Supplementary Table 5. Continued

Reference position	Gene	Chromosome	Coding sequence	Coverage	Allele change	Patient no.
1733216553	BRWD2	10	8	28	insT	3
1737221823	ZRANB1	10	1	17	insA	3
1738045786	MMP21	10	7	33	insG	3
1748226082	C11orf21	11	4	63	insG	1
1750053615	RRM1	11	14	17	insT	3
1753342600	SYT9	11	4	18	insG	3
1760006709[a]	SPON1	11	5	72	insC	4
1764016157	SAAL1	11	7	40	delT	4
1771005317	LUZP2	11	12	34	insA	3
1782417168	TRAF6	11	6	24	delG	3
1782519665	RAG2	11	1	21	insA	3
1792247476[a]	CREB3L1	11	12	40	insG	1
1802120506	TCN1	11	7	13	insA	3
1802663567[a]	MS4A14	11	2	61	delTT	4
1802663568[a]	MS4A14	11	2	22	delT	3
1803663946[a]	TMEM216	11	3	54	insA	4
1804797590	AHNAK	11	3	12	insG	3
1805556025	SLC22A10	11	1	17	insC	3
1810263379[a]	UNC93B1	11	7	53	insG	3
1810284280[a]	ALDH3B1	11	2	63	insC	2
1810287509[a]	ALDH3B1	11	6	18	insC	1
1810293595[a]	ALDH3B1	11	9	28	insC	4
1814065554	LOC729523	11	1	22	delT	3
1826743977	DLG2	11	5	23	insT	3
1832107207	LOC642446	11	1	33	delT	4
1837197723[a]	CWC15	11	5	152	insT	1
1837299118[a]	SFRS2B	11	1	36	insC	4
1850549218	ATM	11	49	24	insT	3
1852355678	ZC3H12C	11	2	25	insC	3
1854201323[a]	DIXDC1	11	7	16	insC	1
1860877259[a]	TREH	11	15	28	insG	2
1861246651[a]	SLC37A4	11	3	37	delC	1
1861288156	VPS11	11	2	13	insC	4
1867800518	EI24	11	9	14	insC	4
1867851321	CHEK1	11	5	44	insC	3
1888645169[a]	PRB3	12	4	34	delG	4
1888731023[a]	PRB1	12	3	136	delC	1
1891856090	ATF7IP	12	11	19	insG	3
1893735417[a]	MGST1	12	2	12	delAA	3
1893735418[a]	MGST1	12	2	18	delA	3
1898574937	SLCO1B1	12	7	17	insC	3
1902256413	BCAT1	12	5	22	insG	3
1913975525	KIF21A	12	10	20	insT	3
1914378775	SLC2A13	12	10	17	insA	3
1927092176	KRT6C	12	1	15	insG	2
1930622534	SUOX	12	3	14	insG	3
1931678522	TMEM194A	12	9	23	insG	3
1932337710	OS9	12	12	17	insA	3
1959863488	LRRIQ1	12	26	12	delA	3
1962616654	C12orf50	12	3	28	insA	3
1978598568[a]	TDG	12	3	14	insA	3
1986789153	LOC100287839	12	9	35	insC	3
1997115077	RSRC2	12	10	28	insG	3
1999523126	UBC	12	1	29	delT	3
2009256491	ZMYM5	13	5	14	insC	3
2012756904	SACS	13	9	20	insT	3
2012761230	SACS	13	9	23	insT	3
2017859185	FLT1	13	4	36	insA	3
2022550582	STARD13	13	5	85	delT	1
2026525487	CSNK1A1L	13	1	13	insC	2
2038965626	RCBTB1	13	8	17	insG	3

