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## Ten millennia of hepatitis B virus evolution

Kocher, A.; Papac, L.; Barquera, R.; Key, F.M.; Spyrou, M.A.; Hubler, R.; ... ; Kuhnert, D.

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## Article

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## Title: Ten millennia of hepatitis B virus evolution

**Authors:** Arthur Kocher<sup>1,\*</sup>, Luka Papac<sup>2</sup>, Rodrigo Barquera<sup>2</sup>, Felix M. Key<sup>2,3</sup>, Maria A. Spyrou<sup>2,4</sup>, Ron Hübler<sup>2</sup>, Adam B. Rohrlach<sup>2,5</sup>, Franziska Aron<sup>2</sup>, Raphaela Stahl<sup>2</sup>, Antje Wissgott<sup>2</sup>, Florian van Bömmel<sup>6</sup>, Maria Pfefferkorn<sup>6</sup>, Alissa Mittnik<sup>2,7,8</sup>, Vanessa Villalba-Mouco<sup>2,9</sup>, Gunnar U. Neumann<sup>2</sup>, Maité Rivollat<sup>2,10</sup>, Marieke S. van de Loosdrecht<sup>2</sup>, Kerttu Majander<sup>2</sup>, Rezeda I. Tukhbatova<sup>2,11</sup>, Lyazzat Musralina<sup>2,12,13</sup>, Ayshin Ghalichi<sup>2</sup>, Sandra Penske<sup>2</sup>, Susanna Sabin<sup>2</sup>, Megan Michel<sup>2,8</sup>, Joscha Gretzinger<sup>2</sup>, Elizabeth A. Nelson<sup>2</sup>, Tiago Ferraz<sup>2,14</sup>, Kathrin Nägele<sup>2</sup>, Cody Parker<sup>2,15</sup>, Marcel Keller<sup>2,16</sup>, Evelyn K. Guevara<sup>2,17</sup>, Michal Feldman<sup>2,4</sup>, Stefanie Eisenmann<sup>2</sup>, Eirini Skourtanioti<sup>2</sup>, Karen Giffin<sup>2</sup>, Guido Alberto Gnechi Ruscone<sup>2</sup>, Susanne Friederich<sup>18</sup>, Vittoria Schimmenti<sup>19</sup>, Valery Khartanovich<sup>20</sup>, Marina K. Karapetian<sup>21</sup>, Mikhail S. Chaplygin<sup>22</sup>, Vladimir V. Kufterin<sup>23</sup>, Aleksandr A. Khokhlov<sup>24</sup>, Andrey A. Chizhevsky<sup>25</sup>, Dmitry A. Stashenkov<sup>26</sup>, Anna F. Kochkina<sup>26</sup>, Cristina Tejedor-Rodríguez<sup>27</sup>, Íñigo García-Martínez de Lagrán<sup>28</sup>, Héctor Arcusa-Magallón<sup>29</sup>, Rafael Garrido-Pena<sup>30</sup>, José Ignacio Royo-Guillén<sup>31</sup>, Jan Nováček<sup>32,33</sup>, Stéphane Rottier<sup>10</sup>, Sacha Kacki<sup>10,34</sup>, Sylvie Saintot<sup>35</sup>, Elena Kaverzneva<sup>36</sup>, Andrej B. Belinskiy<sup>37</sup>, Petr Velemínský<sup>38</sup>, Petr Limburský<sup>39</sup>, Michal Kostka<sup>40</sup>, Louise Loe<sup>41</sup>, Elizabeth Popescu<sup>42</sup>, Rachel Clarke<sup>42</sup>, Alice Lyons<sup>42</sup>, Richard Mortimer<sup>42</sup>, Antti Sajantila<sup>17,43</sup>, Yadira Chinique de Armas<sup>44</sup>, Silvia Teresita Hernandez Godoy<sup>45,46</sup>, Diana I. Hernández-Zaragoza<sup>47,48</sup>, Jessica Pearson<sup>49</sup>, Didier Binder<sup>50</sup>, Philippe Lefranc<sup>51</sup>, Anatoly R. Kantorovich<sup>52</sup>, Vladimir E. Maslov<sup>53</sup>, Luca Lai<sup>54,55</sup>, Magdalena Zoledziewska<sup>56</sup>, Jessica F. Beckett<sup>57</sup>, Michaela Langová<sup>39</sup>, Alžběta Danielisová<sup>39</sup>, Tara