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Correlation between *CTNNB1* Mutation Status and Tumor Phenotype in Hepatitis B virus-related Hepatocellular Carcinoma

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Background

- While *CTNNB1* mutation is one of the most frequent genetic events in hepatocellular carcinoma (HCC), its frequency is lower in Asian countries and in hepatitis B virus (HBV)-related HCCs.
- In this study, we evaluated the frequency and types of *CTNNB1*-mutation in HBV-related HCC and correlated the molecular status with the histomorphological and immunohistochemical features.

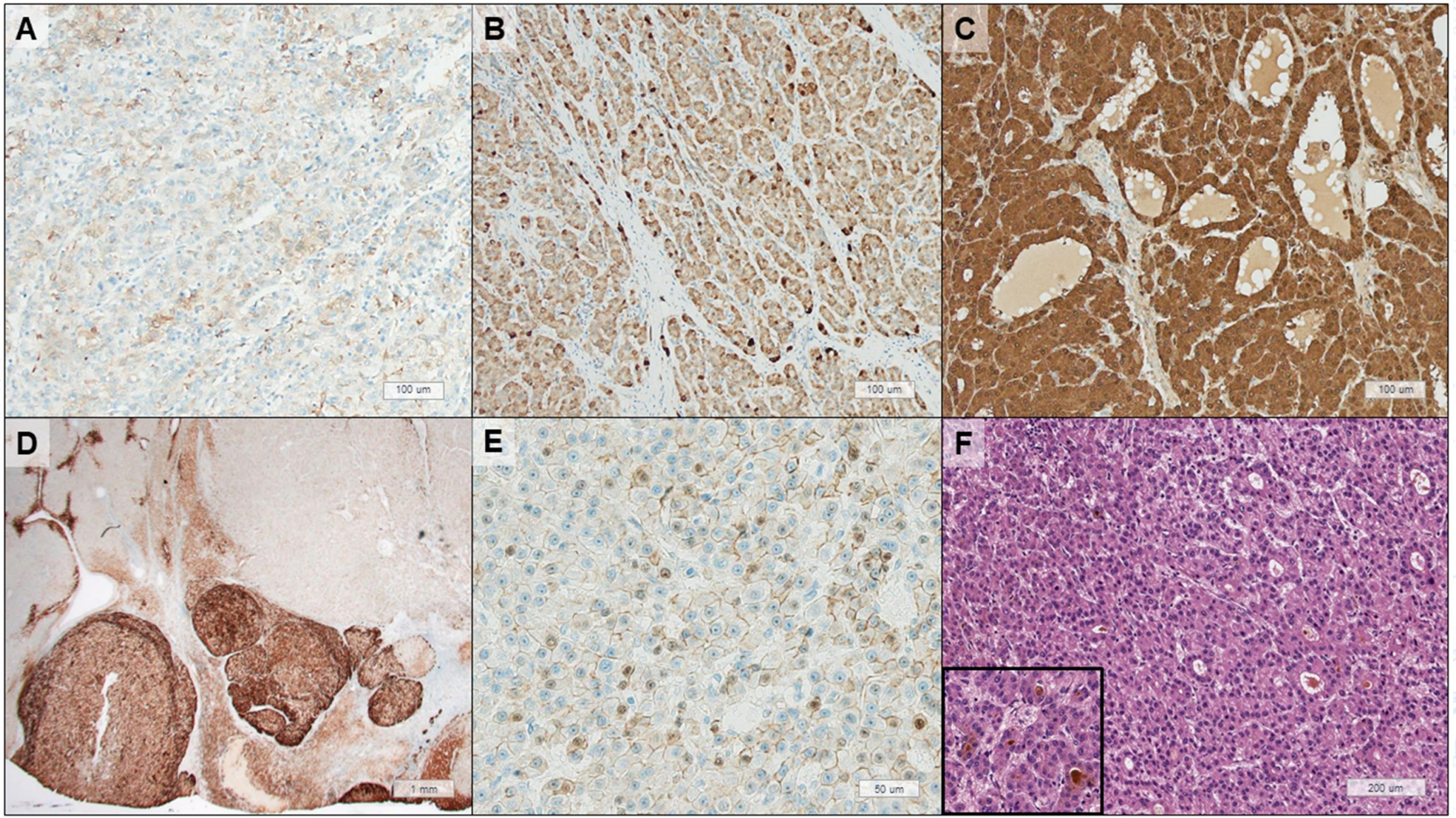
Methods

- A total of 108 consecutive cases of treatment-naïve, surgically resected HBV-related HCCs were selected.
- Targeted sequencing for *CTNNB1* exons 3, 7, and 8 was performed, and the results were correlated with the expression pattern of glutamine synthetase (GS), nuclear beta-catenin expression status, and the histomorphological characteristics of the tumor.

Definition of *CTNNB1* morphology	
1. Predominantly microtrabecular pattern (≥ 50%) 2. Major Edmonson-Steiner (ES) grade 1 or 2 3. Presence of pseudoglands	
- **Classic**	3 of the above features
- **Possibly classic**	2 of the above features
- **Non-classic**	0-1 of the above features

Classification of GS staining
Intensity
Weak
Moderate
Strong
Percentage of tumor cells stained
Focal (< 50%)
Diffuse (≥ 50%)

Expression pattern of GS and nuclear beta-catenin expression, and classic *CTNNB1* morphology

