (54.5)	107 (44.0)
Cholangiocarc. differentiation; N= (% of known)	0	0	0	18 (7.1)
Grading ; N= (% of known)				
1	5 (12.5)	1 (16.7)	4 (11.8)	32 (13.1)
2	19 (47.5)	2 (33.3)	17 (50.0)	135 (55.1)
3	16 (40.0)	3 (50.0)	13 (38.2)	78 (31.8)
Second primary tumor ; N= (%)	10 (21.4)	3 (42.9)	7 (17.5)	47 (16.4)
Malignancy in 1st/2nd degree relatives ; N= (%)	22 (46.8)	3 (42.9)	19 (47.5)	109 (38.0)
Diabetes ; N= (%)	16 (34.0)	1 (14.3)	15 (37.5)	122 (42.5)
Obesity (BMI>30) ; N= (%)	9 (19.1)	2 (28.6)	7 (17.5)	85 (29.6)
Smoking ; N= (%)	19 (40.4)	2 (28.6)	17 (42.5)*	173 (60.3)*

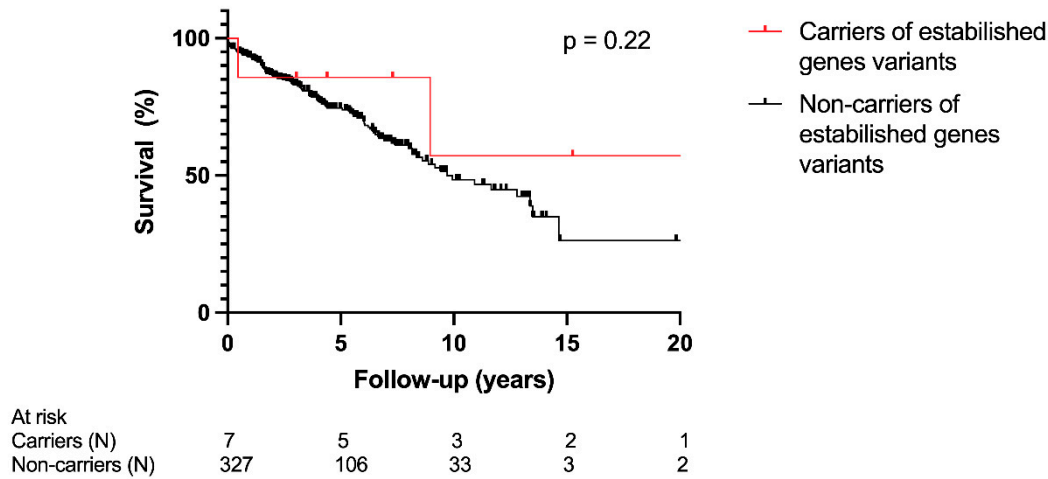
Table S4: Characterization of HCC patients from retrospective CZECAICA consortium database. Positive cancer-related characteristics are highlighted in bold.

Pts #	Mutation	Age at HCC	Other tumor	Family cancer history	
CZE_1	0	39	0	positive	EC (mother@46), RCC (father@58), BC (mother's sister)
CZE_2	<i>BRCA1: c.1016delA (p.Lys339fs)</i>	44	0	positive	OvC (mother@36), RCC (mother's sister)
CZE_3	0	70	0	positive	GaC (father, sister)
CZE_4	0	NA	0	positive	PrC (mother's father@58), OvC (mother's mother@55)
CZE_5	0	NA	BC, RCC	negative	0
CZE_6	0	NA	RCC	negative	0
CZE_7	<i>CHEK2: c.1100delC (p.Thr367fs)</i>	NA	Bilateral BC	positive	PrC (father)
CZE_8	0	NA	EC, LuC	negative	0
CZE_9	0	33	0	positive	BC (mother's mother, mother's sister 1@56, mother's sister 2@50), PaC (father's mother)
CZE_10	0	27	0	negative	0
CZE_11	0	58	0	positive	UtC (mother), GaC (father)
CZE_12	0	64	0	positive	HCC (sister)
CZE_13	0	NA	0	negative	0
CZE_14	0	18	0	negative	0
CZE_15	0	NA	0	negative	0
CZE_16	0	60	0	positive	PaC (father), BC (father's sister), RCC (mother's brother@60; mother's mother), LuC&HCC (mother's father)
CZE_17	0	44	0	positive	CRC (mother's father@65)
CZE_18	0	NA	0	positive	PaC (sister), BC (mother), GaC (mother's sister), OvC (mother's mother)
CZE_19	0	59	BC	positive	GaC (sister@50)
CZE_20	0	NA	CRC	NA	NA

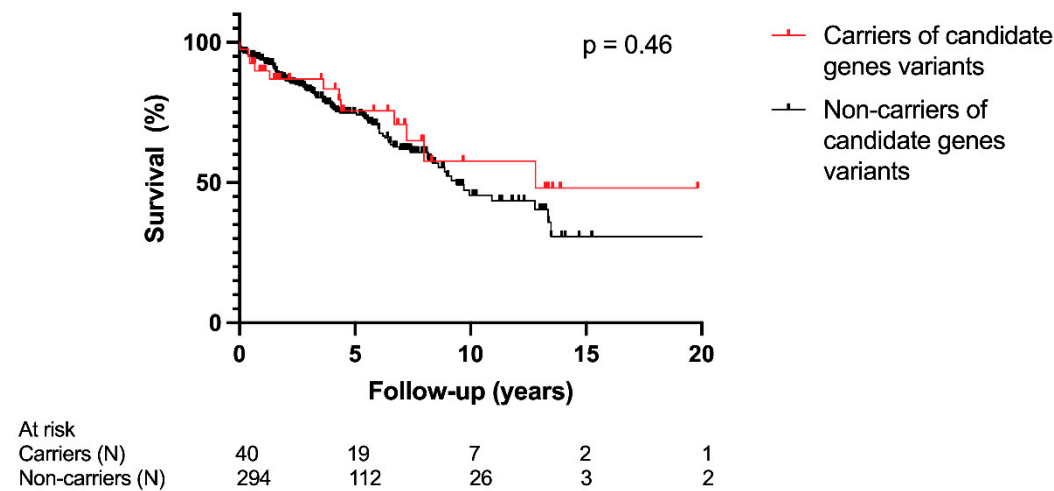
BC - breast cancer; EC – endometrial cancer; GaC – gastric cancer; HCC – hepatocellular carcinoma; LuC – lung cancer; OvC – ovarian cancer; PaC – pancreatic cancer; PrC – prostate cancer; RCC - renal cell carcinoma; UtC – uterine cancer; @ - diagnosis at age

Figure S1: Survival of variant carriers in A. established genes, B. candidate genes, C. MRN genes compared to non-carriers.

A.



B.



C.