Ingman<sup>58</sup>, Gabriel García Atiénzar<sup>59</sup>, Maria Paz de Miguel Ibáñez<sup>59</sup>, Alejandro Romero<sup>59,60</sup>, Alessandra Sperduti<sup>61,62</sup>, Sophie Beckett<sup>63,64,65</sup>, Susannah J. Salter<sup>63,66</sup>, Emma D. Zilivinskaya<sup>23</sup>, Dmitry V. Vasil'ev<sup>67</sup>, Kristin von Heyking<sup>68</sup>, Richard L. Burger<sup>69</sup>, Lucy C. Salazar<sup>69</sup>, Luc Amkreutz<sup>70</sup>, Masnav Navruzbekov<sup>71</sup>, Eva Rosenstock<sup>72</sup>, Carmen Alonso-Fernández<sup>73</sup>, Vladimir Slavchev<sup>74</sup>, Alexey A. Kalmykov<sup>37</sup>, Biaslan Ch. Atabiev<sup>75</sup>, Elena Batieva<sup>76</sup>, Micaela Alvarez Calmet<sup>77</sup>, Bastien Llamas<sup>78,79,80</sup>, Michael Schultz<sup>81</sup>, Raiko Krauß<sup>82</sup>, Javier Jiménez-Echevarría<sup>73</sup>, Michael Francken<sup>83</sup>, Svetlana Shnaider<sup>84</sup>, Peter de Knijff<sup>85</sup>, Eveline Altena<sup>85</sup>, Katrien Van de Vijver<sup>86,87,88</sup>, Lars Fehren-Schmitz<sup>89,90</sup>, Tiffany A. Tung<sup>91</sup>, Sandra Lösch<sup>92</sup>, Maria Dobrovolskaya<sup>53</sup>, Nikolaj Makarov<sup>53</sup>, Chris Read<sup>93</sup>, Melanie Van Twest<sup>63</sup>, Claudia Sagona<sup>94</sup>, Peter C. Ramsi<sup>95</sup>, Murat Akar<sup>96</sup>, K. Aslihan Yener<sup>97</sup>, Eduardo Carmona Ballesteros<sup>98,99</sup>, Francesco Cucca<sup>56,100</sup>, Vittorio Mazzarello<sup>100</sup>, Pilar Utrilla<sup>101</sup>, Kurt Rademaker<sup>102</sup>, Eva Fernández-Domínguez<sup>34</sup>, Douglas Baird<sup>49</sup>, Patrick Semal<sup>86</sup>, Lourdes Márquez-Morfín<sup>103</sup>, Mirjana Rokсандić<sup>44,104,105</sup>, Hubert Steiner<sup>106</sup>, Domingo Carlos Salazar-García<sup>107,108,109</sup>, Natalia Shishlina<sup>36</sup>, Yilmaz Selim Erdal<sup>110</sup>, Fredrik Hallgren<sup>111</sup>, Yavor Boyadzhiev<sup>112</sup>, Kamen Boyadzhiev<sup>112</sup>, Mario Küßner<sup>32</sup>, Duncan Sayer<sup>113</sup>, Päivi Onkamo<sup>114,115</sup>, Robin Skeates<sup>34</sup>, Manuel Rojo-Guerra<sup>27</sup>, Alexandra Buzhilova<sup>21</sup>, Elmira Khussainova<sup>13</sup>, Leyla B. Djansugurova<sup>13</sup>, Arman Z. Beisenov<sup>116</sup>, Zainolla Samashev<sup>117,118</sup>, Ken Massy<sup>119</sup>, Marcello Mannino<sup>120,121</sup>, Vyacheslav Moiseyev<sup>20</sup>, Kristiina Mannermaa<sup>122</sup>, Oleg Balanovsky<sup>123,124,125</sup>, Marie-France Deguilloux<sup>10</sup>, Sabine Reinhold<sup>126</sup>, Svend Hansen<sup>126</sup>, Egor P. Kitov<sup>23,116</sup>, Miroslav Dobeš<sup>39</sup>, Michal Ernée<sup>39</sup>, Harald Meller<sup>18</sup>, Kurt W. Alt<sup>127,128,129</sup>, Kay Prüfer<sup>2</sup>, Christina Warinner<sup>2,130</sup>, Stephan Schiffels<sup>2</sup>, Philipp W. Stockhammer<sup>2,119</sup>, Kirsten Bos<sup>2</sup>, Cosimo Posth<sup>2,4</sup>, Alexander Herbig<sup>2</sup>, Wolfgang Haak<sup>2,131</sup>, Johannes Krause<sup>2,\*</sup>, and Denise Kühnert<sup>1,132,\*</sup>