Supplementary Table 5. Continued

Reference position	Gene	Chromosome	Coding sequence	Coverage	Allele change	Patient no.
2046563396	PRR20	13	2	28	delC	2
2063234131	KLF12	13	4	47	insT	3
2066482633	MYCBP2	13	75	17	insT	3
2066508358	MYCBP2	13	62	14	insC	3
2066632819	MYCBP2	13	22	23	delC	3
2066717508	MYCBP2	13	2	33	delAA	3
2066717509	MYCBP2	13	2	33	delA	3
2088603872	GPR18	13	1	20	insT	3
2105948032	NDRG2	14	1	34	delG	1
2106009532	FLJ10357	14	18	14	delG	3
2108927297	DHRS4L2	14	6	41	insA	4
2109139875[a]	MDP-1	14	6	13	delA	1
2117359342	AKAP6	14	1	20	insA	3
2117747539	AKAP6	14	12	21	insA	3
2137979011	DDHD1	14	10	22	insC	3
2148241015[a]	GPHB5	14	1	18	insG	4
2158414589[a]	C14orf169	14	1	19	insC	3
2159993929[a]	FAM164C	14	1	14	insA	1
2160606560	TTLL5	14	4	17	insA	3
2179419547	SERPINA12	14	2	54	insC	3
2179491154	SERPINA4	14	3	14	insG	3
2181450460	PAPOLA	14	5	33	insC	3
2202211427[a]	CHRFAM7A	15	4	191	delCA	1
2202211428[a]	CHRFAM7A	15	4	252	delA	4
2203996021[a]	CHRNA7	15	6	166	delTG	1
2203996022[a]	CHRNA7	15	6	50	delG	2
2204534873	SCG5	15	5	24	insC	3
2212460825	CASC5	15	10	14	insA	3
2220067652	SLC12A1	15	5	21	insA	3
2237036677	LOC100287371	15	3	32	insG	3
2243652079[a]	NR2E3	15	6	34	delC	1
2251295853	KIAA1024	15	1	14	insT	3
2252413491	ARNT2	15	14	24	insC	3
2256610001	ZSCAN2	15	2	14	insC	3
2257065252	PDE8A	15	4	20	delT	3
2261248094	FANCI	15	2	19	insC	3
2261584966	C15orf42	15	7	21	insT	3
2270957952[a]	LOC145814	15	4	23	insC	4
2271092254[a]	SYNM	15	1	19	insG	3
2274046312[a]	C16orf35	16	12	89	insG	4
2274304546	AXIN1	16	1	20	delC	3
2277509768[a]	NLRC3	16	7	81	delG	1
2285935013[a]	LOC729978	16	4	20	delAT	4
2285935014[a]	LOC729978	16	4	44	delT	1
2292434768	NOMO2	16	24	22	insG	3
2294397443	ACSM2A	16	9	23	delA	3
2294883814	DNAH3	16	53	18	insC	3
2304906998	HSD3B7	16	6	48	delC	2
2332868773	CLEC18C	16	3	24	insA	3
2333553555[a]	HYDIN	16	68	29	delA	4
2338969142[a]	CNTNAP4	16	1	82	insT	1
2351412465[a]	LOC100289580	16	2	67	delC	2
2354387432	PRPF8	17	4	11	insG	3
2356396572[a]	P2RX5	17	3	13	delG	1
2359357840	C17orf100	17	1	14	insG	2
2360272579[a]	SENP3	17	6	20	delA	4
2361527508[a]	PIK3R6	17	16	42	insG	1
2363416732	C17orf48	17	3	19	insA	3
2371198121	LGALS9C	17	9	16	insA	4
2376394518[a]	SEBOX	17	1	29	insG	4
2376430014[a]	SLC46A1	17	4	15	delA	1

