(n=3) tumors that were processed as FF and FFPE samples. The inset shows the numbers of non-synonymous mutations identified in individual MEG samples from mice treated at the specified dosages. (B) Venn diagram of the total numbers of non-synonymous mutations identified uniquely in the FF or FFPE samples and in both FF and FFPE samples for Spontaneous, GBE and MEG sets of tumors at higher (≥0.1) or lower (<0.1) alternate allele frequency. The concordance was calculated as a percentage of FF mutations that were also identified in the FFPE samples.

Figure 3. Analysis of mutational spectra of spontaneous tumors and tumors from mice treated with GBE or MEG. (A) The spectra of mutations based on the trinucleotide content (one nucleotide before to one nucleotide after the mutation). (B) Hierarchical clustering based on the Kullback-Leibler distance method after accounting for the differences in the trinucleotide composition of the human and mouse genomes. The six sets of samples were classified together with 30 “signatures” from COSMIC database

Supplementary Table 1. Number of exome reads and aligned reads for individual hepatocellular carcinoma samples

Supplementary Table 2. Comparison of results for Sanger sequencing and exome sequencing of known cancer genes

Supplementary Table 3. Novel mutations in cancer-related genes

Supplementary Table 4. Numbers of tumor versus normal variant calls for individual hepatocellular carcinoma samples

Supplementary Table 5. Sanger sequencing of variants of Braf and Bves that were identified by exome sequencing

Supplementary Table 6 -The corresponding mutation counts for each tumor type (Fresh frozen (FF-a) and formalin fixed paraffin embedded (FFPE-b)) that correspond to supplemental figure 2a and 2b, respectively.

Supplementary Table 7 - Mutation signatures in B6C3F1/N mouse hepatocellular carcinomas described within the trinucleotide context of the human exome.

Supplementary Figure 1-Depth of coverage for FF and FFPE samples

Supplementary figure 2 (A and B) - Mutation spectra for the fresh frozen (FF-2a) and formalin fixed paraffin embedded (FFPE-2b) hepatocellular carcinomas arising spontaneously or due to exposure to ginkgo biloba extract or methyleugenol. The corresponding mutation counts for each tumor type (fresh frozen (FF) and formalin fixed paraffin embedded (FFPE)) are indicated in Supplementary table 6 (a and b).

Supplementary Table 1. Number of exome reads and aligned reads for individual hepatocellular carcinoma samples

Treatment	Dose (mg/kg)	Preparation method	Tissue ID	Total sequenced reads	#aligned reads	%aligned reads
Normal-1	0	FF	VF268/SO2528	99,909,430	97,705,650	97.79%
		FFPE	9882762	134,489,342	130,906,095	97.34%
Normal-2	0	FF	VF279/SO2522	74,729,280	73,085,061	97.80%
		FFPE	9882767	144,379,422	136,726,125	94.70%
Normal-3	0	FF	VF280/SO2523	89,447,206	87,031,198	97.30%
		FFPE	9882768	122,254,168	117,468,216	96.09%
Spontaneous HCC-1	0	FF	VF202/BC15616	88,546,480	86,676,465	97.89%
		FFPE	700304	102,987,284	99,554,579	96.67%
Spontaneous HCC-2	0	FF	VF245/BC15585	80,122,034	78,341,949	97.78%
		FFPE	700347	150,007,584	144,112,680	96.07%
Spontaneous HCC-3	0	FF	VM8/BC1832	85,722,446	83,277,690	97.15%
		FFPE	9504548	133,591,894	126,845,412	94.95%
GBE-HCC-1	2000	FF	M175/BC15578	108,394,852	105,893,609	97.69%
		FFPE	700277	142,962,030	138,506,289	96.88%
GBE-HCC-2	2000	FF	M181/BC15563	94,837,604	92,776,192	97.83%
		FFPE	700283	137,617,250	133,795,509	97.22%
GBE-HCC-3	2000	FF	F398/BC15605	97,423,454	94,357,457	96.85%
		FFPE	700500	133,073,826	128,536,848	96.59%
GBE-HCC-4	2000	FF	F382/BC15624	92,511,592	87,754,207	94.86%
		FFPE	700484	154,709,004	148,999,350	96.31%
MEG-HCC-1	37	FF	M64/BC1867	90,947,190	87,932,423	96.69%
		FFPE	9504604	133,520,148	128,920,206	96.55%
MEG-HCC-2	75	FF	M129/BC1834	88,163,948	85,982,190	97.53%
		FFPE	9504669	138,456,470	133,507,288	96.43%
MEG-HCC-3	150	FF	M196/BC1885	90,509,450	88,169,757	97.41%
		FFPE	9504736	138,827,804	131,873,116	94.99%

Supplementary Table 2. Comparison of results for Sanger sequencing and exome sequencing of known cancer genes

Treatment	FF-Tissue ID	FFPE-Tissue ID	Gene	Variants identified by Sanger sequencing of FF	Variants identified by exome sequencing of FF	Variants identified by exome sequencing of FFPE
Spontaneous- HCC-1	VF202/BC15616	700304	*Hras*	Q61K	Q61K	Q61K
Spontaneous- HCC-2	VF245/BC15585	700347	*Hras*	Q61K	Q61K	Q61K

Spontaneous- HCC-3	VM8/BC1832	9504548				
GBE-HCC-1, 2000 mg/kg	M175/BC15578	700277	*Ctnnb1*	Δ5-26	-	-
GBE-HCC-2, 2000 mg/kg	M181/BC15563	700283	*Ctnnb1*	Δ5-13	-	-
GBE-HCC-3, 2000 mg/kg	F398/BC15605	700500	*Ctnnb1*	S45F	-	-
GBE-HCC-4, 2000 mg/kg	F382/BC15624	700484	*Ctnnb1*	T41A	T41A	-
				T42P	-	-
MEG-HCC-1, 37 mg/kg	M64/BC1867	9504604	*Ctnnb1*	D32Y	-	-
			Hras	Q61R	Q61R	Q61R
MEG-HCC-2, 75 mg/kg	M129/BC1834	9504669	*Ctnnb1*	D32N	D32N	-
				Q28L	-	-
MEG-HCC-3, 150 mg/kg	M196/BC1885	9504736	*Ctnnb1*	G34R	D32Y	
			Hras	Q34L	-	-

