Introduction

Hepatocellular carcinoma (HCC) is the sixth common cancer and the second leading cause of cancer deaths worldwide. The prevalence of HCC varies considerably, with the highest in East, Southeast Asia and Sub-Saharan Africa, and China alone accounts for approximately 50% of all cases [1]. The known etiologies of HCC include chronic infections with hepatitis B or C virus (HBV or HCV), aflatoxin B1 exposure, alcohol consumption, and drug abuse [2]. Among them, chronic infection with HBV is the main etiological factor for developing HCC to majority of HCC cases in China. More than 90% of perinatal infection by HBV eventually develop liver cirrhosis and HCC. These epidemiology studies indicated that an individual’s genetic makeup might play an important role in the HCC carcinogenesis [4].

In the recent years, several genome-wide association studies (GWAS) identified 31 loci in 10 chromosomal regions associated with susceptibility of CHB [5–11] or HBV-related HCC [12–16]. Evidence has been accumulated to show that some susceptible variants might also be associated with survival time of patients with colorectal cancer, gastric cancer or prostate cancer [17–20]. However, relationship between these GWAS-identified susceptibility loci and survival of HCC patients are still unknown. To evaluate the association between CHB or HBV-related HCC susceptibility loci and survival of HCC patients might also affect the prognosis of patients with HBV-related HCC.
360 patients (8.3%) were excluded from the study and finally 330 patients were enrolled in the further study. All patients were unrelated ethnic Han Chinese. The diagnosis of HCC was all histopathologically confirmed by at least two local pathologists. We selected the samples for HBV positive but HCV negative according to serology tests and infection history. Serum hepatitis B surface Antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B e Antigen (HBeAg), hepatitis B e Antibody (anti-HBe), hepatitis B core antibody (anti-HBc), and antibody to the hepatitis C virus (anti-HCV) were measured by ELISA (Roche, Shanghai, China) according to the manufacturer’s instruction. In addition, patients had to meet criteria as follows: a Karnofsky performance score (KPS) of at least 70, a life expectancy of at least three months, and having adequate organ functions. We collected demographic data of each patient such as sex, age, smoking status, and alcohol consumption. Tumor-node-metastasis (TNM) stages were evaluated and classified according to American Joint Commission for Cancer Staging (AJCCS) in 2009, the seventh edition. Individuals who smoked daily for at least one year were defined as smokers, and those who consumed alcohol drinks more than one time per week for over six months were considered drinkers. Written informed consent was obtained from each patient and this study was approved by the Institutional Review Board of Chinese Academy of Medical Sciences Cancer Institute.

Follow-up study
Overall survival (OS) time of patients was measured from the date of treatment to the date of last follow-up or death. Whether and when a patient had died was obtained from inpatient and outpatient records, patients’ relatives, or local Public Security Census Register Office through follow-up telephone calls. The last date of follow-up was 30th December 2013 and no patients were lost. Patients alive on the last follow-up date were considered censored. The median follow-up time was 68 months for this cohort.

SNP selection and genotype analysis
Genomic DNA were extracted from patients’ peripheral blood samples. Blood DNA kit (catalog number: DP31902) was provided by Tiangen Biochemical Technology Co., Ltd. (Beijing, China). The procedure was performed strictly following the manufacturer’s instructions. 31 SNPs were reported by six CHB and five HCC susceptibility GWAS in Asian population [5–16]. Among them, 22 SNPs with minor allele frequency $>0.05$ in Chinese Han population were selected based on the genotypes of samples from 1000 Genome project November 2010 ASN (Asian) and genotyped using the MassARRAY system from Sequenom. Genotyping of the other nine SNPs failed because of no appropriate primers for them. Several quality-control measures