## Affiliations:

- <sup>1</sup>Transmission, Infection, Diversification & Evolution Group, Max-Planck Institute for the Science of Human History, Kahlaische Str. 10, 07745 Jena, Germany.
- 5 <sup>2</sup>Department of Archaeogenetics, Max-Planck Institute for the Science of Human History, Kahlaische Str. 10, 07745 Jena, Germany.
- <sup>3</sup>Max Planck Institute for Infection Biology, Charitéplatz 1, 10117 Berlin, Germany.
- <sup>4</sup>Archaeo- and Palaeogenetics group, Institute for Archaeological Sciences, Eberhard Karls University Tübingen, Rümelinstrasse 23, 72070 Tübingen, Germany.
- 10 <sup>5</sup>ARC Centre of Excellence for Mathematical and Statistical Frontiers, School of Mathematical Sciences, The University of Adelaide, Adelaide, SA 5005, Australia.
- <sup>6</sup>Division of Hepatology, Department of Medicine II, Leipzig University Medical Center, Leipzig, Germany.
- <sup>7</sup>Department of Genetics, Harvard Medical School, Boston, MA, USA.
- <sup>8</sup>Department of Human Evolutionary Biology, Harvard University, 11 Divinity Ave., Cambridge, MA 02138 USA.
- 15 <sup>9</sup>Institute of Evolutionary Biology, CSIC-Universitat Pompeu Fabra, Barcelona, Spain.
- <sup>10</sup>Université de Bordeaux, CNRS, PACEA UMR 5199, Pessac, France.
- <sup>11</sup>Laboratory of Structural Biology, Kazan Federal University, Kazan, Russia.
- <sup>12</sup>Al-Farabi Kazakh National University, Almaty, Kazakhstan.
- <sup>13</sup>Institute of Genetics and Physiology, 050060, al-Farabi ave., 93, Almaty, Kazakhstan.
- 20 <sup>14</sup>Departamento de Genética e Biologia Evolutiva, Instituto de Biociências, Universidade de São Paulo, São Paulo, SP, Brazil.
- <sup>15</sup>Arizona State University School of Human Evolution and Social Change, Tempe Arizona, USA.
- <sup>16</sup>Estonian Biocentre, Institute of Genomics, University of Tartu, Tartu, Estonia.
- <sup>17</sup>Department of Forensic Medicine, University of Helsinki, Helsinki, Finland.
- 25 <sup>18</sup>State Office for Heritage Management and Archaeology Saxony-Anhalt and State Museum of Prehistory, D-06114 Halle, Germany.
- <sup>19</sup>Museo Archeologico Regionale “Antonino Salinas”, Palermo, Via Bara all’Olivella 24, 90133, Italy.
- <sup>20</sup>Peter the Great Museum of Anthropology and Ethnography (Kunstkamera) RAS, 199034 St. Petersburg, Russia.
- 30 <sup>21</sup>Anuchin Research Institute and Museum of Anthropology, Lomonosov Moscow State University, Moscow, Russia.
- <sup>22</sup>Sterlitamak Museum of Local History, Sterlitamak, Russia.
- <sup>23</sup>Institute of Ethnology and Anthropology, Russian Academy of Sciences, Moscow, Russia.
- <sup>24</sup>Samara State University of Social Sciences and Education, Samara, Russia.
- 35 <sup>25</sup>Institute of Archaeology named after A. Kh. Khalikov, Tatarstan Academy of Sciences, Kazan, Russia.
- <sup>26</sup>Samara Museum for Historical and Regional Studies named after P.V. Alabin, Samara, Russia.
- <sup>27</sup>Department of Prehistory and Archaeology, Faculty of Philosophy and Letters, University of Valladolid, Spain.
- <sup>28</sup>Department of Prehistory and Archaeology, National Distance Education University (UNED), Madrid, Spain.

