

DAFTAR PUSTAKA

- Alexopoulou, A., Karayiannis, P., 2014. HBeAg negative variants and their role in the natural history of chronic hepatitis B virus infection. *World J. Gastroenterol.* WJG 20, 7644–7652.
<https://doi.org/10.3748/wjg.v20.i24.7644>
- Allain, J.-P., Belkhiri, D., Vermeulen, M., Crookes, R., Cable, R., Amiri, A., Reddy, R., Bird, A., Candotti, D., 2009. Characterization of occult hepatitis B virus strains in south african blood donors. *Hepatology* 49, 1868–1876. <https://doi.org/10.1002/hep.22879>
- Al-Qahtani, A.A., Al-Anazi, M.R., Nazir, N., Abdo, A.A., Sanai, F.M., Al-Hamoudi, W.K., Alswat, K.A., Al-Ashgar, H.I., Khan, M.Q., Albenmousa, A., El-Shamy, A., Alanazi, S.K., Dela Cruz, D., Bohol, M.F.F., Al-Ahdal, M.N., 2018. The Correlation Between Hepatitis B Virus Precore/Core Mutations and the Progression of Severe Liver Disease. *Front. Cell. Infect. Microbiol.* 8, 355. <https://doi.org/10.3389/fcimb.2018.00355>
- Angouna, B.M., Ngouloubi, G.H., Dzia, A.B., Boumba, L.M.A., Baha, W., Moukassa, D., Ahombo, G., Ennaji, M.M., Ibara, J.-R., 2016. Molecular characterization of hepatitis B virus among chronic hepatitis B patients from Pointe Noire, Republic of Congo. *Infect. Agent. Cancer* 11, 51. <https://doi.org/10.1186/s13027-016-0088-3>
- Ayari, R., Lakhoua-Gorgi, Y., Bouslama, L., Safar, I., Kchouk, F.H., Aouadi, H., Jendoubi-Ayed, S., Najjar, T., Ayed, K., Abdallah, T.B., 2012. Investigation of DNA Sequence in the Basal Core Promoter, Precore, and Core Regions of Hepatitis B Virus from Tunisia Shows a Shift in Genotype Prevalence. *Hepat. Mon.* 12. <https://doi.org/10.5812/hepatmon.6191>
- Beck, J., Nassal, M., 2007. Hepatitis B virus replication. *World J. Gastroenterol.* WJG 13, 48–64. <https://doi.org/10.3748/wjg.v13.i1.48>
- Ben-Porath, E., Wands, J.R., Marciniak, R.A., Wong, M.A., Hornstein, L., Ryder, R., Canlas, M., Lingao, A., Isselbacher, K.J., 1985. Structural analysis of hepatitis B surface antigen by monoclonal antibodies. *J. Clin. Invest.* 76, 1338–1347. <https://doi.org/10.1172/JCI112108>
- Bertoletti, A., 2006. The immune response during hepatitis B virus infection. *J. Gen. Virol.* 87, 1439–1449. <https://doi.org/10.1099/vir.0.81920-0>
- Bertoletti, A., Kennedy, P.T., 2015. The immune tolerant phase of chronic HBV infection: new perspectives on an old concept. *Cell. Mol. Immunol.* 12, 258–263. <https://doi.org/10.1038/cmi.2014.79>
- Biswas, A., Banerjee, A., Chandra, P.K., Datta, S., Panigrahi, R., Dutta, D., De, B.K., Pal, M., Guha, S.K., Chakrabarti, S., Chakravarty, R., 2011. Variations in the functional domain of basal core promoter of hepatitis B virus among Eastern Indian patients with prevalence of genotypes A, C,

- and D among the same ethnic population. *J. Med. Virol.* 83, 253–260. <https://doi.org/10.1002/jmv.21979>
- Block, T.M., 2008. Molecular virology of hepatitis B virus for clinicians 21.
- Bousali, M., Papatheodoridis, G., Paraskevis, D., Karamitros, T., 2021. Hepatitis B Virus DNA Integration, Chronic Infections and Hepatocellular Carcinoma. *Microorganisms* 9, 1787. <https://doi.org/10.3390/microorganisms9081787>
- Carter, J.B., Saunders, V.A., 2007. *Virology: principles and applications*. John Wiley & Sons, Chichester, England ; Hoboken, NJ.
- Cereda, C., Gagliardi, S., Cova, E., Diamanti, L., Ceroni, M., 2012. The Role of TNF-Alpha in ALS: New Hypotheses for Future Therapeutic Approaches, in: Maurer, M. (Ed.), *Amyotrophic Lateral Sclerosis*. InTech. <https://doi.org/10.5772/31223>
- Chan, H.L., Wong, G.L., Tse, C., Chim, A.M., Yiu, K.K., Chan, H., Sung, J.J., Wong, V.W., 2009. Hepatitis B Virus Genotype C Is Associated With More Severe Liver Fibrosis Than Genotype B. *Clin. Gastroenterol. Hepatol.* 7, 1361–1366. <https://doi.org/10.1016/j.cgh.2009.08.004>
- Chan, H.L.-Y., Tse, C.-H., Ng, E.Y.-T., Leung, K.-S., Lee, K.-H., Tsui, S.K.-W., Sung, J.J.-Y., 2006. Phylogenetic, Virological, and Clinical Characteristics of Genotype C Hepatitis B Virus with TCC at Codon 15 of the Precore Region. *J CLIN MICROBIOL* 44, 7.
- Chen, B., Liu, C., Jow, G., Chen, P., Kao, J., Chen, D., 2006. High Prevalence and Mapping of Pre-S Deletion in Hepatitis B Virus Carriers With Progressive Liver Diseases. *Gastroenterology* 130, 1153–1168. <https://doi.org/10.1053/j.gastro.2006.01.011>
- Chen, C., Hung, C., Lee, C., Hu, T., Wang, Jing-Houng, Wang, Jyh-Chwan, Lu, S., Changchien, C., 2007. Pre-S Deletion and Complex Mutations of Hepatitis B Virus Related to Advanced Liver Disease in HBeAg-Negative Patients. *Gastroenterology* 133, 1466–1474. <https://doi.org/10.1053/j.gastro.2007.09.002>
- Chen, Q.-Y., Harrison, T.J., Sabin, C.A., Li, G.-J., Huang, G.-M., Yang, J.-Y., Wang, X.-Y., Li, H., Liu, M.-H., Fang, Z.-L., 2014. The Effect of HBV Genotype C on the Development of HCC Differs Between Wild-Type Viruses and Those With BCP Double Mutations (T1762A1764). *Hepat. Mon.* 14. <https://doi.org/10.5812/hepatmon.16214>
- Cheong, J.Y., Cho, S.W., Hwang, I.L., Yoon, S.K., Lee, J.H., Park, C.S., Lee, J.E., Hahm, K.B., Kim, J.H., 2006. Association between chronic hepatitis B virus infection and interleukin-10, tumor necrosis factor-alpha gene promoter polymorphisms. *J. Gastroenterol. Hepatol.* 21, 1163–1169. <https://doi.org/10.1111/j.1440-1746.2006.04304.x>
- Chu, C., Hussain, M., Lok, A.S.F., 2002. Hepatitis B virus genotype B is associated with earlier HBeAg seroconversion compared with hepatitis B virus genotype C. *Gastroenterology* 122, 1756–1762. <https://doi.org/10.1053/gast.2002.33588>

