

and a higher prevalence of basal core promoter mutations^{5,6,7} The precore (G1896A) and core promoter (A1762T, G1764A) mutations of the HBV gene are known to be associated with changes in immunologic phase or the progression to complicated liver disease in adults. HBV with TCC at nucleotides 1856 to 1858 of the precore region might represent a specific HBV strain associated with more aggressive liver disease than other genotype C HBV strains⁸. Sung et al. demonstrated that HBV genotype Ce is associated with a higher risk of HCC and cirrhosis when compared to genotypes B and Cs⁹. However, the result is not statistically significant.

[0004] With the development of health awareness in the general public, HCC comes to medical attention at earlier stages where often it is hard to determine the prognosis using classical histopathological measurements such as tumor multinodularity and vascular invasion.

[0005] Furthermore, all previous reports only disclose the relationship between genotypes and the risk of HCC and/or cirrhosis. Currently there is no reliable guide on the relationship between HBV genotypes and other clinical parameters like survival and recurrence.

SUMMARY OF THE INVENTION

[0006] The present disclosure provides a method for making a prognosis with respect to the clinical outcome of hepatocellular carcinoma (HCC) in a patient comprising the steps of a) detecting the presence of a Hepatitis B virus (HBV) in a sample obtained from said patient; b) identifying the genotype and strain of said HBV in said sample; and c) making a prognosis with respect to the clinical outcome of HCC based on the identity of the HBV genotype and strain detected.

DEFINITIONS

[0007] This section is intended to provide guidance on the interpretation of the words and phrases set forth below (and where appropriate grammatical variants thereof). Further guidance on the interpretation of certain words and phrases as used herein (and where appropriate grammatical variants thereof) may additionally be found in other sections of this specification.

[0008] The invention illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically

CLAIMS

1. A method for making a prognosis with respect to the clinical outcome of hepatocellular carcinoma (HCC) in a HCC patient comprising the steps of:
 - a. detecting the presence of a Hepatitis B virus (HBV) in a sample obtained from said HCC patient;
 - b. identifying the genotype and strain of said HBV in said sample;
 - c. making a prognosis with respect to the clinical outcome of HCC based on the identity of the HBV genotype and strain detected.
2. The method as claimed in claim 1, wherein said step of detecting the presence of said HBV further comprises detecting if said HBV has integrated into the genome of said patient.
3. The method as claimed in claim 2, wherein said step of detecting if said HBV has integrated into said genome further comprises identifying if said HBV has integrated into one or more genes in said genome.
4. The method as claimed in claim 3, wherein said one or more genes are selected from the group consisting of hTERT, MLL4, CCNE1, SENP5 and ROCK1.
5. The method as claimed in claim 4, wherein the one or more genes are hTERT, MLL4 or CCNE1.
6. The method as claimed in any one of claims 1 to 5, wherein the sample comprises a nucleic acid obtained from a biological material.

7. The method as claimed in claim 6, wherein the nucleic acid is selected from a single or double-stranded RNA or DNA molecule, cDNA and genomic DNA.
8. The method as claimed in claim 7, wherein the nucleic acid is genomic DNA.
9. The method as claimed in any one of claims 6 to 8, wherein the biological material is selected from the group consisting of a sample of fresh tissue, frozen tissue, paraffin- preserved tissue and/or ethanol preserved tissue.
10. The method as claimed in any one of claims 6 to 8, wherein said biological material is selected from the group consisting of whole blood or a component thereof, lymph, bile fluid, cerebrospinal fluid, bronchioalveolar lavage fluid, synovial fluid, semen, ascitic tumour fluid, breast milk, amniotic fluid, a buccal smear and pus.
11. The method as claimed in any one of claims claim 1 to 10, wherein the genotype of HBV is selected from the group consisting of HBV genotype A, HBV genotype B, HBV genotype C, HBV genotype D, HBV genotype E, HBV genotype F, HBV genotype G and HBV genotype H.
12. The method as claimed in any claim 11, wherein the HBV genotype A is selected from the group consisting of subtype A1, A2 and A3.
13. The method as claimed in any claim 11, wherein the HBV genotype B is selected from the group consisting of subtype B1, B2, B3 and B4.
14. The method as claimed in claim 11 or claim 13, wherein the HBV genotype B is HBV-B2.

15. The method as claimed in any claim 11, wherein the HBV genotype D is selected from the group consisting of subtype D1, D2, D3 and D4.
16. The method as claimed in claim 11, wherein the HBV genotype F is selected from the group consisting of subtype F1 and F2.
17. The method as claimed in claim 11, wherein the HBV genotype C is selected from the group consisting of subtype C1, C2, C3, C4 and C5.
18. The method as claimed in claim 11 or claim 17, wherein the HBV genotype C strain is selected from the group consisting of CHN-H155, GZ-DYH, CHN-H172, HK2100, HK858 and I182.
19. The method as claimed in claim 18, wherein the HBV genotype C strain is CHN-H155.
20. The method as claimed in claim 19, wherein said CHN-H155 comprises the mutation C2288A.
21. The method as claimed in any one of claims 6 to 20, wherein the nucleic acid sample is amplified by a polymerase chain reaction into one or more amplicons.
22. The method as claimed in claim 21, wherein the one or more amplicons are subjected to sequencing.