Gene	SIFT score		S1-FF	S1-FFPE	S2-FF	S2-FFPE	S3-FF	S3-FFPE
		ID:	VF202/BC	700304	VF245/BC	700347	VM8/BC1	9504548
2900026A02Rik	0		0	0	0	0	0	0
4930447C04Rik	0		0	0	0	0	0	0
4933403O08Rik	0		0	0	0	0	0	0
9330159F19Rik	0.01		0	0	0	0	0	0
A330021E22Rik	0		0	0	0	0	0	0
Abhd13	0		0	0	0	0	0	0
Acaca	0.01		G547A	0	0	0	0	0
Acad8	0		0	0	0	0	0	0
Acot4	0.02		0	0	0	0	0	0
Actn1	0.02		0	0	0	0	0	0
Adnp2	0.03		0	0	0	0	0	0
Akap6	0		0	0	0	0	0	0
Alb	0.02		0	0	0	0	0	0
Angel2	0		0	0	0	0	0	0
Ankrd5	0		0	0	0	0	0	0
Ano5	0.03		0	0	0	0	0	0
Apc	0.01		T617N	0	0	0	0	0
Atp1a2	0		0	0	0	0	0	0
Atp6v0a2	0		0	0	0	0	0	0
Atp8a2	0		0	0	0	0	0	0
B4galnt3	0.04		0	0	0	0	0	0
Bahd1	0.02		0	0	0	0	0	0
Baiap3	0.02		0	0	0	0	0	0
Best3	0		0	0	0	0	0	0
Blk	0		0	0	0	0	0	0
Bpifa1	0.01		0	0	0	0	0	0
Bpifb1	0		0	0	0	0	0	0
Bves	0		0	0	M66K	0	0	0
Bves	0		0	0	0	0	R180S	0
Bves	0		0	0	0	0	P195L	0
C3	0.04		0	0	0	0	0	0
C4b	0.02		0	S194P	0	0	0	0
C6	0		0	0	0	0	0	0
Cadps	0		0	0	0	0	0	0
Card10	0.01		0	0	0	0	0	0
Ccdc85b	0		0	0	0	0	0	0
Ccnb2	0.01		0	0	0	0	0	0
Ccr3	0.02		0	0	0	D134H	0	0
Cd200r4	0		0	0	0	0	0	0
Cd209b	0.03		K147M	0	0	0	0	0
Cdh7	0.03		0	0	0	0	0	0
Celsr3	0.01		0	0	0	0	0	0
Cfp	0		0	0	0	0	0	0
Chrna7	0.02		0	0	0	0	0	0

Ckmt2	0	0	0	0	0	0	0
Cramp1l	0	0	0	0	0	0	0
Dach1	0.01	0	0	0	0	0	0
Dct	0.02	0	0	0	0	0	0
Ddx26b	0	0	0	0	0	0	0
Ddx54	0.03	0	0	0	0	0	0
Dgcr14	0.02	0	0	0	0	0	0
Dhx29	0.01	0	0	0	0	0	0
Dhx35	0	L204F	0	L204F	0	0	0
Dhx38	0	0	0	0	0	0	0
Dmrta2	0	0	0	0	0	0	0
Dnahc7b	0.04	0	0	0	0	0	0
Dnm1	0.03	F582C	F582C	0	0	0	0
Dock10	0		0		0		0
Dub1	0	0	0	0	0	0	0
Dub3	0	0	0	0	0	0	0
Emb	0.04	0	0	0	0	0	0
Erbb4	0.03	0	0	0	0	0	0
Ercc5	0.03	0	0	0	0	0	0
Esr2	0	0	0	0	0	0	0
Etv5	0.01	0	0	0	0	0	0
F8	0.03	0	0	0	0	0	0
Fam108c	0	0	0	0	0	0	0
Fam151b	0.03	0	0	0	0	0	0
Fasn	0.04	E1830G	E1830G	0	0	0	0
Fat2	0	0	0	0	0	0	0
Fbln2	0.02	0	0	0	0	0	0
Fbln5	0	0	0	0	0	0	0
Flrt2	0	0	0	0	0	0	0
Fn1	0.03	0	0	0	0	0	0
Frmd3	0	0	0	0	0	0	0
Gal3st3	0	0	0	0	0	0	0
Gm10324	0	0	0	0	0	0	0
Gm15800	0	0	0	0	0	0	0
Gm6588	0.01	0	0	0	0	0	0
Gm7173	0.01	0	0	0	0	0	R632C
Gnas	0	0	0	0	0	0	0
Gpaa1	0	0	0	0	0	0	0
Gpr17	0	0	0	0	0	0	0
Gpr179	0.01	0	0	0	0	0	0
Gria1	0.02	0	0	0	0	0	0
Grip1	0	0	0	0	0	0	0
Grk4	0	0	0	0	0	0	0
Gspt1	0	0	0	0	0	0	0
Gyltl1b	0.02	0	0	0	0	0	0
H2-Q1	0.02	0	0	0	0	0	0
H6pd	0	0	0	0	0	0	0

Haghl	0.04	0	0	0	0	0	0
Hat1	0	0	0	0	0	0	0
Hfm1	0	0	0	0	0	0	0
Hist1h2ak	0	0	0	0	0	0	0
Hist1h2bc	0	0	0	0	R73C	0	R73C
Hkdc1	0.03	0	0	0	0	0	0
Hmcn1	0.01	0	0	0	0	0	0
Hnf4g	0	0	0	0	0	0	0
Hsd3b7	0	0	0	0	0	0	0
Htra2	0	0	0	0	0	0	0
Ibtk	0.01	0	0	0	0	0	0
Igf1r	0.02	0	0	0	0	0	0
Igsf9b	0.01	0	0	0	0	0	0
Impdh1	0.02	0	0	0	0	0	0
Inpp1	0	0	0	0	0	0	0
Inpp4b	0	0	0	0	0	0	0
Irx2	0	0	0	0	0	0	0
Islr2	0.01	E617D	0	0	0	0	0
Itga3	0.01	0	0	0	0	0	0
Jkamp	0	0	0	0	0	0	0
Kcnc3	0	0	0	0	0	0	0
Kcnd1	0.02	0	0	0	P10S	0	0
Kcnq3	0.01	0	0	0	0	0	0
Kif17	0	0	0	0	0	0	0
Kif5a	0	0	0	0	0	0	0
Kif5c	0	0	0	0	0	0	0
Klc2	0.01	0	0	0	0	0	0
Klf11	0.04	0	0	0	0	0	0
Klhl1	0	0	0	0	0	0	0
Klhl29	0.03	0	0	0	0	0	0
Krt25	0	0	0	0	0	0	0
Lamtor2	0	0	0	0	0	0	0
Ldb2	0	I320F	0	0	0	0	0
Liph	0.01	0	0	0	0	0	0
Lpin1	0.02	0	0	0	0	0	0
Lrp6	0.02	0	0	0	0	0	0
Lrrc15	0	0	0	0	0	0	0
Lrrc50	0.02		0		0		0
Map3k5	0	0	0	0	K339M	0	0
Mid1	0	0	0	0	0	0	0
Mipol1	0	0	0	0	0	0	0
Mtr	0	0	0	0	0	0	0
Mxra8	0	0	0	0	0	0	0
Naglu	0	0	0	0	0	0	R563H
Nap1l2	0.01	0	0	0	0	0	0
Nckap1l	0	0	0	0	0	0	0
Ndufs7	0.04	0	0	0	0	0	0