- <sup>29</sup>Private Technical Archaeologist.
- <sup>30</sup>Department of Prehistory and Archaeology, Faculty of Philosophy and Letters, Autonomous University of Madrid, Spain.
- <sup>31</sup>Technical Archaeologist, Government of Aragón, Spain.
- 5 <sup>32</sup>Thuringian State Office for Heritage Management and Archaeology, Humboldtstraße 11, 99423 Weimar, Germany.
- <sup>33</sup>University Medical School Göttingen, Institute of Anatomy and Cell Biology, Kreuzberggring 36, 37075 Göttingen, Germany.
- <sup>34</sup>Department of Archaeology, Durham University, South Road, Durham. DH1 3LE. UK.
- 10 <sup>35</sup>INRAP, ARAR UMR 5138, Maison de l’Orient et de la Méditerranée, Lyon, France.
- <sup>36</sup>State Historical Museum, Moscow, Red Square 1, Russian Federation.
- <sup>37</sup>Nasledie Cultural Heritage Unit, 355006 Stavropol, Russia.
- <sup>38</sup>Department of Anthropology, The National Museum, Prague, Czech Republic.
- <sup>39</sup>Institute of Archaeology of the Czech Academy of Sciences, Prague, Czech Republic.
- 15 <sup>40</sup>The City of Prague Museum, Prague, Czech Republic.
- <sup>41</sup>Oxford Archaeology South, Janus House, Osney Mead, Oxford, OX2 0ES, UK.
- <sup>42</sup>Oxford Archaeology East, 15 Trafalgar Way, Bar Hill, Cambridge, CB23 8SQ, UK.
- <sup>43</sup>Forensic Medicine Unit, National Institute of Health and Welfare, Finland.
- <sup>44</sup>Department of Anthropology, University of Winnipeg, Winnipeg, MB, Canada.
- 20 <sup>45</sup>Grupo de Investigación y Desarrollo, Dirección Provincial de Cultura, Matanzas, Cuba.
- <sup>46</sup>Universidad de Matanzas, Matanzas, Cuba.
- <sup>47</sup>Molecular Genetics Laboratory, Escuela Nacional de Antropología e Historia (ENAH), Mexico City, Mexico.
- <sup>48</sup>Immunogenetics Unit, Técnicas Genéticas Aplicadas a la Clínica (TGAC), Mexico City, Mexico.
- 25 <sup>49</sup>Department of Archaeology, Classics and Egyptology, University of Liverpool, 8–14 Abercromby Square, Liverpool, L69 7WZ, UK.
- <sup>50</sup>Université Côte d’Azur, CNRS, CEPAM UMR 7264, Nice, France.
- <sup>51</sup>Université de Strasbourg, CNRS, Archimède UMR 7044, Strasbourg, France.
- <sup>52</sup>Department of Archaeology, Faculty of History, Lomonosov Moscow State University, Lomonosovsky pr. 27/4, 119192, Moscow, Russia.
- 30 <sup>53</sup>Institute of Archaeology, Russian Academy of Sciences, Dm. Uljanova str., 19, Moscow 117292, Russia.
- <sup>54</sup>Department of Anthropology, University of South Florida, Tampa, FL, USA.
- <sup>55</sup>Department of Anthropology, University of North Carolina at Charlotte, Charlotte, NC, USA.
- <sup>56</sup>Istituto di Ricerca Genetica e Biomedica - CNR, Monserrato, Italy.
- <sup>57</sup>Private contractor, Cagliari, Sardinia, Italy.
- 35 <sup>58</sup>Koç University, Research Center for Anatolian Civilizations, Istanbul 34433, Turkey.
- <sup>59</sup>Institute for Research in Archaeology and Historical Heritage (INAPH); University of Alicante, 03690, Alicante, Spain.
- <sup>60</sup>Departamento de Biotecnología, Facultad de Ciencias, Universidad de Alicante, 03690, Alicante, Spain.
- <sup>61</sup>Bioarchaeology Service, Museum of the Civilizations, Rome, Italy.