Supplementary Table 5. Continued

Reference position	Gene	Chromosome	Coding sequence	Coverage	Allele change	Patient no.
2382300534	CCL7	17	2	24	insT	3
2383802642[a]	MMP28	17	4	28	insC	4
2384283858	TBC1D3C	17	13	31	insG	1
2388631071	KRT10	17	1	14	delC	3
2392844842[a]	PLCD3	17	10	24	insC	1
2393016586[a]	MAP3K14	17	4	16	insG	2
2407377091	CLTC	17	3	28	insT	3
2409792732	MED13	17	2	24	insA	3
2411313186[a]	WDR68	17	5	42	delG	1
2412151377	DDX5	17	8	23	insT	3
2434290839	MYOM1	18	8	16	insA	3
2448603454	RBBP8	18	14	22	insC	3
2451555232	LOC100287386	18	2	31	insA	1
2471234235	SLC14A2	18	4	39	delC	3
2492044315	CDH19	18	11	24	insA	3
2501962862	ZNF516	18	2	27	delG	2
2508173565[a]	SPPL2B	19	7	26	insC	2
2510788089	UHRF1	19	14	13	insC	3
2514792389	MUC16	19	3	18	insA	3
2514803399	MUC16	19	3	29	insT	3
2518236406	ZNF799	19	4	25	insA	3
2521463907[a]	CYP4F8	19	4	79	insC	1
2522001621[a]	HSH2D	19	5	71	delA	2
2538892348	C19orf55	19	9	17	delG	2
2543188059	ZNF780B	19	2	24	insC	3
2543756504[a]	LTBP4	19	24	14	insG	1
2544255517[a]	CYP2F1	19	1	53	insC	4
2544853028	CEACAM5	19	4	26	insT	3
2547650400[a]	CEACAM20	19	8	54	delT	1
2547930257[a]	CBLC	19	8	18	insC	3
2552076265[a]	DHDH	19	4	55	insG	2
2552600822	ALDH16A1	19	10	73	insC	2
2554469302[a]	LOC147645	19	10	37	insG	4
2555437083[a]	ZNF480	19	1	51	delG	1
2555750854	ZNF83	19	1	26	insG	3
2559350849	ZSCAN5C	19	1	50	insA	2
2560590155	ZNF749	19	3	34	insA	1
2560866399	ZNF671	19	4	14	insA	3
2561351770[a]	ZNF274	19	4	78	insG	2
2562070563	DEFB126	20	2	20	delCC	3
2562070564	DEFB126	20	2	20	delC	3
2567847490[a]	CHGB	20	4	28	delGA	2
2567847491[a]	CHGB	20	4	70	delA	2
2580083985	CSRP2BP	20	4	17	insG	3
2583130413[a]	NCRNA00153	20	7	49	insG	1
2606534089	DDX27	20	4	21	insA	3
2608270909	MOCS3	20	1	23	insG	3
2640900547[a]	KRTAP7-1	21	1	27	delA	4
2643647262[a]	SON	21	12	40	insA	1
2643647273[a]	SON	21	12	33	delA	4
2654166830	TRAPPC10	21	21	24	insT	3
2656193953[a]	LOC100288508	21	5	14	insC	1
2670991039	HORMAD2	22	2	23	insG	3
2681753989	DNAJB7	22	1	66	insA	1
2683020374	CYP2D6	22	5	18	insG	4
2701397266	WWC3	X	7	15	insG	3
2708217926	RBBP7	X	2	16	insC	3
2709924320	CDKL5	X	4	26	insC	3
2711314268	CXorf23	X	3	22	delG	3
2713575280	PHEX	X	19	29	insG	3
2736210225	KDM6A	X	17	17	insC	3

Supplementary Table 5. Continued

Reference position	Gene	Chromosome	Coding sequence	Coverage	Allele change	Patient no.
2736225869	KDM6A	X	24	16	insA	3
2737802282	SLC9A7	X	7	21	insC	3
2739406485	SSX1	X	6	45	insT	3
2739444455[a]	SSX9	X	2	11	delC	2
2741301867[a]	DGKK	X	22	55	insG	1
2743920170	SSX2B	X	6	35	insC	3
2745406637	WNK3	X	16	40	insA	3
2755460714	OPHN1	X	8	18	insC	3
2757668459	KIF4A	X	28	24	insG	3
2758547967	NONO	X	6	22	insT	3
2761842615	RLIM	X	3	18	insG	3
2771580011	HDX	X	5	18	insA	3
2779112744	PCDH11X	X	2	18	insT	3
2788398590	CENPI	X	20	19	insC	3
2789376503	TCEAL6	X	1	24	insG	2
2789554171	NXF2	X	7	14	insT	3
2789554906	NXF2	X	10	29	insA	3
2802179110	IL13RA2	X	4	18	insT	3
2823639589	ARHGEF6	X	18	16	insA	3
2840930428[a]	LCAP	X	1	57	insC	2
2841794077	MPP1	X	7	14	insG	3

[a]These indels commonly occurred in more than one HCC.