Nell1	0	0	0	0	0	0	0
Nkpd1	0.01	0	0	0	0	0	0
Nlrp4f	0.02	0	0	0	0	0	0
Nr4a3	0	0	0	0	0	0	0
Nudt12	0.04	0	0	0	0	0	0
Oc90	0.02	0	0	0	0	0	0
Olfml2a	0.03	0	0	0	V534M	0	0
Olfr103	0	0	0	0	0	0	0
Olfr1046	0	0	0	0	0	0	0
Olfr1095	0.02	0	0	0	0	0	0
Olfr1106	0	0	0	0	0	0	0
Olfr1138	0.03	0	0	0	0	0	0
Olfr1197	0	0	0	0	0	0	T197R
Olfr1198	0	0	0	0	0	0	0
Olfr1272	0	0	0	0	0	0	0
Olfr1301	0	0	0	0	0	0	0
Olfr1355	0.01	0	0	0	0	0	0
Olfr1387	0.01	0	0	0	0	0	0
Olfr1414	0	0	0	0	0	0	0
Olfr142	0	0	0	0	0	0	0
Olfr1471	0	0	0	0	0	0	0
Olfr169	0.02	G253V	G253V	0	0	0	0
Olfr318	0	0	0	0	0	0	0
Olfr412	0.02	0	0	0	0	0	0
Olfr482	0	0	0	0	0	0	0
Olfr524	0.03	0	0	0	0	0	S195P
Olfr628	0.04	0	0	0	I19V	0	0
Olfr924	0	0	0	0	0	0	0
Onecut2	0	0	0	0	0	0	0
Otop3	0.04	0	0	0	0	0	0
P2ry2	0.03	0	0	0	0	0	0
Pbxip1	0	0	0	0	0	0	0
Pcdh19	0.01	0	0	0	0	0	0
Pcsk5	0	0	0	0	0	0	0
Pde10a	0	0	0	0	0	0	0
Pdk2	0	0	0	0	0	0	0
Pdzrn4	0	0	0	0	0	0	0
Pes1	0.03	0	0	0	0	0	0
Phex	0.01	A552S	0	0	0	0	0
Pik3ip1	0	0	0	0	0	0	0
Pkm	0	0	L140P	0	0	0	0
Pkm	0	0	I142S	0	I142S	0	0
Plag1	0	0	0	0	0	0	0
Plce1	0	0	0	0	0	0	0
Pmepa1	0.03	0	0	0	0	0	0
Ppp2r5a	0	0	0	0	0	0	0
Prdm16	0	0	0	0	0	0	0

Prokr1	0	0	0	0	0	0	0
Psmb3	0	0	0	A179V	0	0	0
Rad21	0.03	0	0	0	0	0	0
Rcor1	0	0	0	0	0	0	0
Rcor2	0	0	0	0	0	0	0
Rgs3	0	0	0	0	0	0	0
Rnpc3	0.03	M494V	M494V	0	0	0	0
Rorb	0	0	0	0	0	0	0
Ros1	0	0	0	0	0	0	0
Rpa1	0	0	0	0	0	0	0
Rpl35	0	0	P80L	0	0	0	P80L
Rpn1	0	0	0	0	0	0	0
Rps5	0	0	0	0	0	0	0
Rsl24d1	0	0	0	0	0	0	0
Rxrb	0	0	0	0	0	0	0
Sec31a	0	0	0	0	0	0	0
Sf3b4	0	0	0	0	S121R	0	0
Siglec1	0.03	0	0	0	0	0	0
Siglec1	0.03	0	0	0	0	0	0
Slc28a1	0.01	0	0	0	0	0	0
Smarca5	0	0	0	M450I	0	0	0
Snrnp35	0.03	G21S	0	0	0	0	0
Sort1	0.01	0	0	0	S491I	0	0
Spata5	0	0	0	0	0	0	0
Spint4	0	0	0	0	0	0	0
Stox2	0	0	0	0	0	0	0
Sulf1	0	0	0	0	0	0	Y135N
Sun5	0	0	0	0	0	0	0
Sycp2	0.04	0	0	0	0	0	0
Tacc1	0.01	0	0	0	0	0	0
Tbx1	0.01	0	0	0	E127D	0	0
Tcl1b4	0	0	0	0	0	0	0
Tec	0	0	0	0	0	0	0
Tia1	0.04	0	0	0	0	0	0
Tmem171	0.03	0	0	0	0	0	0
Tmem245	0.03	0	0	0	0	0	0
Tmem33	0	0	0	0	0	0	0
Tmem81	0.01	0	0	0	0	0	0
Tmppe	0.04	0	0	0	0	0	0
Tnik	0	0	0	0	0	0	0
Trim75	0	0	0	0	0	0	0
Trpc1	0	0	0	0	0	0	0
Trpc2	0.01	0	0	0	0	0	0
Trpm4	0.02	0	0	0	0	0	0
Tspyl2	0	0	0	0	0	0	0
Tulp4	0.02	0	0	0	0	0	0
Tulp4	0	0	0	0	0	0	0

Ubn1	0.04	0	0	0	0	0	0
Ulk1	0	G97C	G97C	0	0	0	0
Unc13c	0	0	0	0	0	0	0
Usp13	0	0	0	0	0	0	0
Usp22	0.01	0	0	0	0	0	0
Vmn1r15	0.01	0	0	0	0	0	0
Vmn1r199	0.02	0	0	0	0	0	0
Vmn1r235	0	0	0	0	M22K	0	0
Vmn2r27	0	0	0	0	0	0	0
Vmn2r41	0.02	0	0	0	0	0	0
Vmn2r89	0.02	0	0	0	S298L	0	0
Vmn2r90	0.01	0	0	0	0	0	0
Vwf	0.01	0	0	0	0	0	0
Vwf	0.02	0	0	0	0	0	0
Wdr67	0	0	0	0	0	0	0
Wnk2	0	0	0	0	0	0	0
Zc3h6	0	0	0	0	0	0	0
Zfp652	0	0	0	0	0	0	0
Zhx3	0	0	0	0	0	0	0
Zkscan14	0.02	0	0	0	0	0	0

GBE1-FF	GBE1-FFPE	GBE2-FF	GBE2-FFPE	GBE3-FF	GBE3-FFPE	GBE4-FF	GBE4-FFPE	MEG1-FF
M175/BC	700277	M181/BC	700283	F398/BC1	700500	F382/BC1	700484	M64/BC1
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	D226E	D226E	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	P904A	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	R180S
P195L	0	P195L	0	0	0	0	0	P195L
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	P221H	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	V34I	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0

0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	S50Y
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	G3D	0	0
L204F	0	L204F	0	L204F	0	L204F	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	T2729A
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	0		0		0		0	
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	R240C	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	G4335S	G4335S	0
0	0	0	E324K	0	0	0	0	0
0	0	0	0	0	0	0	0	C113W
0	0	0	0	0	0	0	0	L618H
0	0	0	0	0	0	0	F371L	0
0	0	0	0	0	0	0	0	0
0	0	0	D212Y	0	0	0	0	0
0	0	0	0	0	K430I	0	0	0
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0	0	W1786C	0	0	0	0	0	0
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0	0	0	0	0	G235V	0	0	0
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0	P36A	0	0	0	0	0	0	0
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0	0	0	0	0	0	0	0	0
0	0	0	R73C	0	0	0	R73C	0
0	0	0	0	0	S679N	0	0	0
0	0	0	0	0	R4384L	0	0	0
0	R48H	0	0	0	0	0	0	0
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0	T457R	0	0	0	0	0	0	0
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0	0	0	0	0	0	0	0	G782W
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0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	C76Y
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	G813R	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
	0		0		0		0	
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
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0	G16D	0	0	0	0	0	0	0