23. The method as claimed in claim 22, wherein the sequence of the one or more amplicons is compared with sequences of known HBV genotypes to determine the HBV genotype in the sample.

24. The method as claimed in claim 1, wherein the HBV strain is selected from CHN-H155, GZ-DYH, CHN-H172, HK2100, HK858, I182 and HBV-B2.

25. The method as claimed in any one of claims 1 to 24, wherein said step of making a prognosis with respect to the clinical outcome comprises correlating the genotype of said HBV in said patient sample with one or more factors associated with said HBV genotype in said patient relative to a patient having another HBV genotype.

26. The method as claimed in claim 25, wherein said one or more factors is selected from one or more of HBV genomic integration, genomic data of said patient, mutational status of the HBV strain identified in said sample or transcriptome profile.

CLAIMS

1. A method for making a prognosis with respect to the clinical outcome of hepatocellular carcinoma (HCC) in a patient comprising the steps of:
 - a. detecting the presence of a Hepatitis B virus (HBV) in a sample obtained from said patient;
 - b. identifying the genotype of said HBV in said sample;
 - c. making a prognosis with respect to the clinical outcome of HCC based on the identity of the HBV genotype detected.
2. The method as claimed in claim 1, wherein said step of detecting the presence of said genotype of HBV further comprises detecting if said HBV genotype has integrated into the genome of said patient.
3. The method as claimed in claim 2, wherein said step of determining whether said HBV genotype has integrated into said genome further comprises identifying if said HBV genotype has integrated into one or more genes in said genome.
4. The method as claimed in claim 3, wherein said one or more genes are selected from the group consisting of hTERT, MLL4, CCNE1, SENP5 and ROCK1.
5. The method as claimed in claim 4, wherein the one or more genes are hTERT, MLL4 or CCNE1.
6. The method as claimed in any one of claims 1 to 5, wherein the sample comprises a nucleic acid obtained from a biological material.

7. The method as claimed in claim 6, wherein the nucleic acid is selected from a single or double-stranded RNA or DNA molecule, cDNA and genomic DNA.
8. The method as claimed in claim 7, wherein the nucleic acid is genomic DNA.
9. The method as claimed in any one of claims 6 to 8, wherein the biological material is selected from the group consisting of a sample of fresh tissue, frozen tissue, paraffin- preserved tissue and/or ethanol preserved tissue.
10. The method as claimed in any one of claims 6 to 8, wherein said biological material is selected from the group consisting of whole blood or a component thereof, lymph, bile fluid, cerebrospinal fluid, bronchioalveolar lavage fluid, synovial fluid, semen, ascitic tumour fluid, breast milk, amniotic fluid, a buccal smear and pus.
11. The method as claimed in any one of claims claim 1 to 10, wherein the genotype of HBV is selected from the group consisting of HBV genotype A, HBV genotype B, HBV genotype C, HBV genotype D, HBV genotype E, HBV genotype F, HBV genotype G and HBV genotype H.
12. The method as claimed in any claim 11, wherein the HBV genotype A is selected from the group consisting of subtype A1, A2 and A3.
13. The method as claimed in any claim 11, wherein the HBV genotype B is selected from the group consisting of subtype B1, B2, B3 and B4.
14. The method as claimed in claim 11 or claim 13, wherein the HBV genotype B is HBV-B2.

15. The method as claimed in any claim 11, wherein the HBV genotype D is selected from the group consisting of subtype D1, D2, D3 and D4.

16. The method as claimed in claim 11, wherein the HBV genotype F is selected from the group consisting of subtype F1 and F2.

17. The method as claimed in claim 11, wherein the HBV genotype C is selected from the group consisting of subtype C1, C2, C3, C4 and C5.

18. The method as claimed in claim 11 or claim 17, wherein the HBV genotype C is selected from the group consisting of CHN-H155, GZ-DYH, CHN-H172, HK2100, HK858 and I182.

19. The method as claimed in claim 18, wherein the HBV genotype C is CHN-H155.

20. The method as claimed in claim 19, wherein said CHN-H155 comprises the mutation C2288A.

21. The method as claimed in any one of claims 6 to 20, wherein the nucleic acid sample is amplified by a polymerase chain reaction into one or more amplicons.

22. The method as claimed in claim 21, wherein the one or more amplicons are subjected to sequencing.

23. The method as claimed in claim 22, wherein the sequence of the one or more amplicons is compared with sequences of known HBV genotypes to determine the HBV genotype in the sample.

24. The method as claimed in claim 23, wherein the HBV strain is selected from CHN-H155, GZ-DYH, CHN-H172, HK2100, HK858, I182 and HBV-B2.

25. The method as claimed in any one of claims 1 to 24, wherein said step of making a prognosis with respect to the clinical outcome comprises correlating the genotype of said HBV in said patient sample with one or more factors associated with said HBV genotype in said patient relative to a patient having another HBV genotype.

26. The method as claimed in claim 25, wherein said one or more factors is selected from one or more of HBV genomic integration, genomic data of said patient, mutational status of the HBV strain identified in said sample or transcriptome profile.