### Table 1. Demographic and Clinical characteristics of 330 patients with HBV-related HCC.

| Characteristics          | N=330 | No. (%) | MST (month) | \( p \) |
|--------------------------|-------|---------|-------------|--------|
| Dead                     |       | 521 (59.6) | 18          |        |
| Alive                    |       | 353 (40.4) |             |        |
| Sex                      |       |          |             |        |
| Male                     |       | 282 (85.5) | 18          | 0.9064 |
| Female                   |       | 48 (14.5)  | 23          |        |
| Age                      |       |          |             |        |
| <54 years                |       | 164 (49.7) | 18          | 0.8157 |
| ≥54 years                |       | 166 (50.3) | 21          |        |
| Smoking status           |       |          |             |        |
| Nonsmoker                |       | 184 (55.8) | 23          | 0.0904 |
| Smoker                   |       | 146 (44.2) | 15          |        |
| Drinking status          |       |          |             |        |
| Nondrinker               |       | 227 (68.8) | 24          | 0.0346 |
| Drinker                  |       | 103 (31.2) | 14          |        |
| TNM stage                |       |          |             | <0.0001|
| I                        |       | 100 (30.3) | 51          |        |
| II                       |       | 106 (32.1) | 25          |        |
| III                      |       | 124 (37.6) | 10          |        |
| Surgery                  |       |          |             | <0.0001|
| No                       |       | 240 (72.7) | 13          |        |
| Yes                      |       | 90 (27.3)  | 67          |        |
| KPS                      |       |          |             | 0.0049 |
| 70                       |       | 65 (19.7)  | 11          |        |
| 80                       |       | 126 (38.2) | 15          |        |
| 90                       |       | 139 (42.1) | 28          |        |

Abbreviation: No., number of patients; MST, median survival time.

\( p \) values for log-rank test.

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implemented in genotyping analysis are as follows: duplicated samples were mixed in the plates; persons performing the genotyping assays were not aware of the status of the duplicated samples; both positive and negative (no DNA) control samples were included on every 384-well assay plate; and 20% random samples were genotyped twice by different investigators and all results were completely concordant, with the concordance being 100%.

Statistical analysis

Kaplan-Meier method was used to estimate survival curves. Log-rank test was adopted to assess the association between SNPs and OS, demographic characteristics, and clinical features. The Cox regression under a log additive genetic model was used to assess the effect of individual SNPs on OS. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated with adjustment for age, sex, smoking status, drinking status, KPS, surgery, and clinical stage. All data were analyzed using SAS software (version 9.2; SAS Institute Inc., Cary, NC, USA) with two-sided P-values (P < 0.05 were considered significant).

Results

Characteristics of the Study Population

The demographic and clinical characteristics of the 330 patients enrolled in this study are shown in Table 1. During the follow-up period, 256 (77.6%) patients died of HCC, with a median survival time (MST) of 18 months. The median age at diagnosis was 54 years (range, 25–88 years). 282 males (85.5%) and 48 females (14.5%) were included. There were 184 smokers (55.8%) and drinkers (68.8%). 65 (19.7%), 126 (38.2%), and 139 (42.2%) patients were with KPS 70, 80, and 90–100, respectively. 90 (27.3%) patients received liver resection, and the other 240 (72.7%) patients received non-surgery treatment including transcatheter arterial chemoembolization (TACE), TACE combined with radiofrequency ablation, or TACE combined with targeted therapy. Corresponding MST were 51, 25, and 10 months, respectively. TNM stage, drinking status, KPS, and surgical treatment showed a significant association with OS in patients with HBV-related HCC (Log-rank P < 0.05).

Genetic variants associated with OS in patients with HBV-related HCC

Among 22 SNPs genotyped, three SNPs (rs1419881 T>C, rs7439390 G>A and rs7768538 T>C) identified by CHB susceptibility GWAS and three SNPs (rs2275959 C>T, rs7821974 T>C and rs9997872 G>A) identified by HCC susceptibility GWAS, were significantly associated with OS in patients with HBV-related HCC in this study using the Cox regression after adjusting for covariates including age, gender, KPS, smoke, alcohol, surgery, and TNM stage (Table 2). (Kaplan-Meier survival curves for patients with HBV-related HCC were calculated with multivariate Cox regression under an additive genetic model adjusted for age, sex, smoking status, drinking status, KPS, surgery, and clinical stage. doi:10.1371/journal.pone.0101586.t002

Table 2. Associations of 22 candidate SNPs and overall survival in patients with HBV-related HCC.