- <sup>62</sup>Dipartimento Asia Africa e Mediterraneo, Università di Napoli L'Orientale, Napoli, Italy.
- <sup>63</sup>Sedgeford Historical and Archaeological Research Project, Old Village Hall, Sedgeford, Hunstanton PE36 5LS, UK.
- <sup>64</sup>Melbourne Dental School, The University of Melbourne, Victoria 3010 Australia.
- 5 <sup>65</sup>Cranfield Forensic Institute, Cranfield Defence and Security, Cranfield University, College Road, Cranfield, MK43 0AL, UK.
- <sup>66</sup>Department of Veterinary Medicine, University of Cambridge, Cambridge CB3 0ES, UK.
- <sup>67</sup>Astrakhan State University, Astrakhan, Russia.
- <sup>68</sup>SNSB, State Collection for Anthropology and Palaeoanatomy, Karolinenplatz 2a, 80333 Munich, Germany.
- 10 <sup>69</sup>Department of Anthropology, Yale University, New Haven, CT 06511, USA.
- <sup>70</sup>National Museum of Antiquities, Papengracht 30, P.O. Box 11114, 2301 EC Leiden, The Netherlands.
- <sup>71</sup>Institute of History, Archaeology and Ethnography, Dushanbe, Tajikistan.
- <sup>72</sup>Freie Universität Berlin, Einstein Center Chronoi, Otto-von-Simson-Str. 7, 14195 Berlin, Germany.
- <sup>73</sup>Cronos S.C. Arqueología y Patrimonio, Burgos, Spain.
- 15 <sup>74</sup>Regional Historical Museum Varna, Varna, BG-9000, Maria Luiza Blvd. 41, Bulgaria.
- <sup>75</sup>Institute for Caucasus Archaeology, Ul. Katkhanova 30, 361401 Nalchik, Republic Kabardino-Balkaria, Russia.
- <sup>76</sup>Azov History, Archaeology and Palaeontology Museum-Reserve, Moskovskaya Street 38/40, Azov 346780, Russia.
- 20 <sup>77</sup>Museo de Sitio Puellana, Calle General Borgoño crd.8 s/n Miraflores 18 Lima, Peru.
- <sup>78</sup>Australian Centre for Ancient DNA, School of Biological Sciences and The Environment Institute, Adelaide University, Adelaide, SA 5005, Australia.
- <sup>79</sup>Centre of Excellence for Australian Biodiversity and Heritage (CABAH), University of Adelaide, Adelaide, SA 5005, Australia.
- 25 <sup>80</sup>National Centre for Indigenous Genomics, Australian National University, Canberra, ACT 0200, Australia.
- <sup>81</sup>University Medical School Göttingen, Institute of Anatomy and Embryology, Kreuzberggring 36, 37075 Göttingen, Germany.
- <sup>82</sup>Institute for Prehistory, Early History and Medieval Archaeology, University of Tübingen, 72070 Tübingen, Germany.
- 30 <sup>83</sup>State Office for Cultural Heritage Baden-Württemberg, Stromeyersdorfstraße 3, 78467 Konstanz, Germany.
- <sup>84</sup>ArchaeoZoology in Siberia and Central Asia - ZooSCAn, CNRS – IAET SB RAS International Research Laboratory, IRL 2013, Novosibirsk, Russia.
- <sup>85</sup>Department of Human Genetics, Leiden University Medical Center, Leiden, 2333 ZC, The Netherlands.
- <sup>86</sup>Royal Belgian Institute of Natural Sciences, Brussels, Belgium.
- 35 <sup>87</sup>Center for Archaeological Sciences, University of Leuven, Belgium.
- <sup>88</sup>Dienst Archeologie - Stad Mechelen, Belgium.
- <sup>89</sup>UCSC Paleogenomics Lab, Department of Anthropology, University of California at Santa Cruz, Santa Cruz, CA 95064, USA.
- <sup>90</sup>UCSC Genomics Institute, University of California at Santa Cruz, Santa Cruz, CA 95064, USA.
- 40 <sup>91</sup>Department of Anthropology, Vanderbilt University, VU Station B 356050, Nashville, TN 37235, USA.