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0	0	P776H	0	0	0	0	0	0
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0	0	0	0	0	0	0	0	0
0	0	0	T270I	0	0	0	0	0
0	0	0	0	M282T	0	0	0	0
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0	0	0	0	0	0	0	0	0
0	A233D	0	0	0	0	0	0	0
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A340G	A340G	0	0	0	0	0	0	0
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0	0	0	0	0	0	0	0	0
0	0	0	0	R892H	R892H	0	0	0
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0	E52K	0	0	0	E52K	0	E52K	0
0	0	0	0	0	0	0	0	0

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0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	Q8R	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	A873T	0	0	0
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0	0	0	0	0	0	R125W	R125W	0
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0	0	0	0	0	0	0	0	P68H
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0	0	0	0	0	Q38H	0	0	0
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0	0	H205L	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	R754W	0	0	0	0	0	0	0
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0	0	0	0	0	0	0	0	S807P
0	0	0	0	0	0	0	0	0
0	0	0	0	S298L	0	0	0	0
0	0	0	0	0	0	0	0	0
0	S2519P	0	0	0	0	0	0	0
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0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	R927W	0

MEG1-FFPE	MEG2-FF	MEG2-FFPE	MEG3-FF	MEG3-FFPE
9504604	M129/BC	9504669	M196/BC	9504736
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0	0	S531F		0
0	0	0	0	
0	0	0	S162C	S162C
0	0	0	0	E759G
0	0	0	S221I	S221I
0	0	0	0	0
0	0	0	0	D74Y
0	0	0	0	P368S
0	0	0	0	0
0	0	0	P860A	P860A
0	0	L644V	0	0
0	0	0	S502G	S502G
0	0	0	0	Y291C
0	0	0	I573F	0
0	0	0	0	L76M
0	0	0	0	0
0	0	0	0	G728A
R451Q	0	0	0	0
0	0	0	V756E	V756E
0	0	0	0	0
0	S673N	S673N	0	0
0	0	0	0	L746P
0	0	0	D312N	D312N
0	G388V	G388V	0	0
0	0	0	0	H262R
0	S280I	S280I	0	0
0	0	0	0	0
0	R180S	0	R180S	0
0	P195L	0	P195L	0
0	0	0	0	Y1428C
0	0	0	0	0
0	0	0	N625K	N625K
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0	0	0	A700V	A700V
0	0	0	L30Q	L30Q
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0	0	0	0	0
0	E165D	E165D	0	0
0	0	0	0	0
0	0	0	Y784C	0
T785R	0	0	0	0
0	0	0	0	R278W
0	0	0	A294P	0

0	0	0	L17Q	0
0	0	0	0	G702D
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0	0	0	S132F	S132F
0	0	0	0	V32E
0	T196P	T196P	0	0
0	0	0	Y421C	Y421C
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0	0	0	0	0
0	0	0	M978L	M978L
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0	0	0	0	0
0		0		Y1946C
0	0	0	G306R	G306R
0	0	0	G532V	G532V
0	L97F	L97F	0	0
0	0	0	C559S	C559S
0	D955A	D955A	0	0
0	0	0	0	I329N
0	0	R240C	0	R240C
0	0	0	C1775S	C1775S
0	0	0	F115I	0
0	S181I	S181I	0	0
0	0	0	0	0
0	0	0	0	0
0	0	0	0	0
0	0	0	0	0
0	0	0	0	0
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0	Y77S	Y77S	0	0
0	0	0	0	0
0	0	0	0	0
0	0	0	0	R3052H
0	K307N	K307N	0	0
0	0	0	0	0
0	R926C	R926C	0	0
0	0	0	K621E	0
0	0	0	A45T	0
0	0	0	0	0
0	D733A	D733A	0	0
0	0	0	L958S	L958S
0	0	0	0	A416D
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0	0	0	H99Y	0
0	0	0	0	0
0	G37R	G37R	0	0

0	0	0	K282N	K282N
0	0	0	Y348C	0
0	0	0	M1K	0
0	L66P	L66P	0	0
0	0	R73C	0	0
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0	0	0	0	0
0	I25T	0	0	0
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0	0	0	0	F253L
0	0	0	L186W	L186W
0	0	0	0	A584T
0	0	0	0	V384A
0	L107F	L107F	0	0
0	R698C	R698C	0	0
0	0	0	Y104S	Y104S
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0	0	0	0	R910C
0	C139S	C139S	0	0
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0	0	0	0	0
0	0	0	V796I	V796I
0	0	0	M308T	M308T
G782W	0	0	0	0
0	D232Y	D232Y	0	0
0	0	0	0	H35L
0	0	0	P358L	P358L
0	0	0	I256N	0
0	0	0	A714T	0
0	R252T	R252T	0	0
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0	0	0	0	0
0	D50E	D50E	0	0
0	0	0	0	0
0	0	0	K470N	0
0	L228H	L228H	0	0
D220N		0		0
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0	0	0	N264Y	0
0	D1253Y	D1253Y	0	0
0	0	0	L65P	L65P
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0	0	0	G36S	G36S
0	M849T	M849T	0	0
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0	0	0	0	L599V
C247F	0	C247F	0	0
0	L75F	L75F	0	0
0	0	0	0	0
0	0	0	0	M57V
T270I	0	T270I	0	0
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0	0	0	A224D	A224D
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0	0	0	0	0
0	0	0	0	0
0	D178N	D178N	0	0
0	C141Y	C141Y	0	0
0	0	0	0	0
0	0	0	L212M	L212M
0	0	0	Y123N	0
0	0	0	M298I	0
0	0	0	L224Q	L224Q
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0	0	0	0	0
R122H	0	0	0	0
0	F15L	F15L	0	0
0	0	0	0	0
0	0	0	0	0
0	0	0	0	N2K
0	0	0	0	0
0	H550N	H550N	0	0
0	0	0	0	A83S
0	W402L	W402L	0	0
0	0	0	S983L	S983L
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0	0	0	C11W	C11W
0	0	0	M1I	0
0	0	0	0	0
0	0	0	0	V426I
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0	0	0	D166N	0
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0	0	0	R197W	R197W
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0	0	0	H257Y	0
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P80L	0	P80L	0	P80L
0	0	0	V360E	0
0	Q65R	Q65R	0	0
0	0	0	R56Q	0
0	0	0	0	0
0	I624N	I624N	0	0
0	0	S121R	0	0
0	R364C	0	0	0
0	0	R364C	0	0
0	F435L	F435L	0	0
0	0	0	0	0
0	0	0	0	0
0	0	0	0	0
0	0	0	0	H557Q
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0	0	0	0	0
0	0	0	0	0
0	0	0	P221R	P221R
0	0	S474L	0	0
0	0	0	D573G	0
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P68H	0	0	0	0
0	0	0	0	K51M
0	0	0	T109A	T109A
0	0	0	0	G150R
P741T	0	0	0	0
0	D3V	0	0	0
0	0	0	K2N	0
0	0	0	0	I378M
0	0	0	0	0
0	0	0	C19F	0
0	0	0	0	0
0	0	0	R195S	R195S
0	0	0	0	0
0	0	G137R	0	G137R
0	Y402C	Y402C	0	0
0	0	0	S386I	0