| SNP ID  | Chr. | Gene  | Minor Allele | MAF  | HR (95% CI) | P  |
|--------|------|-------|--------------|------|-------------|----|
| rs7768538* | 6    | HLA-DQB2 | C            | 0.19 | 0.48 (0.32–0.72) | 0.0004 |
| rs7439390* | 6    | HLA-DQB2 | A            | 0.12 | 0.52 (0.36–0.75) | 0.0004 |
| rs9997872* | 6    | HLA-DQA1 | A            | 0.06 | 0.48 (0.25–0.92) | 0.0266 |
| rs7821974* | 8    | LOC101929604 | T | 0.49 | 0.81 (0.67–0.98) | 0.0335 |
| rs2275959* | 8    | LOC101929604 | A | 0.43 | 1.22 (1.01–1.46) | 0.0351 |
| rs1419881* | 6    | TCF19 | A            | 0.49 | 0.81 (0.66–0.99) | 0.0364 |
| rs3077 | 6    | HLA-DPA1 | A            | 0.38 | 0.86 (0.70–1.06) | 0.1512 |
| rs2647073 | 6    | LOC100507709 | C | 0.08 | 1.17 (0.96–1.44) | 0.1277 |
| rs6468418 | 8    | LOC101929604 | A | 0.42 | 0.87 (0.71–1.06) | 0.1737 |
| rs4821116 | 22   | UBE2L3 | T            | 0.36 | 0.88 (0.71–1.09) | 0.2330 |
| rs4678680 | 3    | GLB1 | G            | 0.06 | 0.79 (0.53–1.18) | 0.2505 |
| rs17401966 | 1    | KIF1B | A            | 0.29 | 1.12 (0.90–1.40) | 0.3003 |
| rs2844619 | 6    | HLA-C | A            | 0.19 | 1.07 (0.78–1.48) | 0.6798 |
| rs9272218 | 6    | HLA-DQA1 | A | 0.48 | 0.94 (0.79–1.11) | 0.4435 |
| rs9444730 | 6    | BACH2 | G            | 0.12 | 0.93 (0.72–1.20) | 0.5773 |
| rs9267673 | 6    | C2 | T            | 0.13 | 1.15 (0.88–1.49) | 0.3035 |
| rs7749730 | 6    | BACH2 | G            | 0.12 | 0.95 (0.73–1.22) | 0.6618 |
| rs2724432 | 11   | FDX1 | T            | 0.06 | 0.90 (0.53–1.52) | 0.6876 |
| rs12100561 | 14   | EFCAB11 | A | 0.38 | 1.04 (0.86–1.25) | 0.7098 |
| rs455804 | 21   | GRIK1 | A            | 0.34 | 1.04 (0.84–1.28) | 0.3746 |
| rs11866328 | 16   | GRIN2A | T | 0.18 | 1.04 (0.82–1.31) | 0.7577 |
| rs7574865 | 2    | STAT4 | T            | 0.35 | 1.00 (0.82–1.23) | 0.9916 |

Abbreviation: MAF, minor allele frequency; HR, hazard ratio; CI, confidence interval.

*The SNPs with P < 0.05.

†Calculated with multivariate Cox regression under an additive genetic model adjusted for age, sex, smoking status, drinking status, KPS, surgery, and clinical stage. doi:10.1371/journal.pone.0101586.t002

GWAS-Identified SNPs Associated with Survival of HBV-Related HCC
HCC stratified by genotypes of these six SNPs are shown in Figure 1.

The rs7768538 A>C locus was the most significant one, with the adjusted HR for death of patients being 0.48 (95% CI, 0.32–0.72; \(P=0.0004\)) under the additive model (Table 2). The MST for the rs7768538 AA and AC genotypes was 16 and 54 months, respectively. The adjusted HR for death of patients with the rs7768538 AC genotype was 0.49 (95% CI, 0.31–0.77; \(P=0.0022\)), compared with the AA genotype (Table 3). In a dominant model, patients with the rs7768538 AC or CC genotype...
had significantly longer MST (55 months) than those with the AA genotype, with the adjusted HR being 0.45 (95% CI, 0.29–0.71; \( P = 0.0005 \)) (Table 3).