- CL Lai, Stephen Locarnini, n.d. Hepatitis B Virus.
- Croagh, C.M., 2015. Genotypes and viral variants in chronic hepatitis B: A review of epidemiology and clinical relevance. *World J. Hepatol.* 7, 289. <https://doi.org/10.4254/wjh.v7.i3.289>
- Croagh, C.M., 2014. Natural history of chronic hepatitis B: Phases in a complex relationship. *World J. Gastroenterol.* 20, 10395. <https://doi.org/10.3748/wjg.v20.i30.10395>
- Cyktor, J.C., Turner, J., 2011. Interleukin-10 and Immunity against Prokaryotic and Eukaryotic Intracellular Pathogens. *Infect. Immun.* 79, 2964–2973. <https://doi.org/10.1128/IAI.00047-11>
- Datta, S., Chatterjee, S., Veer, V., Chakravarty, R., 2012. Molecular Biology of the Hepatitis B Virus for Clinicians. *J. Clin. Exp. Hepatol.* 2, 353–365. <https://doi.org/10.1016/j.jceh.2012.10.003>
- Daud, N., Parewangi, L., Turyadi, T., Ie, S., Zulkifli, A., Akil, F., Massi, M., Bakri, S., Muljono, D., 2015. Association between the viral basal core promoter and precore mutations with the different clinical stages of patients with chronic Hepatitis B virus infection. *J. Viral Hepat.* 22, 32–32. https://doi.org/10.1111/jvh.25_12425
- Erhardt, A., Reineke, U., Blondin, D., Gerlich, W.H., Adams, O., Heintges, T., Niederau, C., Häussinger, D., 2000. Mutations of the core promoter and response to interferon treatment in chronic replicative hepatitis B: Mutations of the Core Promoter and Response to Interferon Treatment in Chronic Replicative Hepatitis B. *Hepatology* 31, 716–725. <https://doi.org/10.1002/hep.510310323>
- Eskdale, J., Keijser, V., Huizinga, T., Gallagher, G., 1999. Microsatellite alleles and single nucleotide polymorphisms (SNP) combine to form four major haplotype families at the human interleukin-10 (IL-10) locus. *Genes Immun.* 1, 151–155. <https://doi.org/10.1038/sj.gene.6363656>
- Fang, X., Wu, H.-H., Ren, J.-J., Liu, H.-Z., Li, K.-Z., Li, J.-L., Tang, Y.-P., Xiao, C.-C., Huang, T.-R., Deng, W., n.d. Associations between serum HBX quasispecies and their integration in hepatocellular carcinoma 10.
- Fang, Z.-L., Sabin, C.A., Dong, B.-Q., Ge, L.-Y., Wei, S.-C., Chen, Q.-Y., Fang, K.-X., Yang, J.-Y., Wang, X.-Y., Harrison, T.J., 2008. HBV A₁₇₆₂T, G₁₇₆₄A Mutations Are a Valuable Biomarker for Identifying a Subset of Male HBsAg Carriers at Extremely High Risk of Hepatocellular Carcinoma: A Prospective Study. *Am. J. Gastroenterol.* 103, 2254–2262. <https://doi.org/10.1111/j.1572-0241.2008.01974.x>
- Fattovich, G., Bortolotti, F., Donato, F., 2008. Natural history of chronic hepatitis B: Special emphasis on disease progression and prognostic factors. *J. Hepatol.* 48, 335–352. <https://doi.org/10.1016/j.jhep.2007.11.011>
- Feld, J.J., Ayers, M., El-Ashry, D., Mazzulli, T., Tellier, R., Heathcote, E.J., 2007. Hepatitis B virus DNA prediction rules for hepatitis B e antigen-negative chronic hepatitis B. *Hepatology* 46, 1057–1070. <https://doi.org/10.1002/hep.21811>

- Fujiko, M., Chalid, M.T., Turyadi, Ie, S.I., Maghfira, Syafri, Wahyuni, R., Roni, M., Patellongi, I., Massi, M.N., Muljono, D.H., 2015. Chronic hepatitis B in pregnant women: is hepatitis B surface antigen quantification useful for viral load prediction? *Int. J. Infect. Dis.* 41, 83–89.
<https://doi.org/10.1016/j.ijid.2015.11.002>
- Funk, M.L., Rosenberg, D.M., Lok, A.S.F., 2002. World-wide epidemiology of HBeAg-negative chronic hepatitis B and associated precore and core promoter variants. *J. Viral Hepat.* 9, 52–61.
<https://doi.org/10.1046/j.1365-2893.2002.00304.x>
- Gandhe, S.S., Chadha, M.S., Arankalle, V.A., 2003. Hepatitis B virus genotypes and serotypes in western India: Lack of clinical significance. *J. Med. Virol.* 69, 324–330. <https://doi.org/10.1002/jmv.10292>
- Gao, L., Chen, X., Zhang, L., Wu, D., Zhao, H., Niu, J., 2016. Association of IL-10 polymorphisms with hepatitis B virus infection and outcome in Han population. *Eur. J. Med. Res.* 21, 23. <https://doi.org/10.1186/s40001-016-0218-9>
- Gao, Q.-J., Xie, J.-X., Wang, L.-M., Zhou, Q., Zhang, S.-Y., 2017. Interaction effects among IFN- γ -874, IL-2-330, IL-10-1082, IL-10-592 and IL-4-589 polymorphisms on the clinical progression of subjects infected with hepatitis B virus and/or hepatitis C virus: a retrospective nested case-control study. *BMJ Open* 7, e013279. <https://doi.org/10.1136/bmjopen-2016-013279>
- Gao, S., Joshi, S.S., Osiowy, C., Chen, Y., Coffin, C.S., Duan, Z.-P., 2017. Chronic hepatitis B carriers with acute or chronic liver failure show increased HBV surface gene mutations, including immune escape variants. *Virol. J.* 14, 203. <https://doi.org/10.1186/s12985-017-0870-x>
- Ghosh, S., Klein, R.S., 2017. Sex Drives Dimorphic Immune Responses to Viral Infections. *J. Immunol.* 198, 1782–1790.
<https://doi.org/10.4049/jimmunol.1601166>
- Gil-García, A.I., Madejón, A., Francisco-Recuero, I., López-López, A., Villafranca, E., Romero, M., García, A., Olveira, A., Mena, R., Larrubia, J.R., García-Samaniego, J., 2019. Prevalence of hepatocarcinoma-related hepatitis B virus mutants in patients in grey zone of treatment. *World J. Gastroenterol.* 25, 5883–5896.
<https://doi.org/10.3748/wjg.v25.i38.5883>
- Gunardi, H., Iskandar, M.Y., Turyadi, Ie, S.I., Dwipoerwantoro, P.G., Gani, R.A., Muljono, D.H., 2017. Hepatitis B virus infection in children of HBV-related chronic liver disease patients: a study of intra-familial HBV transmission. *Hepatol. Int.* 11, 96–104. <https://doi.org/10.1007/s12072-016-9764-z>
- Heidari, Z., Moudi, B., Mahmoudzadeh Sagheb, H., Moudi, M., 2016. Association of TNF- α Gene Polymorphisms with Production of Protein and Susceptibility to Chronic Hepatitis B Infection in the South East Iranian Population. *Hepat. Mon.* 16.
<https://doi.org/10.5812/hepatmon.41984>