Supplementary Table 6. List of 81 Nucleotide Positions in 77 Genes With Indels at a Frequency of >20% of Reads in 4 Nontumorous Tissues From 4 Patients

Reference position	Gene	Chromosome	Coding sequence	Coverage	Allele change	Patient no.
36247083	THRAP3	1	4	18	delG	1
75174421	SLC44A5	1	16	19	delT	1
114430296	TRIM33	1	20	23	delC	1
133132499	YY1AP1	1	7	37	insT	1
133844355	RHBG	1	9	48	delC	4
201121914	CAPN2	1	3	14	delC	1
201173637	TP53BP2	1	13	22	delG	1
247664301	C2orf43	2	4	18	delA	2
319394229	SNRNP200	2	37	20	delA	1
322653290	AFF3	2	14	35	delA	1
331834049	RANBP2	2	20	16	delG	1
332901065	RGPD5	2	20	22	delT	1
374789589	NEB	2	4	37	insT	4
382950536	LY75	2	5	19	delA	4
401635744	TTN	2	274	25	delA	1
409835043	FAM171B	2	8	17	delT	1
412064501	COL3A1	2	14	21	insA	4
454784716	PTMA	2	4	14	delT	1
463724350[a]	AQP12B	2	1	27	delC	3
463734336	AQP12A	2	2	14	delG	2
503335742	DLEC1	3	4	20	delT	1
503335743	DLEC1	3	4	20	delA	1
735406533	CNOT6L	4	10	21	delG	1
785877214	LARP2	4	14	23	delA	1
798021293	SCOC	4	1	18	insC	1
810971969	TRIM2	4	5	18	delC	1
883256725	PRLR	5	3	29	delG	4
939146286	ANKRD32	5	16	15	insC	1
985314450[a]	LOC100288105	5	1	27	delC	3
1033746568	BMP6	6	5	24	delC	1
1068664364	KIAA0240	6	4	17	insT	4
1193244025	FAM120B	6	1	43	insA	1
1222659823	KIAA0644	7	1	463	delC	4
1282877394	CDK6	7	3	21	delA	1
1289880816	CYP3A4	7	12	45	delG	1
1333766765	LOC441294	7	1	13	delA	4
1340012514	SSPO	7	76	53	delA	3
1356372261	XKR5	8	6	130	delA	4
1490189877[a]	JRK	8	1	29	delC	3
1490189878[a]	JRK	8	1	15	delA	2
1492082552[a]	RECQL4	8	14	43	delG	3
1505961686	MPDZ	9	2	28	insG	4
1526015264	NFX1	9	3	36	delT	1
1573925487	GABBR2	9	17	59	insT	4
1580509237	ABCA1	9	4	24	insT	1
1637516682	ARMC3	10	18	19	delT	1
1637516683	ARMC3	10	18	19	delT	1
1657313100[a]	AGAP4	10	7	19	delT	2
1657313101[a]	AGAP4	10	7	14	delT	3
1807397040	SYVN1	11	7	15	insA	1
1832107207	LOC642446	11	1	18	delT	4
1855967268	ZW10	11	8	40	delC	1
1861246651	SLC37A4	11	3	143	delC	4
1884320486	ATN1	12	4	15	delA	1
1929584670	KIAA0748	12	6	31	delC	4
1955959709	PPFIA2	12	18	52	delA	4
1994379801	CIT	12	17	28	delG	1
1995110709	DYNLL1	12	2	14	delG	1
1997144069	KNTC1	12	2	31	delC	4
2105624179	RNASE4	14	1	15	delC	1