The rs7453920 G>A, rs3997872 G>A, rs7821974 C>T, and rs1419881 T>C were also significantly associated with survival time in HBV-related HCC patients, with the adjusted HR being 0.52 (95% CI, 0.36–0.75; \( P = 0.0004 \)), 0.55 (95% CI, 0.37–0.82; \( P = 0.0030 \)), 0.81 (95% CI, 0.67–0.98; \( P = 0.0351 \)), and 0.81 (95% CI, 0.66–0.99; \( P = 0.0364 \)), respectively (Table 2). In the dominant model, patients carrying one or two minor alleles would survive significantly longer, compared to those carrying homozygous common genotypes. Patients carrying the rs7453920 G>A, rs3997872 G>A, rs7821974 C>T, and rs1419881 T>C were with the adjusted HR being 0.51 (95% CI, 0.34–0.75; \( P = 0.0007 \)), 0.55 (95% CI, 0.37–0.82; \( P = 0.0030 \)), 0.66 (95% CI, 0.49–0.88; \( P = 0.0046 \)), and 0.69 (95% CI, 0.49–0.88; \( P = 0.0046 \)), respectively (Table 3).

In contrast with the above five loci showing decreased risk of minor alleles on patient’s survival, rs2275959 C>T locus was significantly associated with an increased risk of death, with the adjusted HR for death of patients being 1.22 (95% CI, 1.01–1.46; \( P = 0.0351 \)) under the additive model. In addition, rs2275959 was significantly associated with an increased HBV-related HCC risk in a recessive manner. Patients with TT genotype had significant shorter survival time (MST, 15 months; adjusted HR = 1.50, 95% CI, 1.12–2.01; \( P = 0.0067 \)) compared to those with the CT or CC genotype.

### Cumulative effects of risk genotypes associated with OS in HBV-related HCC patients

We further estimated the cumulative effects of risk genotypes associated with OS in HBV-related HCC patients by counting the number of associated genotypes in each subject on the basis of the best-fitting genetic model from single-locus analysis. For

| Genotype  | No. | Dead/Alive | MST (months) | HR (95% CI)† | \( P \) |
|----------|-----|-----------|--------------|--------------|------|
| rs7768538 | AA  | 273 220/53 | 16           | 1.00 (Reference) |      |
|          | AC  | 36 22/14  | 54           | 0.49 (0.31–0.77) | 0.0022 |
|          | CC  | 3 1/2     | na           | 0.17 (0.02–1.25) | 0.0823 |
|          | AC+CC| 39 23/16 | 55           | 0.45 (0.29–0.71) | 0.0005 |
| rs7453920 | GG  | 279 225/54 | 17           | 1.00 (Reference) |      |
|          | GA  | 47 29/18  | 54           | 0.55 (0.37–0.82) | 0.0030 |
|          | AA  | 3 1/2     | na           | 0.16 (0.02–1.19) | 0.0740 |
|          | GA+AA| 50 30/20 | 54           | 0.51 (0.34–0.75) | 0.0007 |
| rs3997872 | TT  | 306 243/63 | 18           | 1.00 (Reference) |      |
|          | TA  | 22 11/11  | 66           | 0.48 (0.25–0.92) | 0.0266 |
|          | AA  | 0 0/0     | na           | na            |      |
|          | TA+AA| 22 11/11 | 66           | 0.48 (0.25–0.92) | 0.0266 |
| rs7821974 | CC  | 92 81/11  | 15           | 1.00 (Reference) |      |
|          | CT  | 140 100/40 | 21           | 0.64 (0.46–0.88) | 0.0059 |
|          | TT  | 70 53/17  | 21           | 0.69 (0.47–1.00) | 0.0525 |
|          | CT+TT| 210 153/57| 21           | 0.66 (0.49–0.88) | 0.0046 |
| rs2275959 | GG  | 91 69/22  | 21           | 1.00 (Reference) |      |
|          | GA  | 159 114/45 | 20           | 1.00 (0.73–1.36) | 0.9980 |
|          | AA  | 80 73/7   | 15           | 1.45 (1.02–2.07) | 0.0395 |
|          | GA+AA| 239 187/52| 18           | 1.13 (0.85–1.51) | 0.3942 |
| rs1419881 | GG  | 132 109/23 | 18           | 1.00 (Reference) |      |
|          | GA  | 151 112/39 | 19           | 0.72 (0.55–0.96) | 0.0258 |
|          | AA  | 45 33/12  | 24           | 0.78 (0.51–1.18) | 0.2330 |
|          | GA+AA| 196 145/51| 21           | 0.73 (0.56–0.95) | 0.0204 |

Abbreviation: No., number of patients; MST, median survival time; HR, hazard ratio; CI, confidence interval. Because of genotyping failure of some DNA samples, the number of subjects may not add up to the total number.