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0	0	0	0	0
0	T814R	T814R	0	0
0	0	0	H196Q	0
0	0	0	V235F	V235F
0	0	0	0	0
0	0	0	0	0
0	0	0	0	0
0	0	0	0	M593K
0	0	0	0	0
0	0	0	A241T	0
0	0	0	0	0
0	0	0	0	L622V
Q827L	0	0	0	0
0	0	0	P1331H	P1331H
0	P835L	P835L	0	0
0	0	0	H374Y	0
0	0	0	P414A	0
0	0	0	A56V	0

Supplementary Table 4. Numbers of tumor *versus* normal variant calls for individual hepatocellular carcinoma samples

Treatment	Preparation method	Tissue ID	Non-synonymous variant calls	Synonymous + Non-synonymous variant calls
Spontaneous HCC-1, 0 mg/kg	FF	VF202/BC15616	37	50
	FFPE	700304	38	61
Spontaneous HCC-2, 0 mg/kg	FF	VF245/BC15585	21	27
	FFPE	700347	47	81
Spontaneous HCC-3, 0 mg/kg	FF	VM8/BC1832	12	20
	FFPE	9504548	40	65
GBE-HCC-1, 2000 mg/kg	FF	M175/BC15578	18	19
	FFPE	700277	48	77
GBE-HCC-2, 2000 mg/kg	FF	M181/BC15563	26	41
	FFPE	700283	35	57
GBE-HCC-3, 2000 mg/kg	FF	F398/BC15605	23	35
	FFPE	700500	34	59
GBE-HCC-4, 2000 mg/kg	FF	F382/BC15624	19	39
	FFPE	700484	32	68
MEG-HCC-1, 37 mg/kg	FF	M64/BC1867	39	53
	FFPE	9504604	51	78
MEG-HCC-2, 75 mg/kg	FF	M129/BC1834	128	183
	FFPE	9504669	151	221
MEG-HCC-3, 150 mg/kg	FF	M196/BC1885	232	299
	FFPE	9504736	247	323

Supplementary Table 5. Sanger sequencing of variants of *Braf* and *Bves* that were identified by exome sequencing

Treatment	FF-Tissue ID	FFPE-Tissue ID	Gene	Variant	Exome-seq of FF	Exome-seq of FFPE	Sanger sequencing of FF	Alternate allele frequency for FF
Spontaneous-HCC-1	VF202/BC15616	700304						
Spontaneous-HCC-2	VF245/BC15585	700347	*Bves*	M66K	yes	-	-	0.32
Spontaneous-HCC-3	VM8/BC1832	9504548	*Bves*	R180S	yes	-	-	0.091
				P195L	yes	-	-	0.134
GBE-HCC-1, 2000 mg/kg	M175/BC15578	700277	*Bves*	P195L	yes	-	-	0.063
GBE-HCC-2, 2000 mg/kg	M181/BC15563	700283	*Bves*	P195L	yes	-	-	0.063
GBE-HCC-3, 2000 mg/kg	F398/BC15605	700500						
GBE-HCC-4, 2000 mg/kg	F382/BC15624	700484						
MEG-HCC-1, 37 mg/kg	M64/BC1867	9504604	*Bves*	R180S	yes	-	-	0.114
				P195L	yes	-	-	0.139
MEG-HCC-2, 75 mg/kg	M129/BC1834	9504669	*Bves*	R180S	yes	-	-	0.089
				P195L	yes	-	-	0.13
MEG-HCC-3, 150 mg/kg	M196/BC1885	9504736	*Braf*	V637E	yes	yes	yes	0.368
			Bves	R180S	yes	-	-	0.059
				P195L	yes		-	0.119

Supplementary Table 6 –The corresponding mutation counts for each tumor type (Fresh frozen (FF-a) and formalin fixed paraffin embedded (FFPE-b)) that correspond to supplemental figure 2a and 2b, respectively.

Suppl. Table 6a.

FF	4S	5S	6S	GBE7	GBE8	GBE9	GBE13	MEG10	MEG11	MEG12
C>A	15	8	3	8	13	16	13	16	71	89
C>G	9	5	0	6	10	5	5	8	26	45
C>T	29	25	16	18	34	29	34	26	69	88
T>A	3	3	4	2	6	4	3	6	20	55
T>C	10	3	6	6	7	3	10	10	28	71
T>G	2	2	1	3	2	1	2	0	7	12

Suppl. Table 6b.

FFPE	4S	5S	6S	GBE7	GBE8	GBE9	GBE13	MEG10	MEG11	MEG12
C>A	19	23	12	24	18	20	16	18	73	73
C>G	13	12	8	22	13	14	13	17	38	56
C>T	49	61	51	57	52	51	72	59	102	97
T>A	3	8	11	8	6	8	9	8	21	55
T>C	32	24	27	23	25	15	22	27	43	97
T>G	7	9	6	6	8	4	5	6	11	17