Supplementary Table 6. Continued

Reference position	Gene	Chromosome	Coding sequence	Coverage	Allele change	Patient no.
2162358340	C14orf133	14	13	15	delT	1
2243652079	NR2E3	15	6	129	delC	4
2256057594	ADAMTSL3	15	12	26	delT	1
2277509768[a]	NLRC3	16	7	12	delG	2
2302633200	EIF3C	16	4	18	delG	4
2303380808	SULT1A4	16	3	24	delA	1
2351412465	LOC100289580	16	2	103	delC	4
2356396572	P2RX5	17	3	40	delG	4
2376621991	SPAG5	17	3	13	delC	1
2386619109	CCDC49	17	5	14	delT	1
2413869089	APOH	17	5	24	delC	1
2501962862	ZNF516	18	2	29	delG	3
2507200605	MUM1	19	8	36	delG	1
2538892348	C19orf55	19	9	20	delG	2
2565046537	UBOX5	20	2	15	delG	1
2587599923	ZNF337	20	4	19	delT	1
2598525448	ZHX3	20	1	19	delT	1
2625038622	NRIP1	21	1	24	delG	1
2661518554	FAM108A5	22	2	13	delG	3
2748277559	SPIN2B	X	1	13	delG	2
2792445004	TEX13A	X	2	18	delC	3

[a]These indels commonly occurred in more than one HCC.

Supplementary Table 7. List of 40 Somatic Mutations With Amino Acid Changes Commonly Detected in Both the Tumor (at a Frequency of More Than 20% of Reads) and Matched Nontumorous Cirrhotic Liver (at a Frequency of More Than 5% of Reads) of the Same Patient

					Tumor		Nontumor	
Gene	Reference position	Chromosome	Reference nucleotide	Mutation nucleotide	Mutation frequency (%)	Patient no.	Mutation frequency (%)	Patient no.
LEPR	65548341	1	C	A	25.8	3	15.0	3
							21.9	1
ZNF408	1792629936	11	T	A	20.4	2	16.0	2
							15.8	4
HRNR	129676984	1	G	C	28.9	3	5.4	3
PXDN	228577682	2	G	C	45.1	4	47.2	4
POTEF	353150970	2	T	A	41.8	4	31.0	4
ALPP	455451136	2	C	T	32.5	4	37.5	4
GPR125	682521774	4	C	A	38.1	2	40.0	2
HERC6	746068457	4	T	A	36.5	4	44.9	4
EGFLAM	886579974	5	T	G	23.3	3	5.3	3
C4A	1057829599	6	T	G	25.0	2	11.5	2
WISP3	1134999625	6	T	G	43.3	4	64.3	4
C7orf10	1234451360	7	T	A	25.0	3	8.3	3
PVRIG	1290339880	7	C	T	23.5	1	21.3	1
MUC17	1291200140	7	G	A	21.2	4	12.5	4
PLOD3	1291376235	7	G	C	48.2	4	51.7	4
COL27A1	1589933932	9	A	G	56.8	4	54.6	4
AGAP9	1658906463	10	T	G	36.7	4	16.2	4
POLL	1713935693	10	G	T	44.8	4	38.6	4
MUC5AC	1747183167	11	G	A	43.9	4	43.8	4
MRGPRX3	1764064669	11	T	C	40.0	4	42.5	4
TMEM133	1843211533	11	A	C	59.5	4	83.3	4
TMEM123	1844621025	11	G	A	27.3	2	7.3	2
TMPRSS4	1860336319	11	C	T	54.4	4	41.3	4
DHRS4L2	2108914889	14	G	T	20.5	3	11.5	3
GOLGA6C	2247104814	15	A	T	21.7	4	9.6	4
PRSS22	2276813235	16	C	T	50.0	4	36.7	4
FAM38A	2351390771	16	C	T	21.4	4	54.3	4
GGT6	2357265990	17	G	A	92.3	4	41.7	4
COX10	2366897810	17	C	T	55.2	4	36.3	4
KIAA0100	2376657621	17	A	C	47.8	4	60.0	4
TBC1D3B	2384202011	17	C	T	63.0	4	27.4	4
TBC1D3D	2385938140	17	A	G	45.9	4	21.0	4
ERBB2	2387531879	17	A	G	66.7	4	54.6	4
CSH2	2411602334	17	C	T	90.9	4	79.5	4
QRICH2	2423941144	17	T	G	50.0	4	60.4	4
MOCOS	2461870479	18	T	C	72.0	4	62.2	4
CPAMD8	2522819358	19	G	A	21.8	3	15.2	3
MAP4K1	2541732174	19	G	A	36.0	4	54.3	4
PSG8	2545901763	19	C	A	28.3	3	9.5	3
KRTAP12-2	2654734983	21	C	T	59.3	4	43.5	4

NOTE. The first 2 genes listed were recurrently mutated in the nontumorous inflamed livers of 2 patients.