- <sup>92</sup>Department of Physical Anthropology, Institute of Forensic Medicine, University of Bern, Bern, Switzerland.
- <sup>93</sup>Applied Archaeology School of Science, Institute of Technology Sligo, Ireland.
- <sup>94</sup>School of Historical and Philosophical Studies, The University of Melbourne, Victoria 3010, Australia.
- <sup>95</sup>Institute of Prehistoric and Historical Archaeology, University of Vienna, Austria.
- 5 <sup>96</sup>Department of Archaeology, Hatay Mustafa Kemal University, Alahan-Antakya, Hatay 31060, Turkey.
- <sup>97</sup>Institute for the Study of the Ancient World (ISAW), New York University, New York, NY 10028, USA.
- <sup>98</sup>Territorial Service of Culture and Tourism from Valladolid, Castilla y León Regional Government, C/ San Lorenzo, 5, 47001, Valladolid, Spain.
- 10 <sup>99</sup>Department of History, Geography and Communication, University of Burgos, Paseo de Comendadores, s/n 09001 Burgos (Burgos), Spain.
- <sup>100</sup>Dipartimento di Scienze Biomediche, Università di Sassari, Sassari, Italy.
- <sup>101</sup>Área de Prehistoria, P3A DGA Research Group, IPH, University of Zaragoza, C/ Pedro Cerbuna 12, 50009, Zaragoza, Spain.
- <sup>102</sup>Department of Anthropology, Michigan State University, East Lansing, MI 48824, USA.
- 15 <sup>103</sup>Osteology Laboratory, Post Graduate Studies Division, Escuela Nacional de Antropología e Historia (ENAH), Mexico City, Mexico.
- <sup>104</sup>Caribbean Research Institute, Univeristy of Winnipeg, Winnipeg, MB, Canada.
- <sup>105</sup>DFG Center for Advanced Studies ‘Words, Bones, Genes, Tools’, University of Tübingen, Tübingen, Germany.
- 20 <sup>106</sup>South Tyrol Provincial Heritage Service.
- <sup>107</sup>Grupo de Investigación en Prehistoria IT-1223-19 (UPV-EHU)/IKERBASQUE-Basque Foundation for Science, Vitoria, Spain.
- <sup>108</sup>Departament de Prehistòria, Arqueologia i Història Antiga, Universitat de València, València, Spain.
- <sup>109</sup>Department of Geological Sciences, University of Cape Town, Cape Town, South Africa.
- 25 <sup>110</sup>Human\_G laboratory, Department of Anthropology, Hacettepe University, Ankara 06800, Turkey.
- <sup>111</sup>The Cultural Heritage Foundation, 722 12 Västerås, Sweden.
- <sup>112</sup>National Archaeological Institute with Museum at the Bulgarian Academy of Sciences, Sofia, 1000, 2 Saborna str., Bulgaria.
- <sup>113</sup>School of Natural Sciences, University of Central Lancashire, Preston, UK.
- 30 <sup>114</sup>Department of Biosciences, University of Helsinki, Viikinkaari 9, 00014 Helsinki, Finland.
- <sup>115</sup>Department of Biology, University of Turku, Vesilinnantie 5, 20500 Turku, Finland.
- <sup>116</sup>Institute of archaeology named after A.Kh. Margulan, 050010, Dostyk ave., 44, Almaty, Kazakhstan
- <sup>117</sup>Branch of Institute of Archaeology named after A.Kh. Margulan, 010011, Republic ave., 24, of. 511, Nur-Sultan, Kazakhstan.
- 35 <sup>118</sup>State Historical and Cultural Museum-Reserve “Berel”, 070906, set. Zhambyl, Katon-Karagay district, East Kazakhstan region, Kazakhstan.
- <sup>119</sup>Institut für Vor- und Frühgeschichtliche Archäologie und Provinzialrömische Archäologie, Ludwig-Maximilians-Universität München, 80539 Munich, Germany.
- 40 <sup>120</sup>Department of Archeology and Heritage Studies, Aarhus University, Højbjerg, Moesgård Allé 20, 8270, Denmark.

<sup>121</sup>Department of Human Evolution, Max Planck Institute for Evolutionary Anthropology (MPI-EVA), Leipzig, Deutscher Platz 6, D-04103, Germany.

<sup>122</sup>Department of Cultures, Archaeology, University of Helsinki, Unioninkatu 38 F, 00170 Helsinki, Finland.

<sup>123</sup>Research Centre for Medical Genetics, Moscow, Russia.

5 <sup>124</sup>Biobank of North Eurasia, Moscow, Russia.

<sup>125</sup>Vavilov Institute of General Genetics, Moscow, Russia.

<sup>126</sup>Eurasia Department, German Archaeological Institute, Berlin, Germany.

<sup>127</sup>Danube Private University, Center of Natural and Cultural Human History, Steiner Landstrasse 124, A - 3500 Krems-Stein, Austria.

10 <sup>128</sup>Integrative Prehistory and Archaeological Science, Spalenring 145, CH-4055 Basel, Switzerland.