Substitution T	Trinucleotide	Somatic Muta	FF.spontaneo	FF.GBE	FF.MEG	FFPE.spontan
C>A	ACA	A[C>A]A	0	0.0118898	0.01911188	0.01014596
C>A	ACC	A[C>A]C	0.01331027	0	0.01184964	0.01022229
C>A	ACG	A[C>A]G	0.0138919	0.00833514	0.00618372	0.00266725
C>A	ACT	A[C>A]T	0.01363868	0.02045802	0.02731952	0.01047451
C>A	CCA	C[C>A]A	0.03348236	0.0482146	0.03875053	0.01285723
C>A	CCC	C[C>A]C	0.03147256	0.01416265	0.02801885	0.03021366
C>A	CCG	C[C>A]G	0	0.00513009	0.01902971	0.00328326
C>A	CCT	C[C>A]T	0.01392907	0.02507232	0.02325099	0.01069752
C>A	GCA	G[C>A]A	0.01421437	0	0.01739997	0.00272916
C>A	GCC	G[C>A]C	0.00818615	0.00491169	0.01275369	0.00628696
C>A	GCG	G[C>A]G	0	0.00490073	0.00363578	0.0188188
C>A	GCT	G[C>A]T	0	0.01588711	0.01620633	0
C>A	TCA	T[C>A]A	0.0209544	0.00838176	0.01554577	0.01341082
C>A	TCC	T[C>A]C	0.00679162	0.00814995	0.01209266	0.00260798
C>A	TCG	T[C>A]G	0	0	0.00306633	0.00529045
C>A	TCT	T[C>A]T	0.01227203	0.02945287	0.02048499	0.00942492
C>G	ACA	A[C>G]A	0	0.00396327	0.01029101	0.01014596
C>G	ACC	A[C>G]C	0	0.00798616	0.00888723	0.01022229
C>G	ACG	A[C>G]G	0.0138919	0.01667028	0	0.00266725
C>G	ACT	A[C>G]T	0	0	0.00455325	0
C>G	CCA	C[C>G]A	0	0	0.01192324	0.00257145
C>G	CCC	C[C>G]C	0	0	0.00350236	0.00302137
C>G	CCG	C[C>G]G	0.01710031	0	0.00380594	0.02298282
C>G	CCT	C[C>G]T	0	0	0.00775033	0
C>G	GCA	G[C>G]A	0	0.00426431	0.00790908	0
C>G	GCC	G[C>G]C	0.02455844	0.0392935	0.02186346	0.00628696
C>G	GCG	G[C>G]G	0.00816788	0	0	0
C>G	GCT	G[C>G]T	0	0	0.01325972	0.0203355
C>G	TCA	T[C>G]A	0.0139696	0.0209544	0.01088204	0.01072866
C>G	TCC	T[C>G]C	0.01358325	0	0.00302317	0
C>G	TCG	T[C>G]G	0	0	0.00306633	0
C>G	TCT	T[C>G]T	0.01227203	0.01840804	0.012291	0.00235623
C>T	ACA	A[C>T]A	0.00660544	0.0118898	0.0132313	0.03043788
C>T	ACC	A[C>T]C	0.00665514	0.02795157	0.01333084	0.02300015
C>T	ACG	A[C>T]G	0.0277838	0.06251356	0.01236744	0.04000868
C>T	ACT	A[C>T]T	0.04091604	0.03273284	0.00910651	0.02618627
C>T	CCA	C[C>T]A	0.02008942	0.00803577	0.00596162	0.01542867
C>T	CCC	C[C>T]C	0.03147256	0.07553414	0.0157606	0.03625639
C>T	CCG	C[C>T]G	0.0769514	0.06156112	0.03044754	0.03611586
C>T	CCT	C[C>T]T	0.02785813	0.03342976	0.01550066	0.02406943

C>T	GCA	G[C>T]A	0.08528623	0.04264311	0.02530905	0.03274991
C>T	GCC	G[C>T]C	0.04093073	0.01964675	0.02368542	0.0314348
C>T	GCG	G[C>T]G	0.04900729	0.02940438	0.02545047	0.0282282
C>T	GCT	G[C>T]T	0.00661963	0.01588711	0.02799275	0.0203355
C>T	TCA	T[C>T]A	0.0209544	0.02933617	0.02176408	0.02145731
C>T	TCC	T[C>T]C	0.0271665	0.02037487	0.01360424	0.0156479
C>T	TCG	T[C>T]G	0.04133162	0.01239949	0.00766583	0.02909746
C>T	TCT	T[C>T]T	0.00613601	0.01840804	0.03004465	0.03063098
T>A	ATA	A[T>A]A	0	0	0.00299154	0.0025807
T>A	ATC	A[T>A]C	0	0	0.00768396	0.00265148
T>A	ATG	A[T>A]G	0.00665144	0.00399087	0.01628422	0.00766246
T>A	ATT	A[T>A]T	0.00741945	0.01335501	0.00495395	0
T>A	CTA	C[T>A]A	0	0	0.00883175	0.00253962
T>A	CTC	C[T>A]C	0.0133791	0.01605492	0.01042205	0.00256879
T>A	CTG	C[T>A]G	0	0.01235209	0.01832767	0.00263511
T>A	CTT	C[T>A]T	0.0192489	0	0.0028561	0.00985544
T>A	GTA	G[T>A]A	0	0	0.00147327	0.00254187
T>A	GTC	G[T>A]C	0	0.00386264	0.00429846	0
T>A	GTG	G[T>A]G	0.00656562	0.00393937	0.01022897	0.0025212
T>A	GTT	G[T>A]T	0.00670725	0	0.00149281	0
T>A	TTA	T[T>A]A	0	0.00431221	0.00159958	0.00827944
T>A	TTC	T[T>A]C	0.00689588	0	0.0107435	0.01324009
T>A	TTG	T[T>A]G	0	0.0039669	0.01324342	0
T>A	TTT	T[T>A]T	0	0	0.00664884	0
T>C	ATA	A[T>C]A	0.00672057	0	0.01794921	0.00774209
T>C	ATC	A[T>C]C	0	0.00414294	0.01229434	0.00795443
T>C	ATG	A[T>C]G	0.01330289	0.0119726	0.02368613	0.00255415
T>C	ATT	A[T>C]T	0.0148389	0.00445167	0.00825658	0.01424534
T>C	CTA	C[T>C]A	0.00661359	0.01190446	0.01177567	0.01015848
T>C	CTC	C[T>C]C	0.00668955	0.00401373	0.00744432	0.01027515
T>C	CTG	C[T>C]G	0.01372454	0.01646945	0.00763653	0.02635112
T>C	CTT	C[T>C]T	0	0.00769956	0.00571219	0.01724701
T>C	GTA	G[T>C]A	0	0	0.00883959	0.00762562
T>C	GTC	G[T>C]C	0.00643773	0	0.01146255	0.01483254
T>C	GTG	G[T>C]G	0.00656562	0.01181812	0.00730641	0.02773318
T>C	GTT	G[T>C]T	0.01341451	0	0.00298561	0.0180291
T>C	TTA	T[T>C]A	0	0	0.01119707	0.01103925
T>C	TTC	T[T>C]C	0.02758352	0.02482517	0.00767393	0.01324009
T>C	TTG	T[T>C]G	0.00661149	0.0039669	0.01030044	0.01269406
T>C	TTT	T[T>C]T	0.0074684	0.00448104	0.00997326	0.01433933
T>G	ATA	A[T>G]A	0	0	0.0044873	0

T>G	ATC	A[T>G]C	0.00690489	0.00828587	0.00307358	0.00795443
T>G	ATG	A[T>G]G	0.00665144	0.00399087	0.00296077	0
T>G	ATT	A[T>G]T	0	0	0	0
T>G	CTA	C[T>G]A	0	0	0	0
T>G	CTC	C[T>G]C	0	0	0	0.00770636
T>G	CTG	C[T>G]G	0.00686227	0.00411736	0	0
T>G	CTT	C[T>G]T	0.0064163	0	0.00142805	0.00246386
T>G	GTA	G[T>G]A	0	0	0	0
T>G	GTC	G[T>G]C	0	0	0.00429846	0
T>G	GTG	G[T>G]G	0	0.00393937	0	0.01260599
T>G	GTT	G[T>G]T	0	0	0	0.00515117
T>G	TTA	T[T>G]A	0	0	0.00159958	0.01379906
T>G	TTC	T[T>G]C	0	0	0.00460436	0.00264802
T>G	TTG	T[T>G]G	0	0.00793379	0.00147149	0
T>G	TTT	T[T>G]T	0.0074684	0.00448104	0.00498663	0.00573573