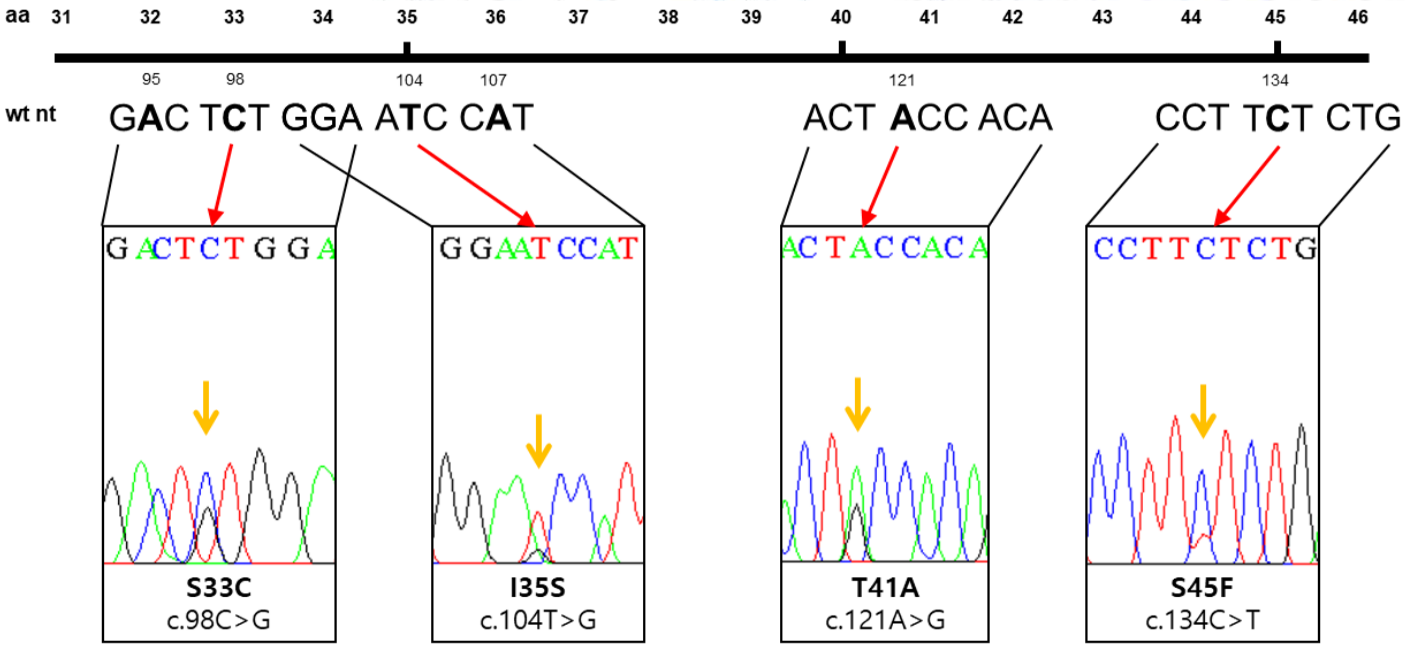


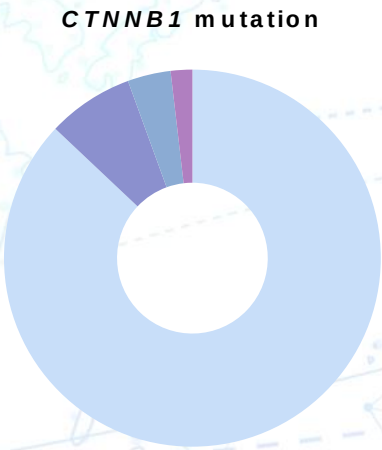
A: Weak GS expression (100x)
B: Moderate GS expression (100x)
C: Diffuse strong GS expression (100x).
D: Focal strong GS expression (40x)
E: Nuclear beta-catenin expression (200x)
F: Classic *CTNNB1* morphology with bile production (100x, inset: 200x)

Results

CTNNB1 mutation status

- *CTNNB1* mutations were identified in 14/108 (13%) HBV-related HCCs; of these cases, mutations were found in D32S, S33C, S33F, S33Y, I35S, H36P, T41A and S45F of exon 3.
- None of the HCCs demonstrated alterations in exons 7 and 8.