†Calculated with multivariate Cox regression models adjusted for age, sex, smoking status, drinking status, KPS, surgery and clinical stage.

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Table 4. Cumulative effect of risk genotypes on survival in HBV-related HCC patients.

| Number of risk genotypes | No. | Dead/Alive | MST (months) | HR (95% CI) | P  | \(P_{\text{log-rank}}\) |
|--------------------------|-----|------------|--------------|-------------|----|-----------------|
| 0–1 (low risk)           | 35  | 17/18      | 56           | 1.00 (Reference) |    | 6.23 \times 10^{-6} |
| 2–3 (medium risk)        | 223 | 173/50     | 19           | 2.14 (1.29–3.58) | 0.0034 | 7.72 \times 10^{-6} |
| 4–5 (high risk)          | 72  | 66/6       | 13           | 3.17 (1.77–5.68) | 0.0001 | 7.72 \times 10^{-6} |

Abbreviation: No., number of patients; MST, median survival time; HR, hazard ratio; CI, confidence interval.

Calculated with multivariate Cox regression models adjusted for age, sex, smoking status, drinking status, KPS, surgery and clinical stage.

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rs7453920 and rs7768538 at chromosome 6p21 were in strong linkage disequilibrium \( (\chi^2 = 0.82) \), we only selected rs7768538, which was more significantly associated with survival in HBV-related HCC patients, for the cumulative analysis. Compared with individuals carrying less than one unfavorable genotype, individuals carrying two or three and four or five unfavorable genotypes had an adjusted HR of 2.14 (95% CI, 1.29–3.58; \( P = 0.0034 \)) and 3.17 (95% CI, 1.77–5.68; \( P = 0.0001 \)), respectively. There was a significant trend of increasing risk of death \( (P_{\text{trend}} = 6.23 \times 10^{-6}) \) with increasing number of putative high-risk alleles (Table 4). Kaplan-Meier analysis showed a trend for significantly shorter MST with increasing number of risk alleles for the OS in patients with HBV-related HCC \( (\text{Log-rank} = 7.72 \times 10^{-6}; \text{Figure 2}) \).

Discussion

In this study, we found that GWAS-identified CHB and HCC susceptibility SNPs (rs2275959 and rs37821974 on 8p12; rs1419881, rs3997872, rs7453920, and rs7768538 on 6p21) may individually or jointly affect clinical outcomes for HBV-related HCC patients. To the best of our knowledge, this is the first study to report the association of CHB and HCC susceptibility loci with survival in patients with HBV-related HCC.

rs2275959 C>T and rs7821974 C>T are two susceptibility loci on 8p12 for HBV-related HCC identified by a GWAS in Southern Chinese population. Region 8p was one of the most frequently deleted regions in HCCs, and the loss of heterozygosity in 8p was associated with metastasis of HCC [21]. Moreover, a liver cancer suppressor gene named DLC-1, which induces apoptosis and exerts inhibitory effects on the cell proliferation of HCC cells [22,23], is located in a site of ~24 Mb upstream of the two SNPs (rs2275959 and rs37821974) on 8p12. Therefore, we suppose that risk-associated 8p12 SNPs might have an interacting effect on the DLC1 locus. Our data show that the variant genotypes of rs2275959 and rs37821974 respectively increase and decrease the risk of death in HBV-related HCC patients, indicating that the two SNPs might play different roles on the interaction with DLC1. Additionally, Chan et al found a 2.3-kb expressed sequence tag (EST) in the region 8p12 using in-silico data mining, sequencing analysis and in-vitro protein translation study, which suggested that the transcript might function as a long non-coding RNA (lncRNA) [14]. Accumulating studies have demonstrated that lncRNAs might be dysregulated in HCC and closely related with carcinogenesis, metastasis, or prognosis [24–26]. However, the biological and molecular mechanisms of lncRNAs are not yet fully understood. The relationship between 8p12 SNPs and lncRNA on the prognosis in HBV-related HCC patients is unknown and further studies are required.