FFPE.GBE	FFPE.MEG
0.00930708	0.01627943
0.00562626	0.00937251
0.00195737	0.00733655
0.00384339	0.01920753
0.01509655	0.02947103
0.02438969	0.03047221
0.00722831	0.00752581
0.01570087	0.01103427
0.00200281	0.008758
0.00230686	0.01152866
0.02531884	0.00718933
0.00746166	0.00932251
0.00787328	0.01106639
0.01339718	0.00836914
0.00970605	0.00485065
0.00691652	0.01188196
0.01675274	0.00930253
0.0093771	0.00585782
0.00978686	0.00489104
0.00192169	0.00720282
0.00377414	0.01060957
0.01108622	0.0069255
0.02168493	0.01505162
0.00196261	0.01103427
0.00400562	0.00625571
0.0115343	0.0158519
0	0
0.01865414	0.02097565
0.00590496	0.01106639
0.00191388	0.00119559
0	0.00242533
0.00691652	0.00972161
0.02978266	0.01511661
0.0187542	0.01288721
0.06263589	0.0269007
0.03266878	0.02160847
0.00754828	0.00707305
0.05099663	0.02077651
0.04096043	0.04063937
0.01570087	0.01961648

0.01401965	0.02001828
0.03690975	0.02593948
0.02531884	0.01006507
0.02238497	0.01981033
0.02558816	0.01967357
0.03062212	0.01554269
0.02329453	0.01576463
0.03112436	0.03240535
0.00378772	0.00236617
0.0019458	0.00729319
0.00749752	0.0163928
0.01045402	0.00522445
0.00186371	0.00349275
0.00188512	0.00588811
0.00386758	0.01328831
0.00542435	0.00338856
0	0.00233057
0.00181416	0.00226659
0.00185019	0.01040225
0.00189011	0
0.0020253	0.0012652
0.00971631	0.00849761
0.00186312	0.01513046
0.0042092	0.00262946
0.00946929	0.0272109
0.0019458	0.01093978
0.00562314	0.0163928
0.01045402	0.00783668
0.00745485	0.01164251
0.01696606	0.01177622
0.01933791	0.01932845
0.01265681	0.0112952
0.00373073	0.01048756
0.00907078	0.01019964
0.02405253	0.01733709
0.00945053	0.0059037
0.01012651	0.01518234
0.00971631	0.00728367
0.00931561	0.01280269
0.0021046	0.00262946
0	0.0070985

0.0058374	0.00243106
0.00374876	0.00117091
0.0020908	0.00261223
0	0
0.00754047	0.00471049
0	0.00120803
0.00180812	0.00112952
0	0
0	0.00339988
0.00185019	0.00231161
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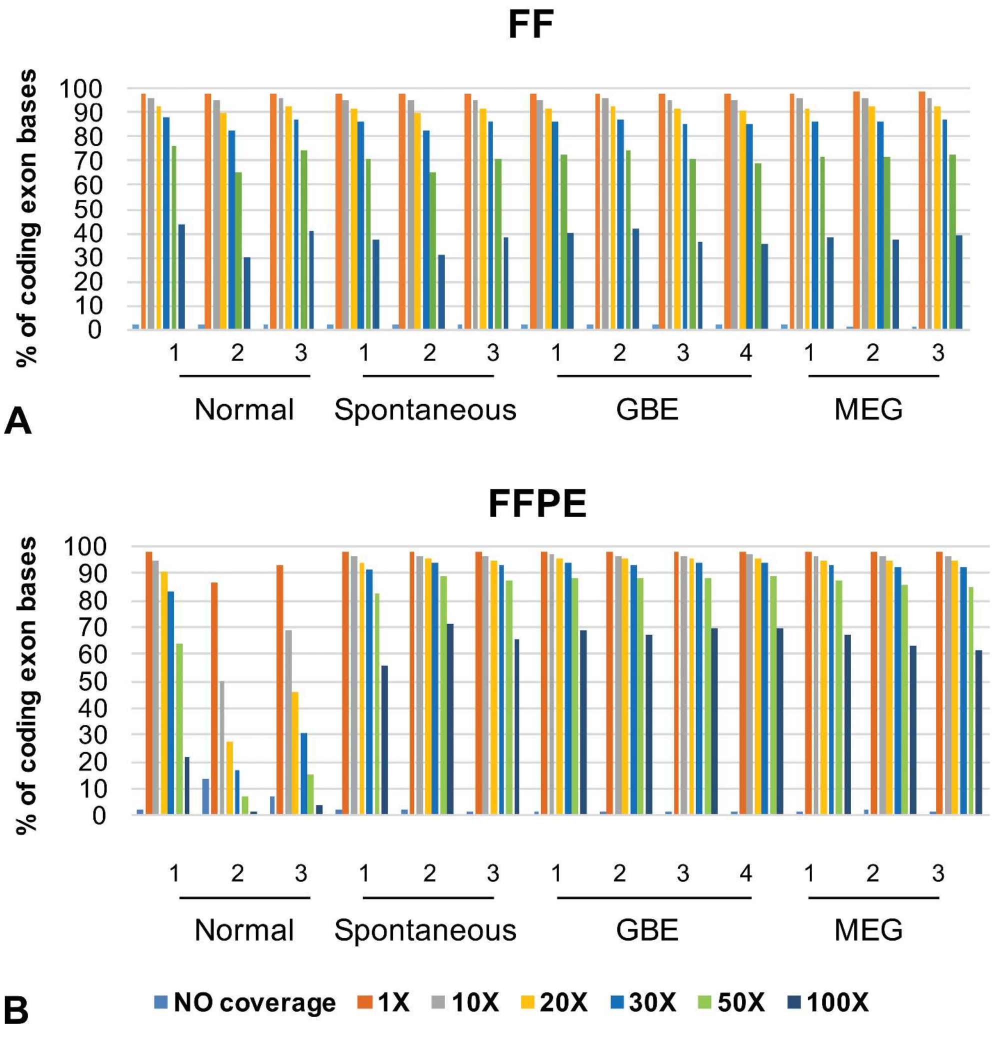
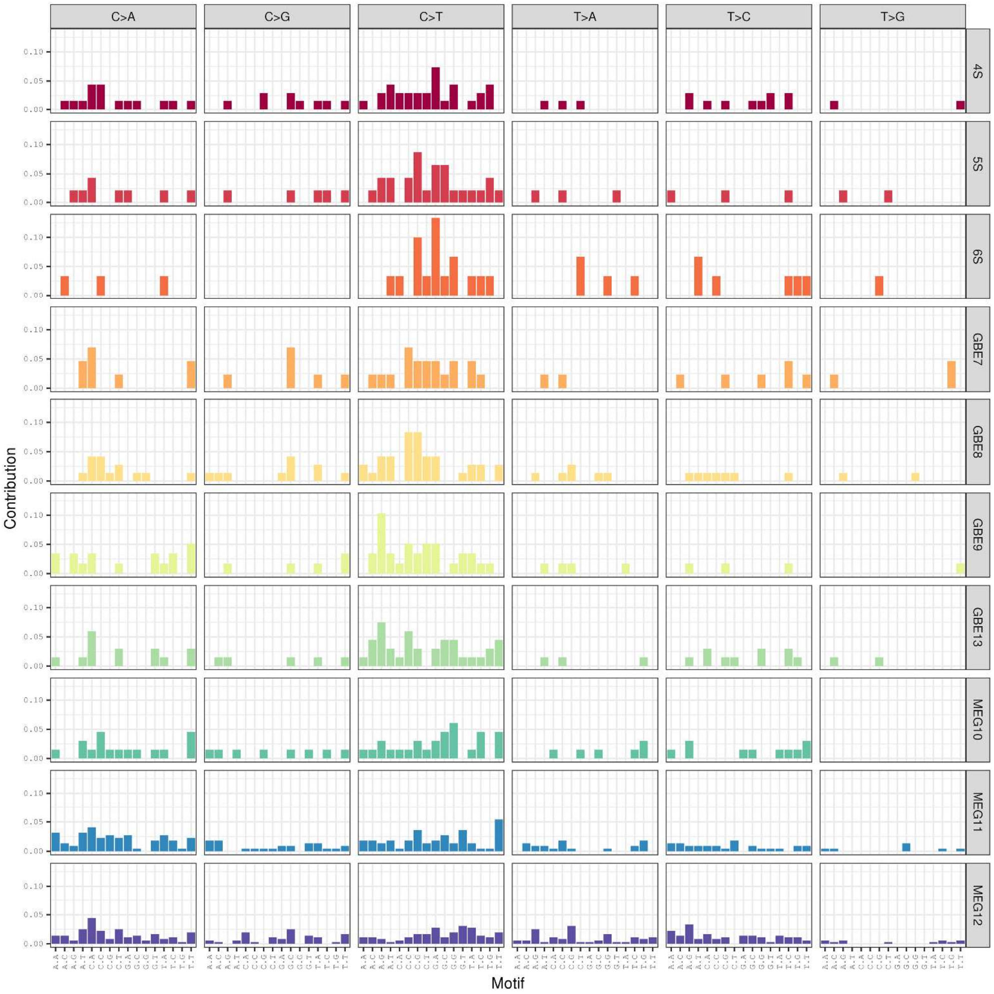