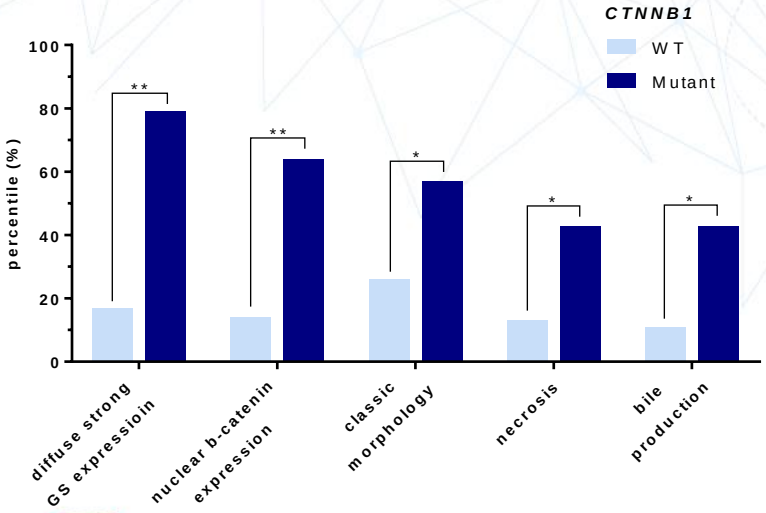


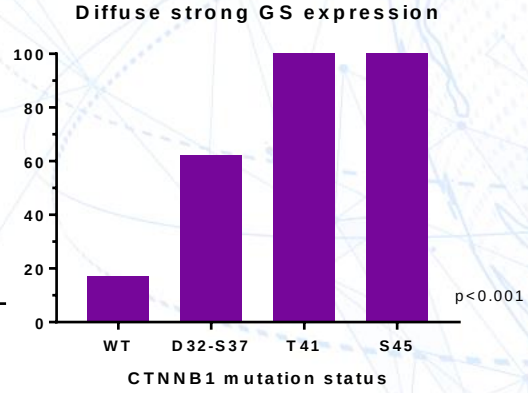


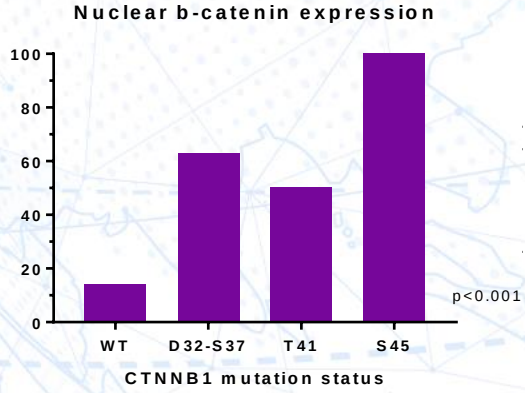
WT	94 (87%)
Exon 3	14 (13%)
D32-S37	8 (7%)
T41	4 (4%)
S45	2 (2%)
Exon 7	0 (0%)
Exon 8	0 (0%)

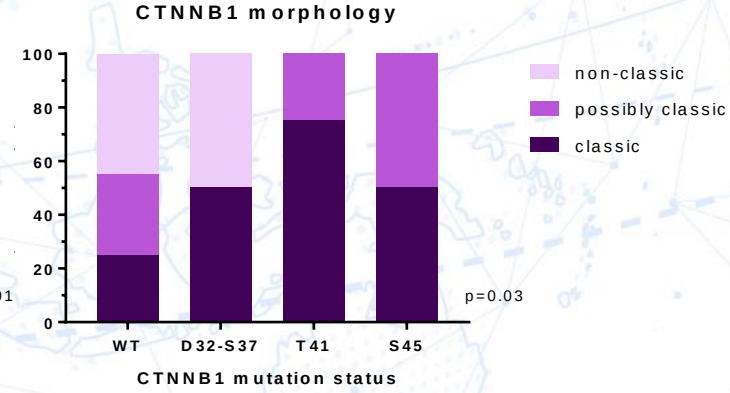
Clinicopathological features according to *CTNNB1* mutation status

- *CTNNB1* mutation was strongly associated with diffuse strong GS expression, nuclear beta-catenin expression, the classic *CTNNB1* morphology, necrosis and bile production.
- Diffuse strong GS expression was observed in 78.6% of the *CTNNB1*-mutated HCCs – 62.5% of the D32-S37-mutated HCCs, and in all of the T41 and S45-mutated HCCs.
- Nuclear beta-catenin expression was identified in 64.3% of the *CTNNB1*-mutated HCCs – 62.5% of the D32-37-mutated HCCs, 50% of the T41-mutated HCCs and all of the S45-mutated HCCs.
- All *CTNNB1*-mutated HCCs with nuclear beta-catenin expression showed diffuse strong GS expression.
- The classic *CTNNB1* morphology was observed in 57% of all *CTNNB1*-mutated HCCs, 50% of the D32-S37-mutated HCCs, 75% of the T41-mutated HCCs, and 50% of the S45-mutated HCCs.