<sup>129</sup>Department of Biomedical Engineering (DBE), Universitätsspital Basel (HFZ), Gewerbestrasse 14-16, Labor 14.03.021-023, CH-4123 Allschwil, Switzerland.

<sup>130</sup>Department of Anthropology, Harvard University, 11 Divinity Ave., Cambridge, MA 02138 USA.

<sup>131</sup>School of Biological Sciences, The University of Adelaide, Adelaide, SA, 5005, Australia.

15 <sup>132</sup>European Virus Bioinformatics Center (EVBC), Jena, Germany.

\*Corresponding author. Email: [kocher@shh.mpg.de](mailto:kocher@shh.mpg.de); [krause@shh.mpg.de](mailto:krause@shh.mpg.de); [kuehnert@shh.mpg.de](mailto:kuehnert@shh.mpg.de)



## Abstract

Hepatitis B virus (HBV) has been infecting humans for millennia and remains a global health problem, but its past diversity and dispersal routes are largely unknown. We generated HBV genomic data from 137 Eurasians and Native Americans dated between ~10,500 and ~400 years ago. We date the most recent common ancestor of all HBV lineages to between ~20,000 and 12,000 years ago, with the virus present in European and South Americans during the early Holocene. Following the European Neolithic transition, Mesolithic HBV strains were replaced by a lineage likely disseminated by early farmers that prevailed throughout western Eurasia for ~4,000 years, declining around the end of the 2nd millennium BCE. The only remnant of this prehistoric HBV diversity is the rare genotype G, which appears to have re-emerged during the HIV pandemic.

### One-Sentence Summary:

Uncovering 10,000 years of hepatitis B virus evolution by analyzing genomes from ancient Eurasians and Native Americans

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## **Main Text:**

The World Health Organization (WHO) estimates that in 2015, 257 million people were living with chronic hepatitis B virus (HBV) infection, which causes close to one million deaths each year (1). HBV is transmitted through contact with bodily fluids, mainly in sexual and perinatal contexts (2), and has no known environmental or animal reservoir. Its spread is therefore tightly linked to the dispersal of humans, whose past population dynamics and migrations have likely shaped the genetic diversity of this partially double-stranded DNA virus, which is currently classified into nine genotypes associated with characteristic ethno-geographic ranges [(3, 4); Fig. 1]. However, the temporal and geographic context of HBV origins in humans, as well as its major routes of dissemination in the past, remain widely debated (5–10). Recent studies have retrieved HBV DNA from archaeological human remains (11–16), providing new avenues to address questions about HBV evolution and phylogeographic history. In particular, these studies revealed the presence of HBV in Europe as early as the Neolithic and ancient HBV lineages that are now seemingly extinct. Ancient DNA data permits molecular clock calibration, and the time to the most recent common ancestor (tMRCA) of all known HBV lineages has been dated to between ~21 and ~9 thousand years ago (ka) (14). However, the extent of the past diversity of this virus remains generally unknown as only 19 ancient HBV genomes with a limited temporal and geographic distribution have been reconstructed to date.

### **The MRCA of all known HBV lineages**

Here, we report genomic evidence of HBV in the skeletal remains of 137 individuals from Eurasia and the Americas dated to between ~10,500 and ~400 years ago (Figs. 1, S1; Data S1). Despite advances in molecular virology and numerous sequences from present-day HBV

genomes, assessing the phylogenetic relationships among HBV genotypes has proven challenging (7, 17–20), and doubts have been cast about its evolutionary rate and molecular clock-like behavior (9, 16, 21). Nevertheless, most HBV phylogenetic reconstructions have recovered a topology in which HBV genotypes typically found in Native Americans (F and H) represent a sister clade to the rest of worldwide HBV diversity (18) (which we refer to as the Eurasian branch). This topology was supported by a study incorporating 12 ancient HBV genomes (14), and is retrieved here (Figs. 2, S2, S3). In particular, the monophyly of the American HBV branch, comprising all ancient genomes from the Americas dating back to as early as ~9 ka from the Cuncaicha rock shelter in the Andean highlands (CUN002), was highly supported. On the other hand, deep nodes within the Eurasian branch were not well resolved, pointing to plausible alternative topologies in which some of the earliest Eurasian lineages would have diverged before the American branch [see (22); Figs. S4, S5]. Our results confirm that HBV genomic data do exhibit a clear temporal structure when incorporating samples spanning several thousand years (fig. S3). Using the best-fitting uncorrelated relaxed clock model, we estimate the tMRCA of HBV, corresponding to the divergence of American and Eurasian HBV branches, between ~16 and ~12 ka [95% Highest Posterior Density (HPD); table S1], within the range of previous findings (14). This suggests that contacts between ancestral Eurasians and First Americans occurred until at least shortly before the Bølling-Allerød interstadial (~15-13 ka), a period of warming corresponding to widespread human expansion in North America (23, 24). However, studies of ancient human genomes indicate that the ancestors of the First Americans likely began diverging from their closest Eurasian relatives between ~25 and 18 ka, possibly reflecting an extended isolation in a Beringian refugium during the Last Glacial Maximum, before dispersing into and across the Americas (25–27). The