- Huang, C.-F., Lin, S.-S., Ho, Y.-C., Chen, F.-L., Yang, C.-C., 2006. The Immune Response Induced by Hepatitis B Virus Principal Antigens. *Mol. Immunol.* 3, 10.
- Huang, Y., Tai, A.W., Tong, S., Lok, A.S.F., 2013. HBV core promoter mutations promote cellular proliferation through E2F1-mediated upregulation of S-phase kinase-associated protein 2 transcription. *J. Hepatol.* 58, 1068–1073. <https://doi.org/10.1016/j.jhep.2013.01.014>
- Hunt, C.M., McGill, J.M., Allen, M.I., Condreay, L.D., 2000. Clinical relevance of hepatitis B viral mutations. *Hepatology* 31, 1037–1044. <https://doi.org/10.1053/he.2000.6709>
- Jalali, M.V., Alavian, S.-M., 2006. Hepatitis B e Antigen-Negative Chronic Hepatitis B. *Hepat. Mon.* 6, 31–35.
- Jia, J., Li, Yonghong, Wei, C., Guo, R., Xu, H., Jia, Y., Wu, Y., Li, Yuanting, Wei, Z., Qi, X., Li, Z., Gao, X., 2019. Factors associated with disease progression and viral replication in patients with chronic hepatitis B virus infection. *Exp. Ther. Med.* <https://doi.org/10.3892/etm.2019.7482>
- Juniaستuti, J., Bimo Aksono, E., Utsumi, T., Yano, Y., Soetjipto, S., Hayashi, Y., Hotta, H., Abdul Rantam, F., Ontoseno Kusumobroto, H., Inge Lusida, M., 2010. Analyses of Precore and Core Promoter Mutations of Hepatitis B Virus in Patients with Chronic Hepatitis B in Surabaya, Indonesia. *Microbiol. Indones.* 4, 143–148. <https://doi.org/10.5454/mi.4.3.8>
- Juniaستuti, Utsumi, T., Aksono, E.B., Yano, Y., Soetjipto, Hayashi, Y., Hotta, H., Rantam, F.A., Kusumobroto, H.O., Lusida, M.I., 2013. Predominance of precore mutations and clinical significance of basal core promoter mutations in chronic hepatitis B virus infection in Indonesia. *Biomed. Rep.* 1, 522–528. <https://doi.org/10.3892/br.2013.106>
- Kao, J., Chen, P., Lai, M., Chen, D., 2003. Basal core promoter mutations of hepatitis B virus increase the risk of hepatocellular carcinoma in hepatitis B carriers. *Gastroenterology* 124, 327–334. <https://doi.org/10.1053/gast.2003.50053>
- Kao, P.-C., Wu, J.-F., Ni, Y.-H., Lin, Y.-T., Chen, H.-L., Huey-Jen Hsu, S., Hsu, H.-Y., Chang, M.-H., 2010. Polymorphisms in tumor necrosis factor and other cytokines as risks for infectious diseases and the septic syndrome. *Liver Int.* 30, 1448–1453. <https://doi.org/10.1111/j.1478-3231.2010.02340.x>
- Khan, M., Dong, J.J., Acharya, S.K., Dhagwahdorj, Y., Abbas, Z., Jafri Sm, W., Mulyono, D.H., Tozun, N., Sarin, S.K., 2004. Hepatology issues in Asia: Perspectives from regional leaders. *J. Gastroenterol. Hepatol.* 19, S419–S430. <https://doi.org/10.1111/j.1440-1746.2004.03728.x>
- Kim, H., Lee, S.-A., Do, S.Y., Kim, B.-J., 2016. Precore/core region mutations of hepatitis B virus related to clinical severity. *World J. Gastroenterol.* 22, 4287. <https://doi.org/10.3748/wjg.v22.i17.4287>
- Kitab, B., Essaid El Feydi, A., Afifi, R., Trepo, C., Benazzouz, M., Essamri, W., Zoulim, F., Chemin, I., Alj, H.S., Ezzikouri, S., Benjelloun, S., 2012.

- Variability in the Precore and Core Promoter Regions of HBV Strains in Morocco: Characterization and Impact on Liver Disease Progression. PLoS ONE 7, e42891. <https://doi.org/10.1371/journal.pone.0042891>
- Knight, J., 2007. Polymorphisms in tumor necrosis factor and other cytokines as risks for infectious diseases and the septic syndrome. *Curr. Infect. Dis. Rep.* 3, 427–439. <https://doi.org/10.1007/s11908-007-1010-3>
- Kramvis, A., 2014. Genotypes and Genetic Variability of Hepatitis B Virus. *Intervirology* 57, 141–150. <https://doi.org/10.1159/000360947>
- Kramvis, A., Arakawa, K., Yu, M.C., Nogueira, R., Stram, D.O., Kew, M.C., 2008. Relationship of serological subtype, basic core promoter and precore mutations to genotypes/subgenotypes of hepatitis B virus. *J. Med. Virol.* 80, 27–46. <https://doi.org/10.1002/jmv.21049>
- Kusakabe, A., Tanaka, Y., Inoue, M., Kurbanov, F., Tatematsu, K., Nojiri, S., Joh, T., Tsugane, S., Mizokami, M., 2011. A population-based cohort study for the risk factors of HCC among hepatitis B virus mono-infected subjects in Japan. *J. Gastroenterol.* 46, 117–124. <https://doi.org/10.1007/s00535-010-0307-4>
- Lampertico, P., Agarwal, K., Berg, T., Buti, M., Janssen, H.L.A., Papatheodoridis, G., Zoulis, F., Tacke, F., 2017. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J. Hepatol.* 67, 370–398. <https://doi.org/10.1016/j.jhep.2017.03.021>
- Lanford, R.E., Kim, Y.-H., Lee, H., Notvall, L., Beames, B., 1999. Mapping of the Hepatitis B Virus Reverse Transcriptase TP and RT Domains by Transcomplementation for Nucleotide Priming and by Protein-Protein Interaction. *J. Virol.* 73, 1885–1893. <https://doi.org/10.1128/JVI.73.3.1885-1893.1999>
- Lau, K.C.K., Burak, K.W., Coffin, C.S., 2020. Impact of Hepatitis B Virus Genetic Variation, Integration, and Lymphotropism in Antiviral Treatment and Oncogenesis. *Microorganisms* 8, 1470. <https://doi.org/10.3390/microorganisms8101470>
- Lee, D., Lyu, H., Chung, Y.-H., Kim, J.A., Mathews, P., Jaffee, E., Zheng, L., Yu, E., Lee, Y.J., Ryu, S.H., 2016. Genomic change in hepatitis B virus associated with development of hepatocellular carcinoma. *World J. Gastroenterol.* 22, 5393. <https://doi.org/10.3748/wjg.v22.i23.5393>
- Lee, H.W., Chan, H.L.-Y., 2020. Unresolved issues of immune tolerance in chronic hepatitis B. *J. Gastroenterol.* 55, 383–389. <https://doi.org/10.1007/s00535-020-01665-z>
- Lee, J.M., 2011. Quantification of HBsAg: Basic virology for clinical practice. *World J. Gastroenterol.* 17, 283. <https://doi.org/10.3748/wjg.v17.i3.283>
- Lee, W.M., 1997. Hepatitis B Virus Infection. *N. Engl. J. Med.* 337, 1733–1745. <https://doi.org/10.1056/NEJM199712113372406>
- Leung, N.W.Y., Lai, C.-L., Chang, T.-T., Guan, R., Lee, C.-M., Ng, K.-Y., Lim, S.-G., Wu, P.-C., Dent, J.C., Edmundson, S., Condreay, L.D., Chien, R.-N., Group, on behalf of the A.H.L.S., 2001. Extended lamivudine