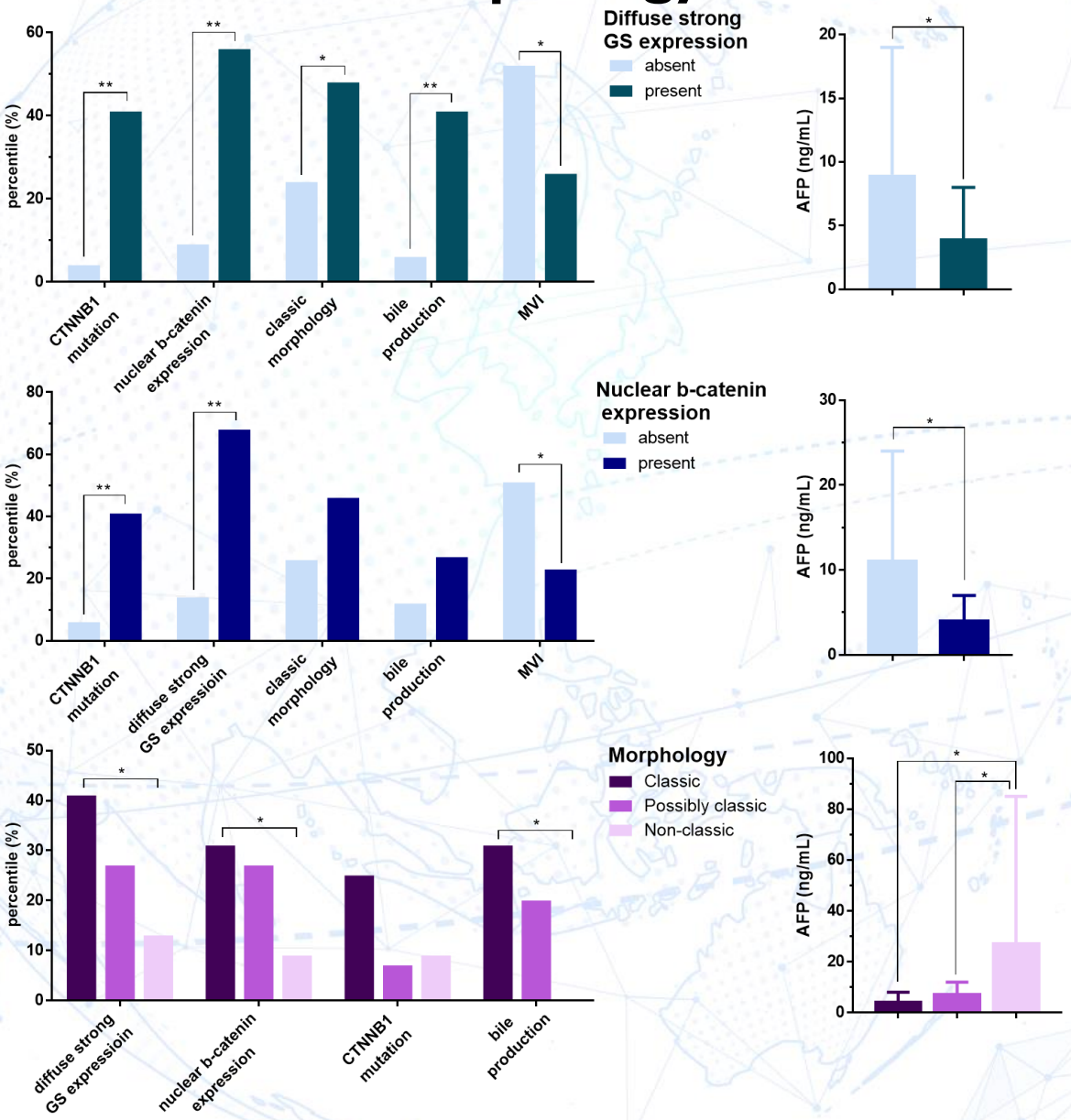






Clinicopathological features according to GS, nuclear beta-catenin expression and *CTNNB1* morphology

- Diffuse strong GS expression was significantly associated with *CTNNB1* mutation, nuclear beta-catenin expression, the classic *CTNNB1* morphology and bile production and inversely associated with microvascular invasion (MVI) and serum alpha-fetoprotein (AFP) level.
- Nuclear beta-catenin expression was strongly associated with *CTNNB1* mutation and diffuse strong GS expression, and negatively associated with MVI and serum AFP level.
- The classic *CTNNB1* morphology was significantly associated with diffuse strong GS expression, nuclear beta-catenin expression and bile production, and inversely correlated with serum AFP level.



Conclusion

- *CTNNB1* mutation was observed in 13% of HBV-related HCCs in this Korean cohort, and was associated with diffuse strong GS expression, nuclear beta-catenin expression and classic *CTNNB1* morphology.