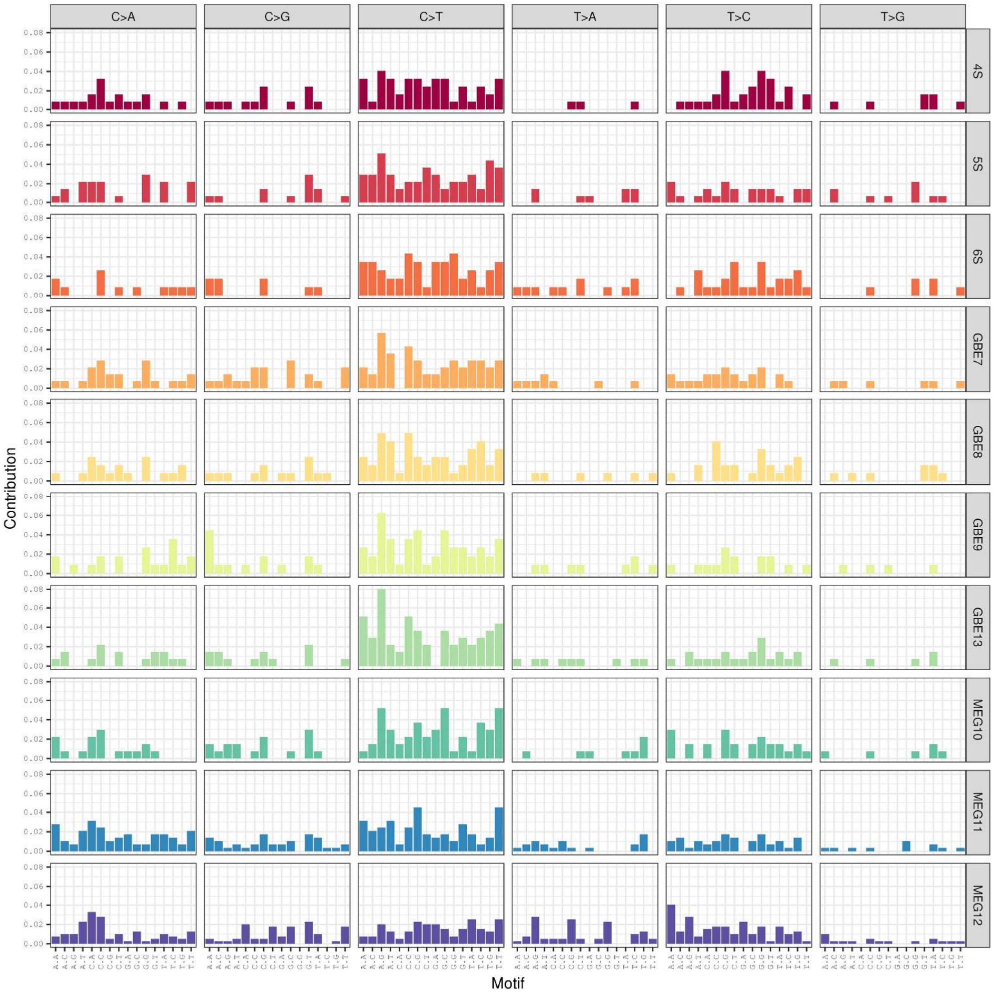
Supplementary Figure 1-Depth of coverage for FF and FFPE samples

132x134mm (1200 x 1200 DPI)



Supplementary figure 2 - Mutation spectra for the fresh frozen (FF-2a) and formalin fixed paraffin embedded (FFPE-2b) hepatocellular carcinomas arising spontaneously or due to exposure to ginkgo biloba extract or methyleugenol. The corresponding mutation counts for each tumor type (fresh frozen (FF) and formalin fixed paraffin embedded (FFPE)) are indicated in Supplementary table 6 (a and b).

187x187mm (508 x 508 DPI)



Supplementary figure 2 - Mutation spectra for the fresh frozen (FF-2a) and formalin fixed paraffin embedded (FFPE-2b) hepatocellular carcinomas arising spontaneously or due to exposure to ginkgo biloba extract or methyleugenol. The corresponding mutation counts for each tumor type (fresh frozen (FF) and formalin fixed paraffin embedded (FFPE)) are indicated in Supplementary table 6 (a and b).

187x187mm (508 x 508 DPI)