rs3997872, which was located in a site of ~23 kb downstream of HLA-DRB1 in the major histocompatibility complex (MHC) class II locus, was associated with the decreased risk of death in patients with HBV-related HCC. MHC class II molecules present antigen to CD4+ T cells. Clifford et al discovered that rs3997872 and other two SNPs might be associated with altered MHC class II proteins that result in an ineffective T-cell response and be involved in antigen processing and presentation pathway [12]. Immune response has been proven to play an important role on development and clinical outcomes of HCC [27–29]. Furthermore, HLA-DR expression was one of the independent risk factors for early intrahepatic recurrence of HCC, which was strongly in correlation with poor prognosis of HCC [30]. These previous findings enhance the biological plausibility that genetic polymorphism in MHC class II region may play an important role on survival in HCC patients.

Due to only a subset of CHB patients develop HCC, it is of great interest to identify whether genetic factors of CHB susceptibility have an effect on the prognosis of HBV-related HCC patients. We identified three SNPs on 6p21, including rs7453920 (HLA-DQB2), rs7768538 (HLA-DQB2), and rs1419881 (TCF19), whose variant allele frequencies significantly associated with decreased death risk in such patients. rs7453920 and rs7768538 are situated in HLA-DQ genes, which are highly polymorphic, especially in exon 2 which encodes antigen-binding sites. Recent studies have showed that HLA-DQ molecules might be critical for the HBV clearance and play an important role in the development of CHB [9,13]. HBV-DNA has been confirmed as the most important predictor of disease progression and HCC development in CHB whereas the benefit of HBV clearance for

Figure 2. Kaplan–Meier curve of HBV-related HCC patients stratified by the number of unfavorable genotypes.

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HCC patients’ survival time is still far from completely understood [31]. Our findings provided a novel insight that genetic variants in HLA-DQ locus might influence the long-term outcomes in patients with HBV-related HCC through impact of HBV clearance. rs1194851 on 6p21.3 is located in the 3’ untranslated region of transcription factor 19 (TCF19). TCF19 was suggested as a late growth-regulated gene related to the risk of type 1 diabetes and psoriasis vulgaris, playing an important role in the transcription of genes required for the later stages of cell cycle progression [32–35]. However, whether TCF19 correlated to survival of HBV-related HCC remains uncertain, and further functional analysis is warranted to fully clarify the molecular mechanism whereby these variations confer survival of HBV-related HCC.

Since the process in clearance of HBV, development of CHB, and progression of HCC are complex, it is unlikely that any single variation would have a dramatic effect on clinical outcomes of HBV-related HCC. However, a combined influence of several SNPs may exert synergistic protection against the development or progression of HCC. Our results support the cumulative effects of risk-associated genotypes of SNPs in modulating survival time of HBV-related HCC, suggesting that screening of these SNPs may provide valuable information in clinical practice to predict different death risk for such patients.

In summary, this is the first study exploring the association of GWAS-identified HCC and CHB susceptibility SNPs with clinical outcomes of patients with HBV-related HCC. GWAS-identified SNPs, including rs2275395, rs37821974, rs1419881, rs3997872, rs7453920, and rs7768538, are significantly associated with survival time of HBV-related HCC. The GWASs from which these SNPs derived are all based on Asian population, making this study more reasonable. Results from cumulative analysis show a gene-dosage effect in these SNPs. Future independent validations in larger population are necessary before these findings translated into clinical practice and beneficial to prognosis in such patients.

Supporting Information

Table S1 Primers for genotyping of candidate SNPs. (XLS)

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Author Contributions

Conceived and designed the experiments: JC HZ. Performed the experiments: CL XB YH MZ. Analyzed the data: CL XB YH HZ. Contributed reagents/materials/analysis tools: XB HZ ZL MZ ZH J. ZHAO J. ZHOU. Contributed to the writing of the manuscript: CL YH. Helped to answer reviewers’ comments: CL XB.

