



## Prof. Dr. Masashi Mizokami

### Professor



My main research is "molecular evolutionary analysis of genomes mutations in various pathogens and hosts and its clinical application.

I graduated from medical school in 1976. At that time in Japan, post-transfusion hepatitis was occurring frequently and liver cancer was also increasing rapidly. Hepatitis B virus (HBV) and non-A, non-B hepatitis virus (NANBHV) were thought to be the main causes. As I have been interested in genetics since I was a child, I learned molecular evolutionary analyses techniques from Dr. Gojyobori T. at the National Institute of Genetics while working as a clinician.

Then, after analysing various HBV nucleotide sequences extracted from international databases, I clarified the following; (1) HBV nucleotide sequences mutation rate is approximately 104 times higher than that of human gene mutations, (2) HBV can be classified into nine genotypes and their serial subtypes worldwide, (3) HBV genotypes are distributed differently worldwide at present, and (4) this can be explained by the African origin of Homo sapiens and its Great journey hypothesis, and finally (5) that the clinical characteristics differs between those genotypes which is very useful for clinical diagnosis and treatment.

On the other hand, the hepatitis C virus (HCV) was discovered in 1988 as the causative virus of

NANBV. Therefore, using HCV nucleotide sequences around the world from the international database and the HCV infection panel of Dr. Alter HJ of NIH, Nobel Prize in 2020, I clarified the following facts about HCV: (1) HCV develops into liver cancer about 30 years after its infection (2) HCV spread out in Japan around 1945 due to social turmoil following the defeat of World War I (3) HCV-associated liver cancer was estimated to increase sharply in the next 10-20 years worldwide.

In addition, I led a clinical trial of an HCV inhibitor in Japan and showed that it is possible to cure 100%. The results are cited in HCV prevention and treatment guidelines around the world, contributing to a significant reduction in liver cancer worldwide in the future.

Currently, I am involved in the development of the Medical Genomics Japan Database, research on preventing the aggravation of Covid-19 infections, and the development of anticancer agents for liver cancer.

My total publication number 689, citations 32,399, and H-index 81 from PubMed as of May 10, 2023. 15 typical papers are listed as below.

- 1) Orito E, Mizokami M, Ina Y, Moriyama EN, Kameshima N, Yamamoto M, T Gojobori T. Host-independent evolution and a genetic classification of the hepadnavirus family based on nucleotide sequences. *Proc Natl Acad Sci USA*. 1989 86(18):7059-62.
- 2) Lau JY, Mizokami M, Ohno T, Diamond DA, Kniffen J, Davis GL. Discrepancy between biochemical and virological responses to interferon-alpha in chronic hepatitis C. *Lancet*. 1993 342(8881):1208-9.
- 3) Mizokami M, Gojobori T, and Lau JY. Molecular evolutionary virology: its application to hepatitis C virus *Gastroenterology*. 1994 107(4):1181-2.
- 4) Mizokami M, Lau JY, Suzuki K, Nakano T, Gojobori T. Different sensitivity of hepatitis C virus quasispecies to interferon-alpha therapy. *J Hepatol*. 1994 Nov;21(5):884-6.
- 5) Kudo T, Morishima T, Tszuki K, Orito E, Mizokami M. Hepatitis G virus in immunosuppressed pediatric allograft recipients. *Lancet*. 1996 Sep 14;348(9029):751.
- 6) Mizokami M, Ohno T, Ohba K, Davis GL, Suzuki K, Orito E, Lau JY. Interferon-alpha therapy exerts selective pressure on hepatitis C virus quasispecies equilibrium. *Antivir Ther*. 1999 4(1): 15-9.
- 7) Mizokami M, Nakano T, Orito E, Tanaka Y, Sakugawa H, Mukaide M, Robertson BH. Hepatitis B virus genotype assignment using restriction fragment length polymorphism patterns. *FEBS Lett*.

1999 450(1-2):66-71.

- 8) Orito E, Ichida T, Sakugawa H, Sata M, Horike N, Hino K, Okita K, Okanoue T, Iino S, Tanaka E, Suzuki K, Watanabe H, Hige H, Mizokami M. Geographic distribution of hepatitis B virus (HBV) genotype in patients with chronic HBV infection in Japan. *Hepatology*. 2001 34(3):590-4.
- 9) Sugauchi F, Orito E, Ichida T, Kato H, Sakugawa H, Kakumu S, Ishida T, Chutaputti A, La CL, Gish RG, Ueda R, Miyakawa Y, Mizokami M. Epidemiologic and virologic characteristics of hepatitis B virus genotype B having the recombination with genotype C. *Gastroenterology*. 2003 124(4):925-32.
- 10) Wakita T, Pietschmann T, Kato T, Date T, Miyamoto M, Zhao Z, Murthy K, Habermann A, Kräusslich HG, Mizokami M, Bartenschlager R, Liang TJ. Production of infectious hepatitis C virus in tissue culture from a cloned viral genome. *Nat Med*. 2005 11(7):791-6.
- 11) Sugiyama M, Tanaka Y, Kurbanov F, Maruyama I, Shimada T, Takahashi S, Shirai T, Hino K, Sakaida I, Mizokami M. Direct cytopathic effects of particular hepatitis B virus genotypes in severe combined immunodeficiency transgenic with urokinase-type plasminogen activator mouse with human hepatocytes. *Gastroenterology* 2009 136(2):652-62.
- 12) Tanaka Y, Nishida N, Sugiyama M, Kurosaki M, Matsuura K, Nakagawa M, Korenaga M, Hino K, Hige S, Ito Y, Mita E, Tanaka E, Mochida S, Murawaki Y, Honda M, Sakai A, Hiasa Y, Nishiguchi S, Koike A, Sakaida I, Imamura M, Ito K, Yano Y, Masaki N, Sugauchi F, Izumi N, Tokunaga K, Mizokami M. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. *Nat Genet*. 2009 41(10):1105-9.
- 13) Kuno A, Ikehara Y, Tanaka Y, Ito K, Matsuda A, Sekiya S, Hige S, Sakamoto M, Kage M, Mizokami M, Narimatsu H. A serum "sweet-doughnut" protein facilitates fibrosis evaluation and therapy assessment in patients with viral hepatitis. *Sci Rep*. 2013;3:1065.a
- 14) Mizokami M, Yokosuka O, Takehara T, Sakamoto N, Korenaga M, Mochizuki H, Nakane K, Enomoto H, Ikeda F, Yanase N, Toyoda H, Genda T, Umemura K, Yatsushashi H, Ide T, Toda N, Nirei K, Ueno Y, Nishigaki Y, Betular J, Gao B, Ishizaki A, Omote M, Mo H, Garrison K, Pang PS, Knox SJ, Symonds WT, McHutchison JG, Izumi N, Omata M. *Lancet Infect Dis*. 2015 Jun; 15(6):645-53.
- 15) Nishijima S, Nagata N, Kojima Y, Miyoshi-Akiyama T, Kimura M, Ohsugi M, Ueki K, Oka S, Mizokami M, Itoi T, Kawai T, Umemura N, Hattori M. Extensive gut virome variation and its associations with host and environmental factors in a population-level cohort. *Nat Commun*. 2022 Sep 6;13(1):5252.

