Supplemental file

|  |  |  |  |
| --- | --- | --- | --- |
| Mutation | Characteristics | Documented genotype with the mutation | Reference |
| L109I | Immune escape, failed detection in some commercial tests | B2, D | [1-3] |
| P120Q | Immune escape | B, D | [4-6] |
| A128V | Occult HBV infection  Immune escape | D, D2, H | [7-11] |
| Q129P | Immune escape, failed detection in commercial tests;  Occult HBV infection | D | [12, 13] |
| Q129H | Immune escape | B, C, H | [3, 6, 8, 10, 14] |
| T131N | Immune escape | A1, B, C, C1 | [3, 8, 15-17] |
| F134V | No difference in antigenicity;  One case in occult HBV infection (with S117G and G145R) without further characterization | B, D2 | [3, 18, 19] |
| P142L | immune escape, failed detection in some commercial tests | D, E | [1, 12, 20] |
| G145R | Immune escape | A-D | [21, 22] |

For comprehensive reviews: [23, 24]

References for Supplementary Data

1. Ly TD, Servant-Delmas A, Bagot S, Gonzalo S, Ferey MP, Ebel A, et al. Sensitivities of four new commercial hepatitis B virus surface antigen (HBsAg) assays in detection of HBsAg mutant forms. J Clin Microbiol 2006;44(7):2321-6. [PMID: 16825343 DOI: 10.1128/JCM.00121-06]

2. Yong-Lin Y, Qiang F, Ming-Shun Z, Jie C, Gui-Ming M, Zu-Hu H, et al. Hepatitis B surface antigen variants in voluntary blood donors in Nanjing, China. Virol J 2012;9:82.[PMID: 22500577 DOI: 10.1186/1743-422X-9-82]

3. Minekawa T, Takehara S, Takahashi M, Okamoto H. Development of a highly sensitive bioluminescent enzyme immunoassay for hepatitis B virus surface antigen capable of detecting divergent mutants. Clin Vaccine Immunol 2013;20(8):1255-65. [PMID: 23761660 DOI:10.1128/CVI.00186-13]

4. Lee KM, Kim YS, Ko YY, Yoo BM, Lee KJ, Kim JH, et al. Emergence of vaccine-induced escape mutant of hepatitis B virus with multiple surface gene mutations in a Korean child. J Korean Med Sci 2001;16(3):359-62.[PMID: 11410701 DOI: 10.3346/jkms.2001.16.3.359]

5. Sticchi L, Caligiuri P, Cacciani R, Alicino C, Bruzzone B. Epidemiology of HBV S-gene mutants in the Liguria Region, Italy: Implications for surveillance and detection of new escape variants. Hum Vaccin Immunother 2013;9(3):568-71.[PMID: 23296324]

6. Hsu HY, Chang MH, Liaw SH, Ni YH, Chen HL. Changes of hepatitis B surface antigen variants in carrier children before and after universal vaccination in Taiwan. Hepatology 1999;30(5):1312-7.[PMID: 10534356 DOI: 10.1002/hep.510300511]

7. Capezzuto C, Franchi E, Urbani S, Romano L, Franchini M. Occult hepatitis B in blood donors: a description of two cases. Blood Transfus 2010;8(4):297-302. [PMID:

20967173 DOI: 10.2450/2010.0119-09]

8. Harris BJ, Holzmayer V, Qureshi H, Khan MA, Khan SA, Salamat N, et al. Hepatitis B genotypes and surface antigen mutants present in Pakistani blood donors. PLoS One 2017;12(6):e0178988.[PMID: 28582431 DOI: 10.1371/journal.pone.0178988 ]

9. Panigrahi R, Biswas A, Datta S, Banerjee A, Chandra PK, Mahapatra PK, et al. Anti-hepatitis B core antigen testing with detection and characterization of occult hepatitis B virus by an in-house nucleic acid testing among blood donors in Behrampur, Ganjam, Orissa in southeastern India: implications for transfusion. Virol J 2010;7:204.[PMID: 20799931 DOI: 10.1186/1743-422X-7-204 ]

10. Ruiz-Tachiquin ME, Valdez-Salazar HA, Juarez-Barreto V, Dehesa-Violante M, Torres J, Munoz-Hernandez O, et al. Molecular analysis of hepatitis B virus "a" determinant in asymptomatic and symptomatic Mexican carriers. Virol J 2007;4:6. [PMID: 17217533 DOI:10.1186/1743-422X-4-6]

