Genetic Predisposition in Metabolic-Driven Hepatocellular Carcinoma: PNPLA3/GCKR Polymorphisms and Their Differential Association Patterns Compared to Viral Etiology

No.62

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Background:

A subset of primary liver cancer patients lacks identifiable etiologies at diagnosis, termed cryptogenic hepatocellular carcinoma (HCC). Increasing evidence suggests metabolic dysfunction-associated steatotic liver disease (MASLD) as a key contributor to cryptogenic HCC. Genetic factors play a critical role in MASLD-associated HCC pathogenesis. This study aims to compare the clinical and genetic profiles of cryptogenic HCC and hepatitis B virus (HBV)-related HCC (HBV-HCC), providing novel insights for early diagnosis and targeted treatment.

Methods:

From January 2017 to December 2023, 41 cryptogenic HCC patients diagnosed at the Department of Hepatology, First Hospital of Jilin University, were enrolled. 212 patients with HBV-HCC diagnosed during the same period were randomly selected. 233 healthy controls (NC group) from the health examination center were included. Demographic characteristics, laboratory parameters, and genetic polymorphisms (PNPLA3 rs738409, TM6SF2 rs58542926, GCKR rs1260326, MBOAT7 rs641738, HSD17B13 rs72613567, ALDH2 rs671) were analyzed to compare NC, cryptogenic HCC and HBV-HCC groups and explore disease-specific features.

Genotype and allele frequency distribution at the PNPLA3 rs738409 locus

Genotypes and allele		NC n=233	HBV-HCC n=212	Cryptogenic HCC n=41	χ^2	*P*
Genotypes	CC	70(30.0)	82 (38.7)	7 (17.1)	18.912	<.001
	CG	113(48.5)	102 (48.1)	18 (43.9)		
	GG	50(21.5)	28 (13.2)	16 (39.0)		
	CG+GG	163(70.0)	130(61.3)	34(82.9)	8.739	0.013
Allele	C	253(54.3)	266(62.7)	32(39.0)	17.826	<.001
	G	213(45.7)	158(37.3)	50(61.0)		

Genotype and allele frequency distribution at the GCKR rs1260326 locus

Genotypes and allele		NC n=233	HBV-HCC n=212	Cryptogenic HCC n=41	χ^2	*P*
Genotypes	CC	59(25.3)	43 (20.3)	5 (12.2)	85.870	<.001
	CT	108(46.4)	166 (78.3)	18 (43.9)		
	TT	66(28.3)	3 (1.4)	18 (43.9)		
Genotypes	CT+TT	174(74.7)	169(79.7)	36(77.8)	4.157	0.125
Allele	C	226(48.5)	252(59.4)	28(34.1)	22.150	<.001
	T	240(51.5)	172(40.6)	54(65.9)		

Genotype and allele frequency distribution of PNPLA3 rs738409 in cryptogenic HCC vs NC

Genotypes and allele		NC n=233	Cryptogenic HCC n=41	χ^2	*P*	OR（95%CI）
Genotypes	CC	70(30.0)	7 (17.1)			1.000
	CG	113(48.5)	18 (43.9)	0.991	0.319	1.593（0.633-4.007）
	GG	50(21.5)	16 (39.0)	6.045	0.014	3.200（1.226-8.353）
	CG+GG	163(70.0)	34(72.9)	2.903	0.088	2.086（0.882-4.931）
Allele	C	253(54.3)	32(39.0)	6.512	0.011	1.000
	G	213(45.7)	50(61.0)			1.856（1.149-2.998）

Genotype and allele frequency distribution of GCKR rs1260326 in cryptogenic HCC vs NC

Genotypes and allele		NC n=233	Cryptogenic HCC n=41	χ^2	*P*	OR（95%CI）
Genotypes	CC	59(25.3)	5 (12.2)			1.000
	CT	108(46.4)	18 (43.9)	1.671	0.196	1.967（0.695-5.566）
	TT	66(28.3)	18 (43.9)	5.131	0.024	3.218（1.125-9.207）
	CT+TT	174(74.7)	36(77.8)	2.902	0.088	2.306（0.862-6.169）
Allele	C	226(48.5)	28(34.1)	5.776	0.016	1.000
	T	240(51.5)	54(65.9)			1.816（1.111-2.968）

Results:

Among 4,545 HCC patients, 85 (1.87%) met cryptogenic HCC criteria. Compared to HBV-HCC patients, cryptogenic HCC patients exhibited older age at diagnosis, higher BMI, increased female predominance, higher rates of non-cirrhotic background and diabetes, and elevated GGT, ALP, and TG levels (all P<0.05). Tumor characteristics (BCLC stage, tumor number, size, and vascular invasion) showed no significant differences. However, cryptogenic HCC demonstrated lower AFP elevation rates but higher distant/lymph node metastasis, and liver dysfunction (P < 0.05). Statistic analysis revealed significant differences in genotype and allele frequencies of PNPLA3 rs738409 and GCKR rs1260326 among cryptogenic HCC, HBV-HCC, and NC groups (all P<0.05). Specifically, PNPLA3 rs738409 homozygous mutation (GG) and allele G were independent risk factors for cryptogenic HCC (GG vs. CC: OR=3.200, 95% CI=1.226-8.353, P=0.014; G vs. C: OR=1.856, 95% CI=1.149-2.998, P=0.011). Similarly, GCKR rs1260326 homozygous mutation (TT) and allele T significantly increased cryptogenic HCC risk (TT vs. CC: OR=3.218, 95% CI = 1.125-9.027, P=0.024; T vs. C: OR=1.816, 95% CI=1.111-2.968, P=0.016), suggesting their potential roles in cryptogenic HCC pathogenesis.

Conclusion:

Patients with cryptogenic HCC exhibit older age at diagnosis, higher BMI, and a higher prevalence of female, diabetes, non-cirrhotic background, distant/lymph node metastasis. Notably, this group demonstrated lower rates of AFP elevation but significantly elevated serum levels of GGT, ALP, and TG compared to HBV-HCC patients. PNPLA3 rs738409 (GG genotype and G allele) and GCKR rs1260326 (TT genotype and T allele) polymorphisms may serve as genetic risk factors for cryptogenic HCC, highlighting their potential involvement in disease development.

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