- treatment in patients with chronic hepatitis B enhances hepatitis B e antigen seroconversion rates: Results after 3 years of therapy. *Hepatology* 33, 1527–1532. <https://doi.org/10.1053/jhep.2001.25084>
- Li, W., Goto, K., Matsubara, Y., Ito, S., Muroyama, R., Li, Q., Kato, N., 2015. The Characteristic Changes in Hepatitis B Virus X Region for Hepatocellular Carcinoma: A Comprehensive Analysis Based on Global Data. *PLOS ONE* 10, e0125555. <https://doi.org/10.1371/journal.pone.0125555>
- Li, Z., Hou, X., Cao, G., 2015. Is mother-to-infant transmission the most important factor for persistent HBV infection? *Emerg. Microbes Infect.* 4, 1–9. <https://doi.org/10.1038/emi.2015.30>
- Liao, Y., Hu, X., Chen, J., Cai, B., Tang, J., Ying, B., Wang, H., Wang, L., 2012. Precore Mutation of Hepatitis B Virus May Contribute to Hepatocellular Carcinoma Risk: Evidence from an Updated Meta-Analysis. *PLoS ONE* 7, e38394. <https://doi.org/10.1371/journal.pone.0038394>
- Liu, L., Hu, B., Ye, C., Ho, R.L.K., Chen, G.G., Lai, P.B.S., 2014. HBx mutants differentially affect the activation of hypoxia-inducible factor-1 α in hepatocellular carcinoma. *Br. J. Cancer* 110, 1066–1073. <https://doi.org/10.1038/bjc.2013.787>
- Liu, S., Zhang, H., Gu, C., Yin, J., He, Y., Xie, J., Cao, G., 2009. Associations Between Hepatitis B Virus Mutations and the Risk of Hepatocellular Carcinoma: A Meta-Analysis. *J. Natl. Cancer Inst.* 101, 1066–1082. <https://doi.org/10.1093/jnci/djp180>
- Liu, Y., Liu, T., Nie, W., Lai, G., Xiu, Q., 2013. Interleukin-13 +1923C/T Polymorphism Is Associated with Asthma Risk: A Meta-Analysis. *BioMed Res. Int.* 2013, 1–9. <https://doi.org/10.1155/2013/394316>
- Lyu, H., Lee, D., Chung, Y.-H., Kim, J.A., Lee, J.-H., Jin, Y.-J., Park, W., Mathews, P., Jaffee, E., Zheng, L., Yu, E., Lee, Y.J., 2013. Synergistic Effects of A1896, T1653 and T1762/A1764 Mutations in Genotype C2 Hepatitis B Virus on Development of Hepatocellular Carcinoma. *J. Viral Hepat.* 20, 219–224. <https://doi.org/10.1111/j.1365-2893.2012.01654.x>
- Maini, M.K., Peppa, D., 2013. NK Cells: A Double-Edged Sword in Chronic Hepatitis B Virus Infection. *Front. Immunol.* 4. <https://doi.org/10.3389/fimmu.2013.00057>
- McMahon, B.J., 2009. The natural history of chronic hepatitis B virus infection. *Hepatology* 49, S45–S55. <https://doi.org/10.1002/hep.22898>
- Miyakawa, Y., Okamoto, H., Mayumi, M., 1997. The molecular basis of hepatitis B e antigen (HBeAg)-negative infections. *J. Viral Hepat.* 4, 1–8. <https://doi.org/10.1046/j.1365-2893.1997.00101.x>
- Moolla, N., Kew, M., Arbuthnot, P., 2002. Regulatory elements of hepatitis B virus transcription. *J. Viral Hepat.* 9, 323–331. <https://doi.org/10.1046/j.1365-2893.2002.00381.x>
- Moudi, B., Heidari, Z., Mahmoudzadeh-Sagheb, H., Hashemi, M., Metanat, M., Khosravi, S., Farrokh, P., 2016. Association Between IL-10 Gene