References

1. Fevay J, Sevomjotarama I, Ervik M, Dhiokrit R, Eser S, et al. (2013) Cancer Incidence and Mortality Worldwide. IARC CancerBase No. 11 [Internet]. GLOBOCAN 2012 v1.0. Available: http://globocan.iarc.fr. Accessed on day/ month/year.
2. Fares N, Persoon JM (2013) [Epidemiology, natural history, and risk factors of hepatocellular carcinoma]. Rev Prat 63: 216–217, 220–212.
3. El-Serag HB (2012) Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 142: 1264–1273.e1261.
4. Chen CJ, Chen DS (2002) Interaction of hepatitis B virus, chemical carcinogen, and genetic susceptibility: multistage hepatocarcinogenesis with multifactorial etiology. Hepatology 36: 1046–1049.
5. Kamatani Y, Wattanapokayakit S, Ochi H, Kawaguchi T, Takahashi A, et al. (2009) A genome-wide association study identifies variants in the HLA-DP locus associated with chronic hepatitis B in Asians. Nat Genet 41: 591–595.
6. Liu L, Li J, Jiao Y, Yu J, Zhang J, et al. (2011) A genome-wide association study with DNA pooling identifies the variant rs11663329 in the GRIN2A gene that affects disease progression of chronic HBV infection. Viral Immunol 24: 397–402.
7. Mihara H, Ochi H, Urao Y, Kumar V, Kubo M, et al. (2011) A genome-wide association study of chronic hepatitis B and identified novel risk locus in a Japanese population. Hum Mol Genet 20: 3884–3892.
8. Ninshia N, Sawai H, Matsunaga K, Setoyama M, Aihara SH, et al. (2012) Genome-wide association study confirming association of HLA-DP with protection against chronic hepatitis B and viral clearance in Japanese and Korean. PLoS One 7: e39175.
9. Hu Z, Liu Y, Zhai X, Dai J, Jin G, et al. (2013) New loci associated with chronic hepatitis B virus infection in Han Chinese. Nat Genet 45: 1499–1503.
10. Kim YJ, Kim HY, Lee JJ, Yu SJ, Yoon JR, et al. (2013) A genome-wide association study identified new variants associated with the risk of chronic hepatitis B. Hum Mol Genet 22: 4233–4238.
11. Al-Qahtani A, Khalak HG, Alkuraya FS, Al-hamoudi W, Alswat K, et al. (2013) A genome-wide association study of chronic hepatitis B virus infection reveals a novel candidate risk allele on 1q22.3. J Med Genet 50: 725–732.
12. Clifford RJ, Zhang J, Meerzaman DM, Lyu MS, Hu Y, et al. (2010) Genetic variations at loci involved in immune response are risk factors for hepatocellular carcinoma. Hepatology 52: 2034–2043.
13. Zhang H, Zhai Y, Hu Z, Wu C, Qian J, et al. (2010) Genome-wide association study identifies rs156822 as a new susceptibility locus for hepatocellular carcinoma in Southern Chinese patients with chronic hepatitis B virus infection. PLoS One 6: e26798.
14. Chan KY, Wong CM, Kwan JS, Lee JM, Chuong KW, et al. (2011) Genome-wide association study of hepatocellular carcinoma in Southern Chinese patients with chronic hepatitis B virus infection. PLoS One 6: e26798.
15. Jiang DK, Sun J, Cao G, Liu Y, Lin D, et al. (2013) Genetic variants in STAT4 and HLA-DQ genes confer risk of hepatitis B virus-related hepatocellular carcinoma. Nat Genet 45: 72–73.
16. Li S, Qian J, Yang Y, Zhao W, Dai J, et al. (2012) GWAS identifies novel susceptibility loci on 6p21.32 and 21q21.3 for hepatocellular carcinoma in chronic hepatitis B virus carriers. PLoS Genet 8: e1002791.
17. Phipps AI, Newcomb PA, Garcia-Albeniz X, Hutter CM, White E, et al. (2012) Association between colorectal cancer susceptibility loci and survival time after diagnosis with colorectal cancer. Gastroenterology 145: 51–54.e4.