11. Mello FC, Souto FJ, Nabuco LC, Villela-Nogueira CA, Coelho HS, Franz HC, et al. Hepatitis B virus genotypes circulating in Brazil: molecular characterization of genotype F isolates. BMC Microbiol 2007;7:103.[PMID: 18036224 DOI: 10.1186/1471-2180-7-103]

12. Cariani E, Pelizzari AM, Rodella A, Gargiulo F, Imberti L, Manca N, et al. Immune-mediated hepatitis-associated aplastic anemia caused by the emergence of a mutant hepatitis B virus undetectable by standard assays. J Hepatol 2007;46(4):743-7.[PMID: 17316877 DOI: 10.1016/j.jhep.2006.11.023 ]

13. Svicher V, Cento V, Bernassola M, Neumann-Fraune M, Van Hemert F, Chen M, et al. Novel HBsAg markers tightly correlate with occult HBV infection and strongly affect HBsAg detection. Antiviral Res 2012;93(1):86-93.[DOI: 10.1016/j.antiviral.2011.10.022]14. Ho M, Mau Y, Lu C, Huang S, Hsu L, Lin S, et al. Patterns of circulating hepatitis B surface antigen variants among vaccinated children born to hepatitis B surface antigen carrier and non-carrier mothers. A population-based comparative study. J Biomed Sci 1998;5(5):355-62.[PMID: 9758909]

15. Kim MH, Kang SY, Lee WI. Occult HBV among Anti-HBc Alone: Mutation analysis if an HBV Surface Gene and Pre-S Gene. Yonsei Medical Journal 2017;58(3):557-563.[PMID: 28332361 DOI: 10.3349/ymj.2017.58.3.557 ]

16. Lee SY, Choi MS, Lee D, Lee JH, Koh KC, Paik SW, et al. Overlapping gene mutations of hepatitis B virus in a chronic hepatitis B patient with hepatitis B surface antigen loss during lamivudine therapy. J Korean Med Sci 2005;20(3):433-7.[PMID: 15953865 DOI: 10.3346/jkms.2005.20.3.433]

17. Huang FY, Wong DK, Seto WK, Zhang AY, Lee CK, Lin CK, et al. Sequence variations of full-length hepatitis B virus genomes in Chinese patients with HBsAg-negative hepatitis B infection. PLoS One 2014;9(6):e99028.[PMID: 24901840 DOI: 10.1371/journal.pone.0099028 ]

18. Hossain MG, Ueda K. Investigation of a Novel Hepatitis B Virus Surface Antigen (HBsAg) Escape Mutant Affecting Immunogenicity. PLoS One 2017;12(1):e0167871.[PMID: 28045894 DOI: 10.1371/journal.pone.0167871]

19. Huang CH, Yuan Q, Chen PJ, Zhang YL, Chen CR, Zheng QB, et al. Influence of mutations in hepatitis B virus surface protein on viral antigenicity and phenotype in occult HBV strains from blood donors. J Hepatol 2012;57(4):720-9.[PMID: 22634131 DOI: 10.1016/j.jhep.2012.05.009]

20. Malagnino V, Salpini R, Maffongelli G, Battisti A, Fabeni L, Piermatteo L, et al. High rates of chronic HBV genotype E infection in a group of migrants in Italy from West Africa: Virological characteristics associated with poor immune clearance. PLoS One 2018;13(3):e0195045.[PMID: 29596494 DOI: 10.1371/journal.pone.0195045 ]

21. Zuckerman AJ, Harrison TJ, Oon CJ. Mutations in S region of hepatitis B virus. Lancet 1994;343(8899):737-8.[PMID: 7907712 ]

22. Carman WF, Zanetti AR, Karayiannis P, Waters J, Manzillo G, Tanzi E, et al. Vaccine-induced escape mutant of hepatitis B virus. Lancet 1990;336(8711):325-9. [PMID: 1697396]

23. Coppola N, Onorato L, Minichini C, Di Caprio G, Starace M, Sagnelli C, et al. Clinical significance of hepatitis B surface antigen mutants. World J Hepatol 2015;7(27):2729-39.[PMID: 26644816 DOI: 10.4254/wjh.v7.i27.2729]

24. Lazarevic I. Clinical implications of hepatitis B virus mutations: recent advances. World J Gastroenterol 2014;20(24):7653-64.[PMID: 24976703 DOI: 10.3748/wjg.v20.i24.7653]