- Promoter Polymorphisms (-592 A/C, -819 T/C, -1082 A/G) and Susceptibility to HBV Infection in an Iranian Population. *Hepat. Mon.* 16. <https://doi.org/10.5812/hepatmon.32427>
- Muljono, D.H., 2017. Epidemiology of Hepatitis B and C in Republic of Indonesia. *Euroasian J. Hepato-Gastroenterol.* 7, 55–59. <https://doi.org/10.5005/jp-journals-l0018-1212>
- Mulyanto, Depamede, S.N., Surayah, K., Tsuda, F., Ichiyama, K., Takahashi, M., Okamoto, H., 2009. A nationwide molecular epidemiological study on hepatitis B virus in Indonesia: identification of two novel subgenotypes, B8 and C7. *Arch. Virol.* 154, 1047–1059. <https://doi.org/10.1007/s00705-009-0406-9>
- Nedwin, G.E., Naylor, S.L., Sakaguchi, A.Y., Smith, D., Jarrett-Nedwin, J., Pennica, D., Goeddel, D.V., Gray, P.W., n.d. Department of Molecular Biology, Genentech, Inc., 460 Point San Bruno Boulevard, South San Francisco, CA 94080, and +Department of Cellular and Structural Biology, The University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78284, USA. *Nucleic Acids Res.* 13.
- Nguyen, T., Thompson, A.J.V., Bowden, S., Croagh, C., Bell, S., Desmond, P.V., Levy, M., Locarnini, S.A., 2010. Hepatitis B surface antigen levels during the natural history of chronic hepatitis B: A perspective on Asia. *J. Hepatol.* 52, 508–513. <https://doi.org/10.1016/j.jhep.2010.01.007>
- Ni, Y., Chang, M., Chen, P., Tsai, K., Hsu, H., Chen, H., Tsuei, D., Chen, D., 2007. Viremia Profiles in Children With Chronic Hepatitis B Virus Infection and Spontaneous e Antigen Seroconversion. *Gastroenterology* 132, 2340–2345. <https://doi.org/10.1053/j.gastro.2007.03.111>
- Ni, Y.-H., Chang, M.-H., Hsu, H.-Y., Tsuei, D.-J., 2004. Longitudinal Study on Mutation Profiles of Core Promoter and Precore Regions of the Hepatitis B Virus Genome in Children. *Pediatr. Res.* 56, 396–399. <https://doi.org/10.1203/01.PDR.0000136282.20470.87>
- Norder, H., Hammas, B., Lofdahl, S., Courouce, A.-M., Magnus, L.O., 1992. Comparison of the amino acid sequences of nine different serotypes of hepatitis B surface antigen and genomic classification of the corresponding hepatitis B virus strains. *J. Gen. Virol.* 73, 1201–1208. <https://doi.org/10.1099/0022-1317-73-5-1201>
- Pan, C.Q., Zhang, J.X., 2005. Natural History and Clinical Consequences of Hepatitis B Virus Infection. *Int. J. Med. Sci.* 36–40. <https://doi.org/10.7150/ijms.2.36>
- Parekh, S., Zoulim, F., Ahn, S.H., Tsai, A., Li, J., Kawai, S., Khan, N., Trépo, C., Wands, J., Tong, S., 2003. Genome Replication, Virion Secretion, and e Antigen Expression of Naturally Occurring Hepatitis B Virus Core Promoter Mutants. *J. Virol.* 77, 6601–6612. <https://doi.org/10.1128/JVI.77.12.6601-6612.2003>

- Parslow, T.G., Stites, D.P., Terr, A.I., Imboden, J.B., 2001. Lange Medical Immunology, 10th edition. ed. McGraw-Hill/Appleton & Lange, New York.
- Pujol, F.H., Navas, M.-C., Hainaut, P., Chemin, I., 2009. Worldwide genetic diversity of HBV genotypes and risk of hepatocellular carcinoma. *Cancer Lett.* 286, 80–88. <https://doi.org/10.1016/j.canlet.2009.07.013>
- Pungpapong, S., Kim, W.R., Poterucha, J.J., 2007. Natural History of Hepatitis B Virus Infection: An Update for Clinicians. *Mayo Clin. Proc.* 82, 967–975. <https://doi.org/10.4065/82.8.967>
- Qin, Y., Zhou, X., Jia, H., Chen, C., Zhao, W., Zhang, J., Tong, S., 2016. Stronger enhancer II/core promoter activities of hepatitis B virus isolates of B2 subgenotype than those of C2 subgenotype. *Sci. Rep.* 6, 30374. <https://doi.org/10.1038/srep30374>
- Qu, L.-S., Zhu, J., Liu, T.-T., Shen, X.-Z., Chen, T.-Y., Ni, Z.-P., Ni, R.-Z., Lu, C.-H., 2014. Effect of combined mutations in the enhancer II and basal core promoter of hepatitis B virus on development of hepatocellular carcinoma in Qidong, China: Combined HBV mutations and HCC. *Hepatol. Res.* 44, 1186–1195. <https://doi.org/10.1111/hepr.12291>
- Quarleri, J., 2014. Core promoter: A critical region where the hepatitis B virus makes decisions. *World J. Gastroenterol.* 20, 425. <https://doi.org/10.3748/wjg.v20.i2.425>
- Ratnam, D., Visvanathan, K., 2008. New concepts in the immunopathogenesis of chronic hepatitis B: the importance of the innate immune response. *Hepatol. Int.* 2, 12–18. <https://doi.org/10.1007/s12072-008-9067-0>
- Razavi-Shearer, D., Gamkrelidze, I., Nguyen, M.H., Chen, D.-S., Van Damme, P., Abbas, Z., Abdulla, M., Abou Rached, A., Adda, D., Aho, I., Akarca, U., Hasan, F., Al Lawati, F., Al Naamani, K., Al-Ashgar, H.I., Alavian, S.M., Alawadhi, S., Albillos, A., Al-Busafi, S.A., Aleman, S., Alfaleh, F.Z., Aljumah, A.A., Anand, A.C., Anh, N.T., Arends, J.E., Arkkila, P., Athanasakis, K., Bane, A., Ben-Ari, Z., Berg, T., Bizri, A.R., Blach, S., Brandão Mello, C.E., Brandon, S.M., Bright, B., Bruggmann, P., Brunetto, M., Buti, M., Chan, H.L.Y., Chaudhry, A., Chien, R.-N., Choi, M.S., Christensen, P.B., Chuang, W.-L., Chulanov, V., Clausen, M.R., Colombo, M., Cornberg, M., Cowie, B., Craxi, A., Croes, E.A., Cuellar, D.A., Cunningham, C., Desalegn, H., Drazilova, S., Duberg, A.-S., Egeonu, S.S., El-Sayed, M.H., Estes, C., Falconer, K., Ferraz, M.L.G., Ferreira, P.R., Flisiak, R., Frankova, S., Gaeta, G.B., García-Samaniego, J., Genov, J., Gerstoft, J., Goldis, A., Gountas, I., Gray, R., Guimarães Pessôa, M., Hajarizadeh, B., Hatzakis, A., Hézode, C., Himatt, S.M., Hoepelman, A., Hrstic, I., Hui, Y.-T.T., Husa, P., Jahis, R., Janjua, N.Z., Jarčuška, P., Jaroszewicz, J., Kaymakoglu, S., Kershenobich, D., Kondili, L.A., Konysbekova, A., Krajden, M., Kristian, P., Laleman, W., Lao, W.C., Layden, J., Lazarus, J.V., Lee, M.-H., Liakina, V., Lim, Y.-S.S., Loo, C.K., Lukšić, B., Malekzadeh, R., Malu, A.O., Mamatkulov, A., Manns, M., Marinho, R.T., Maticic, M., Mauss, S., Memon, M.S., Mendes