Supplementary Table 8. Overview of Selected Exome Sequencing Data From 22 Patients With HCV Infection

		Aligned reads	Aligned sequence (*base pairs*)	Median read depth
TP53	Tumor	29,334	2,035,570	1476.2
	Nontumor	31,848	2,200,641	1575.3
	Lymphocytes	36,690	2,539,944	1917.2
CTNNB1	Tumor	90,022	6,215,000	2344.3
	Nontumor	75,785	5,282,450	1991.2
	Lymphocytes	100,430	7,013,325	2710.8
LEPR	Tumor	34,328	2,390,335	538.3
	Nontumor	60,128	4,219,089	1025.6
	Lymphocytes	86,830	6,085,511	1423.0

NOTE. Selected exome sequencing of *TP53*, *CTNNB1*, and *LEPR* was performed for 22 nontumorous cirrhotic liver tissues, 10 HCC tissues, and matched peripheral lymphocytes from each patient. Aligned reads, aligned sequences (base pairs), and median read depth are shown for each sample.

Supplementary Table 9. Clinical Features and Overview of Deep Sequencing Data of Patients Who Underwent Deep Sequencing of the *LEPR* Gene

	Chronic hepatitis (n = 15)	Normal liver (n = 9)
Age (*y*)	59.3	55.9
Sex (male/female)	6/9	7/2
Aligned reads	4290	3956
Aligned sequence (*base pairs*)	1,044,737	1,275,068
Median read depth	2838	3440
No. of mutations in the *LEPR* gene	0	0

NOTE. We determined the sequences of the *LEPR* gene in the liver of 15 noncirrhotic patients with HCV-associated chronic hepatitis. In addition, normal liver tissues were obtained from 9 liver donors at the time of the operation. Age, sex, aligned reads, aligned sequences (base pairs), median read depth, and numbers of mutations are shown.

Supplementary Table 10. Mean Body Weights and Serum Levels of Insulin, Triglyceride, Total Cholesterol, and Alanine Aminotransferase of C57BL/KsJ-*db/db* (*db/db*) Mice and Misty (Control) Mice After 4 Weeks of Treatment With TAA

	db/db	Control
Body weight (*g*)	46.5 ± 0.6	23.5 ± 0.4
Insulin (*ng/mL*)	30.6 ± 28.3	1.6 ± 0.2
Triglyceride (*mg/dL*)	95.0 ± 5.0	50.0 ± 20.0
Total cholesterol (*mg/dL*)	215.0 ± 15.0	95.0 ± 15.0
Alanine aminotransferase (*IU/L*)	1325.0 ± 1085.0	75.0 ± 35.0

NOTE. All data are presented as mean ± SD.

Supplementary Table 11. Categorization of the Mutated Genes Detected by Whole Exome Sequencing of the AID-Expressing Hepatocyte Cell Line Using the Kyoto Encyclopedia of Genes and Genomes Database

Pathway				
Metabolic pathways	ATP6V0A4	DMGDH	HSD17B3	PGD
	ATP6V1C2	GALNT1	HYAL2	PHGDH
	BCMO1	GATM	NDST1	POLR3B
	CPS1	HKDC1	PAH	
PI3K-Akt signaling pathway	BCL2L11	IBSP NOS3	PRKCZ	TEK
	COL27A1			
MAPK signaling pathway	FLNB	SP1	CACNA1F	PTPN7
Cytokine-cytokine receptor interaction	LEPR	TNFRSF8	TNFRSF10A	
Transcriptional misregulation in cancer	EYA1	GZMB	JMJD7-PLA2G4B	
Proteoglycans in cancer	FLN	ITGB3	TIMP3	VTN
PPAR signaling pathway	CPT1B	CYP4A22	PPARD	
Cell cycle	E2F2	ESPL1	MCM7	
Pathways in cancer	FLT3	TRAF4	PDGFA	
Hedgehog signaling pathway	GLI3	LRP2	CSNK1A1L	
Others	95 genes			