18. Bao BY, Pao JB, Huang CN, Pu YS, Chang TY, et al. (2012) Significant associations of prostate cancer susceptibility variants with survival in patients treated with androgen-deprivation therapy. Int J Cancer 130: 876–879.
19. Dai J, Gu J, Huang M, Eng C, Kopetta ES, et al. (2012) GWAS-identified colorectal cancer susceptibility loci associated with clinical outcomes. Carcinogenesis 33: 1327–1331.
20. Kang M, Ding X, Xu M, Zhu H, Liu S, et al. (2014) Genetic variation rs10484761 on 1p36.22 derived from a genome-wide association study is associated with gastric cancer survival in a Chinese population. Gene 536: 59–64.
21. Wu X, Jia HL, Wang YF, Ren N, Ye QH, et al. (2006) HTTAP gene on chromosome 8p is a candidate metastasis suppressor for human hepatocellular carcinoma. Oncogene 25: 1812–1840.
22. Zhou X, Thorgeirsson SS, Popescu NC (2004) Restoration of DCL-1 gene expression induces apoptosis and inhibits both cell growth and tumorigenicity in human hepatocellular carcinoma cells. Oncogene 23: 1308–1315.
23. Wong CM, Lee JM, Ching YP, Jin DY, Ng IO (2003) Genetic and epigenetic alterations of DCL-1 gene in hepatocellular carcinoma. Cancer Res 63: 7646–7651.
24. Wang X, Arai S, Song X, Reichart D, Du K, et al. (2008) Induced ncRNAs allosterically modify RNA-binding proteins in cis to inhibit transcription. Nature 454: 126–130.
25. Boud AM, Vangeneupel MJ, Sametksy EA, Clark MF, Savage JC, et al. (2009) Balanced gene regulation by an embryonic brain ncRNA is critical for adult hippocampal GABAergic circuitry. Nat Neurosci 12: 1029–1037.
26. Ye H, Meng XM, Huang C, Wu BM, Zhang L, et al. (2014) Long noncoding RNAs: Novel insights into hepatocellular cancer. Cancer Let 344: 20–27.
27. Flecken T, Schmid N, Hild S, Gostick E, Drognitz O, et al. (2014) Immunomodulation and functional alterations of tumor-associated antigen-specific CD8(+T-cell responses in hepatocellular carcinoma. Hepatology 59: 1415–1426.
28. Pan QZ, Pan K, Zhao JJ, Chen JG, Li JJ, et al. (2013) Decreased expression of interleukin-36alpha correlates with poor prognosis in hepatocellular carcinoma. Cancer Immunol Immunother 62: 1675–1683.
29. Liao R, Sun J, Wu H, Yi Y, Wang JX, et al. (2013) High expression of IL-17 and IL-17R associate with poor prognosis of hepatocellular carcinoma. J Exp Clin Cancer Res 32: 3.
30. Matoba K, Izuka N, Gondo T, Ishihara T, Yamada-Okabe H, et al. (2005) Tumor HLA-DR expression linked to early intralobar recurrence of hepatocellular carcinoma. Int J Cancer 115: 231–240.
31. Diepolder HM (2014) Clearance of HBV markers and HCC risk: who is safe? Gut.
32. Ku DH, Chang CD, Koniecki J, Cannizzaro LA, Boghosian-Sell L, et al. (1991) A new growth-regulated complementary DNA with the sequence of a putative trans-activating factor. Cell Growth Differ 2: 179–186.
33. Krishnan BR, Jamry I, Chaplin DD (1995) Feature mapping of the HLA class I region: localization of the POU5F1 and TCF19 genes. Genomics 30: 53–58.
34. Oka A, Tamiya G, Tomizawa M, Ota M, Katsuyama Y, et al. (1999) Association analysis using refined microsatellite markers localizes a susceptibility locus for psoriasis vulgaris within a 111 kb segment telomeric to the HLA-C gene. Hum Mol Genet 8: 2165–2170.
35. Cheung YH, Watkinson J, Anastassiou D (2011) Conditional meta-analysis stratifying on detailed HLA genotypes identifies a novel type 1 diabetes locus around TCF19 in the MHC. Hum Genet 129: 161–176.