- Correa, M.C., Mendez-Sanchez, N., Merat, S., Metwally, A.M., Mohamed, R., Mokhbat, J.E., Moreno, C., Mossong, J., Mourad, F.H., Müllhaupt, B., Murphy, K., Musabaev, E., Nawaz, A., Nde, H.M., Negro, F., Nensesov, A., Nguyen, V.T.T., Njouom, R., Ntagirabiri, R., Nurmatov, Z., Obekpa, S., Ocama, P., Oguche, S., Omede, O., Omuemu, C., Opare-Sem, O., Opio, C.K., Örmeci, N., Papatheodoridis, G., Pasini, K., Pimenov, N., Poustchi, H., Quang, T.D., Qureshi, H., Ramji, A., Razavi-Shearer, K., Redae, B., Reesink, H.W., Rios, C.Y., Rjaskova, G., Robbins, S., Roberts, L.R., Roberts, S.K., Ryder, S.D., Safadi, R., Sagalova, O., Salupere, R., Sanai, F.M., Sanchez-Avila, J.F., Saraswat, V., Sarrazin, C., Schmelzer, J.D., Schréter, I., Scott, J., Seguin-Devaux, C., Shah, S.R., Sharara, A.I., Sharma, M., Shiha, G.E., Shin, T., Sievert, W., Sperl, J., Stärkel, P., Stedman, C., Sypsa, V., Tacke, F., Tan, S.S., Tanaka, J., Tomasiewicz, K., Urbanek, P., van der Meer, A.J., Van Vlierberghe, H., Vella, S., Vince, A., Waheed, Y., Waked, I., Walsh, N., Weis, N., Wong, V.W., Woodring, J., Yaghi, C., Yang, H.-I., Yang, C.-L., Yesmembetov, K., Yosry, A., Yuen, M.-F., Yusuf, M.A.M., Zeuzem, S., Razavi, H., 2018. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. *Lancet Gastroenterol. Hepatol.* 3, 383–403. [https://doi.org/10.1016/S2468-1253\(18\)30056-6](https://doi.org/10.1016/S2468-1253(18)30056-6)
- Ren, X., Xu, Z., Liu, Y., Li, X., Bai, S., Ding, N., Zhong, Y., Wang, L., Mao, P., Zoulim, F., Xu, D., 2010. Hepatitis B virus genotype and basal core promoter/precore mutations are associated with hepatitis B-related acute-on-chronic liver failure without pre-existing liver cirrhosis: HBV core promoter/precore mutations in acute-on-chronic liver failure. *J. Viral Hepat.* 17, 887–895. <https://doi.org/10.1111/j.1365-2893.2009.01254.x>
- Ruggieri, A., Gagliardi, M.C., Anticoli, S., 2018. Sex-Dependent Outcome of Hepatitis B and C Viruses Infections: Synergy of Sex Hormones and Immune Responses? *Front. Immunol.* 9, 2302. <https://doi.org/10.3389/fimmu.2018.02302>
- Santos, K., Lemos-Marini, S.H.V., Baptista, M.T.M., Bonadia, L.C., Pinto Júnior, W., Bertuzzo, C.S., 2006. Frequency of 677C → T and 1298A → C polymorphisms in the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene in Turner syndrome individuals. *Genet. Mol. Biol.* 29, 41–44. <https://doi.org/10.1590/S1415-47572006000100008>
- Sarin, S.K., Kumar, M., Lau, G.K., Abbas, Z., Chan, H.L.Y., Chen, C.J., Chen, D.S., Chen, H.L., Chen, P.J., Chien, R.N., Dokmeci, A.K., Gane, E., Hou, J.L., Jafri, W., Jia, J., Kim, J.H., Lai, C.L., Lee, H.C., Lim, S.G., Liu, C.J., Locarnini, S., Al Mahtab, M., Mohamed, R., Omata, M., Park, J., Piratvisuth, T., Sharma, B.C., Sollano, J., Wang, F.S., Wei, L., Yuen, M.F., Zheng, S.S., Kao, J.H., 2016. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol. Int.* 10, 1–98. <https://doi.org/10.1007/s12072-015-9675-4>

- Schaefer, S., 2007. Hepatitis B virus taxonomy and hepatitis B virus genotypes. *World J. Gastroenterol.* 13, 14. <https://doi.org/10.3748/wjg.v13.i1.14>
- Seeger, C., Mason, W.S., 2015. Molecular biology of hepatitis B virus infection. *Virology* 479–480, 672–686. <https://doi.org/10.1016/j.virol.2015.02.031>
- Sharon, A., Chu, C., 2008. Understanding the molecular basis of HBV drug resistance by molecular modeling. *Antiviral Res.* 80, 339–353. <https://doi.org/10.1016/j.antiviral.2008.07.010>
- Shi, W., Zhang, Z., Ling, C., Zheng, W., Zhu, C., Carr, M.J., Higgins, D.G., 2013. Hepatitis B virus subgenotyping: History, effects of recombination, misclassifications, and corrections. *Infect. Genet. Evol.* 16, 355–361. <https://doi.org/10.1016/j.meegid.2013.03.021>
- Siburian, M.D., Utama, A., Dhenni, R., Arnelis, null, Fanany, I., Intan, M.D., Kurniasih, T.S., Andriani, F., Afadlal, S., Julianto, E.B., Rasman, W.S., Zubir, N., Mathew, G., 2013. High prevalence of hepatitis B virus genotype C/C1 in the Minangkabau ethnic group in Indonesia. *Virol. J.* 10, 27. <https://doi.org/10.1186/1743-422X-10-27>
- Sofian, M., Kalantar, E., Aghakhani, A., Hosseini, S., 2013. No Correlation Between Interleukin-10 Gene Promoter Polymorphisms and Hepatitis B Virus Infection Outcome. *Hepat Mon* 13, 6.
- Somi, M.H., Najafi, L., Noori, B.N., Alizadeh, A.H.M., Aghah, M.R., Shavakhi, A., Ehsani, M.J., Aghazadeh, R., Masoodi, M., Amini, S., Baladast, M., Zali, M.R., 2006. Tumor necrosis factor-alpha gene promoter polymorphism in Iranian patients with chronic hepatitis B. *Indian J. Gastroenterol. Off. J. Indian Soc. Gastroenterol.* 25, 14–15.
- Song, C., Liu, Y., Xu, L., Wen, J., Jiang, D., Chen, J., Zhai, X., Hu, Z., Liu, L., Liu, J., 2016. Hepatitis B virus mutations, expression quantitative trait loci for PTPN 12, and their interactions in hepatocellular carcinoma. *Cancer Med.* 5, 1687–1693. <https://doi.org/10.1002/cam4.712>
- Stanley Lemon, Arie J Zuckerman, n.d. Viral Hepatitis.
- Sunbul, M., 2014. Hepatitis B virus genotypes: Global distribution and clinical importance. *World J. Gastroenterol.* 20, 5427. <https://doi.org/10.3748/wjg.v20.i18.5427>
- Terrault, N.A., Bzowej, N.H., Chang, K.-M., Hwang, J.P., Jonas, M.M., Murad, M.H., 2016. AASLD guidelines for treatment of chronic hepatitis B: Hepatology, Month 2015. *Hepatology* 63, 261–283. <https://doi.org/10.1002/hep.28156>
- Thedja, M.D., Muljono, D.H., Nurainy, N., Sukowati, C.H.C., Verhoef, J., Marzuki, S., 2011. Ethnogeographical structure of hepatitis B virus genotype distribution in Indonesia and discovery of a new subgenotype, B9. *Arch. Virol.* 156, 855–868. <https://doi.org/10.1007/s00705-011-0926-y>
- Tong, M.J., Blatt, L.M., Kao, J.-H., Cheng, J.T., Corey, W.G., 2007. Basal core promoter T1762/A1764 and precore A1896 gene mutations in hepatitis B surface antigen-positive hepatocellular carcinoma: a comparison with