NOTE. The genes categorized in multiple pathways are shown in only one representative pathway. Constitutive AID expression resulted in the accumulation of nucleotide alterations in various genes, including LEPR, of the cultured hepatocyte–derived cells. Whole exome sequencing was performed on DNA derived from established non-neoplastic human primary hepatocyte cells[6] with constitutive AID expression. AID expression in the cultured hepatocytes was performed using a lentiviral system.[5] After 8 weeks of AID expression, the DNA was extracted and subjected to whole exome sequencing as described in Materials and Methods. Overall, a total of 460 nucleotide positions in 380 different genes were defined as mutated in the AID-expressing cultured hepatocytes through the variant filtering process. Among them, pathway analyses by the Kyoto Encyclopedia of Genes and Genomes revealed that many genes, including LEPR, were categorized into well-known signaling pathways: the metabolic pathway, PI3K-Akt signaling pathway, MAPK signaling pathway, cytokine-cytokine receptor interaction pathway, and transcriptional misregulation in cancer pathway. Only categorized genes are shown.

Chronic Rejection Associated with Antiviral Therapy for Recurrent Hepatitis C after Living-Donor Liver Transplantation

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Background. Chronic rejection (CR) has been reported to be associated with antiviral therapy for recurrent hepatitis C in liver transplant (LT) recipients. The aims of this study were to clarify the details of antiviral therapy-associated CR after living-donor liver transplantation (LDLT) and to identify the factors associated with CR.

Methods. A retrospective chart review was performed on 125 recipients who had received antiviral therapy for recurrent hepatitis C after LDLT between January 2001 and September 2012. The characteristics of patients who developed CR during or within 6 months after antiviral therapy were compared with those of 76 patients who did not develop CR despite receiving antiviral therapy for more than 1 year.

Results. Seven of 125 (6%) patients developed CR during or within 6 months after the end of antiviral therapy. CR was diagnosed after a median (range) of 9 (1–16) months of antiviral therapy. In five patients, rejection progressed rapidly and resulted in death within 3 months after diagnosis. Analysis revealed two significant factors associated with CR: reduction of the immunosuppressant dose during antiviral therapy and a low fibrosis score as the indication for antiviral therapy.

Conclusions. CR developed in association with antiviral therapy for recurrent hepatitis C after LDLT. This complication may be prevented by ensuring that the immunosuppressant dose is not reduced during antiviral therapy.

Keywords: Chronic rejection, Hepatitis C, Liver transplantation, Living donor, Antiviral therapy.

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Hepatitis C virus (HCV) infection, which leads to liver cirrhosis and hepatocellular carcinoma, is the most common indication for liver transplantation (LT) in Japan, the United States, and western Europe. Most patients who undergo LT for HCV-related liver disease develop recurrent viral infection, and 70% to 90% suffer from histologically proven recurrent hepatitis (*1–6*). The progression of recurrent hepatitis C is often rapid. Without appropriate antiviral therapy, 10% to 25% of patients develop cirrhosis within 5 years after transplantation, and this explains the relatively poor prognosis for HCV-positive recipients compared with HCV-negative recipients (*7*). Interferon (IFN)–based combination therapy is commonly administered to prevent the progression of hepatitis C after LT (*8, 9*), but its efficacy in LT recipients is limited. The mean (range) sustained virologic response (SVR) rate in patients with recurrent hepatitis C after LT is only 30% (8%–50%) (*10*). One reason for the low SVR rate is the high rate of treatment withdrawal, particularly because of the unique adverse effects of IFN therapy for transplant recipients, including chronic rejection (CR) (*11, 12*).

CR is characterized by progressive ductopenia, with atrophy and loss of the bile ducts in the portal tracts and by arteriopathy with foamy cell infiltration (*13–15*). A cholestatic liver enzyme pattern suggests the diagnosis of CR. If bile duct enlargement and/or hepatic artery changes are excluded by imaging studies as potential causes of abnormal liver function tests, then CR is confirmed or excluded by liver biopsy examination. The incidence of CR after LT is

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