- chronic carriers: BCP T1762/A1764 and PC A1896 gene mutations. *Liver Int.* 27, 1356–1363. <https://doi.org/10.1111/j.1478-3231.2007.01585.x>
- Tong, S., Kim, K.-H., Chante, C., Wands, J., Li, J., 2005. Hepatitis B Virus e Antigen Variants. *Int. J. Med. Sci.* 2–7. <https://doi.org/10.7150/ijms.2.2>
- Tong, S., Li, J., Wands, J.R., Wen, Y., 2013. Hepatitis B virus genetic variants: biological properties and clinical implications. *Emerg. Microbes Infect.* 2, 1–11. <https://doi.org/10.1038/emi.2013.10>
- Tong, S., Revill, P., 2016. Overview of hepatitis B viral replication and genetic variability. *J. Hepatol.* 64, S4–S16. <https://doi.org/10.1016/j.jhep.2016.01.027>
- Tu, W.-H., 2015. Precore/basal core promoter mutants quantification throughout phases of hepatitis B virus infection by Simpleprobe. *World J. Gastroenterol.* 21, 6639. <https://doi.org/10.3748/wjg.v21.i21.6639>
- Turner, D.M., Williams, D.M., Sankaran, D., Lazarus, M., Sinnott, P.J., Hutchinson, I.V., 1997. AN INVESTIGATION OF POLYMORPHISM IN THE INTERLEUKIN-10 GENE PROMOTER. *Eur. J. Immunogenet.* 24, 1–8. <https://doi.org/10.1111/j.1365-2370.1997.tb00001.x>
- Turyadi, Thedja, M.D., Ie, S.I., Harahap, A.R., El-Khobar, K.E., Roni, M., Muljono, D.H., 2013. HBsAg, HBeAg and HBV DNA level changes and precore/basal core promoter mutations in the natural history of chronic hepatitis B in Indonesian patients. *Hepatol. Int.* 7, 969–980. <https://doi.org/10.1007/s12072-013-9438-z>
- Utama, A., 2009. Hepatitis B virus subgenotypes and basal core promoter mutations in Indonesia. *World J. Gastroenterol.* 15, 4028. <https://doi.org/10.3748/wjg.15.4028>
- Vittinghoff, E. (Ed.), 2005. Regression methods in biostatistics: linear, logistic, survival, and repeated measures models, Statistics for biology and health. Springer, New York.
- Wahyuni, R.M., Utsumi, T., Yano, Y., Murti, I.S., Amin, M., Yamani, L.N., Istimagfiroh, A., Purwono, P.B., Lusida, M.I., Hayashi, Y., 2019. Analysis of hepatitis B virus genotype and gene mutation in patients with advanced liver disease in East Kalimantan, Indonesia. *Biomed. Rep.* 8.
- Walsh, R., Locarnini, S., 2012. Hepatitis B Precore Protein: Pathogenic Potential and Therapeutic Promise. *Yonsei Med. J.* 53, 875. <https://doi.org/10.3349/ymj.2012.53.5.875>
- Wang, S.-H., Chen, P.-J., Yeh, S.-H., 2015. Gender disparity in chronic hepatitis B: Mechanisms of sex hormones: Sex hormone roles in chronic hepatitis B. *J. Gastroenterol. Hepatol.* 30, 1237–1245. <https://doi.org/10.1111/jgh.12934>
- Wang, Wei, Shu, Y., Bao, H., Zhao, W., Wang, Weihua, Wang, Q., Lei, X., Cui, D., Yan, Z., 2019. Genotypes and Hot Spot Mutations of Hepatitis B Virus in Northwest Chinese Population and Its Correlation with Diseases Progression. *BioMed Res. Int.* 2019, 1–9. <https://doi.org/10.1155/2019/3890962>

- Wei, Y.-G., Liu, F., Li, B., Chen, X., Ma, Y., Yan, L.-N., Wen, T.-F., Xu, M.-Q., Wang, W.-T., Yang, J.-Y., 2011. Interleukin-10 gene polymorphisms and hepatocellular carcinoma susceptibility: A meta-analysis. *World J. Gastroenterol.* WJG 17, 3941–3947.
<https://doi.org/10.3748/wjg.v17.i34.3941>
- Wen, J., Song, C., Jiang, D., Jin, T., Dai, J., Zhu, L., An, J., Liu, Y., Ma, S., Qin, N., Liang, C., Chen, Jiaping, Jiang, Y., Yang, L., Liu, J., Liu, L., Geng, T., Chen, C., Jiang, J., Chen, Jianguo, Zhu, F., Zhu, Y., Yu, L., Shen, H., Zhai, X., Xu, J., Hu, Z., 2015. Hepatitis B virus genotype, mutations, human leukocyte antigen polymorphisms and their interactions in hepatocellular carcinoma: a multi-centre case-control study. *Sci. Rep.* 5, 16489. <https://doi.org/10.1038/srep16489>
- WHO, 2021. Hepatitis B [WWW Document]. URL <https://www.who.int/news-room/fact-sheets/detail/hepatitis-b> (accessed 10.25.21).
- Woziwodzka, A., Rybicka, M., Sznarkowska, A., Romanowski, T., Dręczewski, M., Stalke, P., Bielawski, K.P., 2019. TNF- α polymorphisms affect persistence and progression of HBV infection. *Mol. Genet. Genomic Med.* 7. <https://doi.org/10.1002/mgg3.935>
- Wright, T.L., 2006. Introduction to Chronic Hepatitis B Infection. *Am. J. Gastroenterol.* 101, S1–S6. <https://doi.org/10.1111/j.1572-0241.2006.00469.x>
- Wu, J.-F., Chang, M.-H., 2015. Natural history of chronic hepatitis B virus infection from infancy to adult life -the mechanism of inflammation triggering and long-term impacts. *J. Biomed. Sci.* 22, 92.
<https://doi.org/10.1186/s12929-015-0199-y>
- Yan, H., Liu, Y., Sui, J., Li, W., 2015. NTCP opens the door for hepatitis B virus infection. *Antiviral Res.* 121, 24–30.
<https://doi.org/10.1016/j.antiviral.2015.06.002>
- Yang, H.-I., Yeh, S.-H., Chen, P.-J., Iloeje, U.H., Jen, C.-L., Su, J., Wang, L.-Y., Lu, S.-N., You, S.-L., Chen, D.-S., Liaw, Y.-F., Chen, C.-J., 2008. Associations Between Hepatitis B Virus Genotype and Mutants and the Risk of Hepatocellular Carcinoma. *J. Natl. Cancer Inst.* 100, 1134–1143. <https://doi.org/10.1093/jnci/djn243>
- Yang, Z., Zhuang, L., Lu, Y., Xu, Q., Tang, B., Chen, X., n.d. Naturally occurring basal core promoter A1762T/G1764A dual mutations increase the risk of HBV-related hepatocellular carcinoma: a meta-analysis 12.
- Yano, Y., 2015. Variations and mutations in the hepatitis B virus genome and their associations with clinical characteristics. *World J. Hepatol.* 7, 583.
<https://doi.org/10.4254/wjh.v7.i3.583>
- Yapali, S., Talaat, N., Lok, A.S., 2014. Management of Hepatitis B: Our Practice and How It Relates to the Guidelines. *Clin. Gastroenterol. Hepatol.* 12, 16–26. <https://doi.org/10.1016/j.cgh.2013.04.036>
- Yin, J., Wang, J., Pu, R., Xin, H., Li, Z., Han, X., Ding, Y., Du, Y., Liu, W., Deng, Y., Ji, X., Wu, M., Yu, M., Zhang, H., Wang, H., Thompson, T.C., Ni, W.,

- Cao, G., 2015. Hepatitis B Virus Combo Mutations Improve the Prediction and Active Prophylaxis of Hepatocellular Carcinoma: A Clinic-Based Cohort Study. *Cancer Prev. Res. (Phila. Pa.)* 8, 978–988.
<https://doi.org/10.1158/1940-6207.CAPR-15-0160>
- Yin, J., Xie, J., Liu, S., Zhang, H., Han, L., Lu, W., Shen, Q., Xu, G., Dong, H., Shen, J., Zhang, J., Han, J., Wang, L., Liu, Y., Wang, F., Zhao, J., Zhang, Q., Ni, W., Wang, H., Cao, G., 2011. Association Between the Various Mutations in Viral Core Promoter Region to Different Stages of Hepatitis B, Ranging of Asymptomatic Carrier State to Hepatocellular Carcinoma: *Am. J. Gastroenterol.* 106, 81–92.
<https://doi.org/10.1038/ajg.2010.399>
- Zhang, A., Wan, Z., You, S., Liu, H., Zhu, B., Chen, J., Rong, Y., Zang, H., Li, C., Wang, H., Xin, S., 2013. Association of Hepatitis B Virus Mutations of A1846T and C1913A/G With Acute-on-Chronic Liver Failure Development From Different Underlying Chronic Liver Diseases. *Hepat. Mon.* 13. <https://doi.org/10.5812/hepatmon.12445>
- Zhang, H., Wu, L.-Y., Zhang, S., Qiu, L.-Y., Li, N., Zhang, X., Zhang, X.-Z., Shan, C.-L., Ye, L.-H., Zhang, X.-D., 2009. Anti-Hepatitis B Virus X Protein in Sera Is One of the Markers of Development of Liver Cirrhosis and Liver Cancer Mediated by HBV. *J. Biomed. Biotechnol.* 2009, 1–6.
<https://doi.org/10.1155/2009/289068>
- Zhang, Q., Cao, G., 2011. Genotypes, mutations, and viral load of hepatitis B virus and the risk of hepatocellular carcinoma. *Hepat. Mon.* 11, 86–91.

LAMPIRAN. Ethical Clearance



**KEMENTERIAN RISET, TEKNOLOGI DAN PENDIDIKAN TINGGI
 UNIVERSITAS HASANUDDIN
 FAKULTAS KEDOKTERAN
 RSPTN UNIVERSITAS HASANUDDIN
 RSUP Dr. WAHIDIN SUDIROHUSODO MAKASSAR
 KOMITE ETIK PENELITIAN KESEHATAN**



Sekretariat : Lantai 3 Gedung Laboratorium Terpadu
 JL.PERINTIS KEMERDEKAAN KAMPUS TAMALANREA KM.10 MAKASSAR 90245.
 Contact Person: dr. Agussalim Bukhari, MMed, PhD, SpGK TELP. 081241850858, 0411 5780103, Fax : 0411-581431

REKOMENDASI PERSETUJUAN ETIK

Nomor : 1036 / H4.8.4.5.31 / PP36-KOMETIK / 2017

Tanggal: 5 Desember 2017

Dengan ini Menyatakan bahwa Protokol dan Dokumen yang Berhubungan Dengan Protokol berikut ini telah mendapatkan Persetujuan Etik :

No Protokol	UH17080594	No Sponsor Protokol	
Peneliti Utama	Turiyadi,S.Si,M.Biomed	Sponsor	Pribadi
Judul Peneliti	Pengaruh faktor Virus dan Maag pada Infeksi Hepatitis B Kronis HBeAg Negatif		
No Versi Protokol	2	Tanggal Versi	5 Desember 2017
No Versi PSP	2	Tanggal Versi	5 Desember 2017
Tempat Penelitian	RSUP dr. Wahidin Sudirohusodo Molekuler Eijkman, Jakarta	Makassar dan Lembaga Biologi	
Dokumen Lain			
Jenis Review	<input type="checkbox"/> Exempted <input checked="" type="checkbox"/> Expedited <input type="checkbox"/> Fullboard Tanggal	Masa Berlaku 5 Desember 2017 sampai 5 Desember 2018	Frekuensi review lanjutan
Ketua Komisi Etik Penelitian	Nama Prof.Dr.dr. Suryani As'ad, M.Sc.,Sp.GK (K)	Tanda tangan 	Tanggal
Sekretaris Komisi Etik Penelitian	Nama dr. Agussalim M.Med.,Ph.D.,Sp.GK (K)	Tanda tangan 	Tanggal

Kewajiban Peneliti Utama:

- Menyerahkan Amandemen Protokol untuk persetujuan sebelum di implementasikan
- Menyerahkan Laporan SAE ke Komisi Etik dalam 24 Jam dan dilengkapi dalam 7 hari dan Lapor SUSAR dalam 72 Jam setelah Peneliti Utama menerima laporan
- Menyerahkan Laporan Kemajuan (progress report) setiap 6 bulan untuk penelitian resiko tinggi dan setiap setahun untuk penelitian resiko rendah
- Menyerahkan laporan akhir setelah Penelitian berakhir
- Melaporkan penyimpangan dari protokol yang disetujui (protocol deviation / violation)
- Mematuhi semua peraturan yang ditentukan

THE EIJKMAN INSTITUTE FOR MOLECULAR BIOLOGY

Project Number
(For Official Use Only)

9	3
---	---



EIJKMAN INSTITUTE RESEARCH ETHICS COMMISSION

ETHICAL APPROVAL

Eijkman Institute Research Ethics Commission (EIREC) has convened a meeting on 26th November 2015 as requested by the Director of Eijkman Institute for Molecular Biology, to review the proposal entitled: "*Molecular Diversity of Hepatitis B Virus (HBV) in Indonesia*" with Prof. David H. Muljono, Ph.D as the Principal Investigator.

After considering the ethical aspects of the research project, EIREC has decided to give a renewal of the ethical approval for the above study for 3 (three) years from the date this approval is given.

Jakarta, 26th November 2015

A handwritten signature in blue ink, appearing to read "R. Sjamsuhidajat".

Prof. Dr. R. Sjamsuhidajat
Chairman