use of a time-dependent rate model yielded an estimate of ~20-17 ka for the HBV tMRCA (95% HPD), which was more consistent in this regard. This suggests that not accounting for the time-dependency of the evolutionary rate may have led to an underestimation of deep divergence times. However, model selection favored the use of a relaxed clock over a TDR model (log BF: 405) (22). Taken together, these results point to a scenario in which the MRCA of all HBV strains examined to date existed around the end of the Pleistocene and gave rise to one or several lineages that spread across Eurasia and eventually reached Africa and Oceania, and to another lineage that spread into the Americas with early settlers of this continent.

Our findings challenge the view that current HBV diversity reflects early human dispersals out of Africa. This model is supported, in particular, by the exclusive association of HBV subgenotype C4 with the Aboriginal people of Australia, suggesting that this subgenotype may have been carried by the first settlers of Australia at least ~50 ka (5, 20). Instead, in accordance with previous findings (14), our results indicate that all known modern and ancient HBV strains descend from a lineage that began to diversify at a more recent stage of human history, and that subgenotype C4 was introduced in the Australian continent after ~4.5 ka (Fig. 2). Nevertheless, the age of the observed MRCA only represents a lower limit for the earliest presence of HBV in humans. Whether the latter has been preceded by long coevolution, a recent spillover from another animal species, or any intermediate scenario, remains an open question. Other viruses from the Hepadnaviridae family have been recovered from a wide range of vertebrates, but none of them appear to represent an ancestral zoonotic source for the human HBV (8).

## **HBV circulated widely in western Eurasia as early as 10 ka**

The retrieval of HBV genomes from around 10 ka in different parts of Europe and Anatolia, indicate that the virus was widespread in western Eurasia at that time (Figs. 1, S1). The oldest HBV strains recovered in Europe form two distinct clades (Figs. 2, S2; table S2): one that was found in three hunter-gatherers (HG) from northwestern Russia, Belgium and Doggerland (Mesolithic 1), and another that was found in a HG from western Russia (Mesolithic 2). These two lineages are placed within the Eurasian branch as sister groups to the modern strains found in non-human primates (NHP) from Southeast Asia and Africa, respectively. The position of NHP HBV lineages within human HBV diversity has been observed in most previous phylogenetic reconstructions and is thought to reflect spillover events from humans to NHPs (7, 22, 28). The HBV genome reconstructed from an early Anatolian farmer forms a separate lineage recovered at a phylogenetic position intermediate to the two European Mesolithic clades. Between ~9 and 7.5 ka, HBV strains found in HGs from Karelia (northwestern Russia), Sweden, Luxembourg and Sicily all belonged to the Mesolithic 2 clade. Thus, although our data do not allow detailed phylogeographic inference, they suggest that, during the early Holocene, HBV strains could spread over large parts of western Eurasia within a few thousand years. This is consistent with evidence of genetic connections between Europe and the Near East that predate the Neolithic transition (29, 30), and with the observed genetic cline from Western to Eastern HGs (31). Our results further highlight that Mesolithic populations likely formed a network through which pathogens could spread.

It has been suggested that most human-adapted pathogens emerged after the Neolithic transition in association with sedentary lifestyles, increased contact with domesticated animals, and higher population densities, a phenomenon sometimes referred to as the “first epidemiological

transition” (32–34). Our finding of widespread HBV in HG populations indicates that HBV was present prior to the advent of agriculture and animal husbandry in different parts of the world. Today, HBV rarely causes lethal fulminant hepatitis, but rather asymptomatic infections that may evolve into chronic forms, sometimes developing into liver complications and possible liver failure after decades of infection (1, 2). Although it is difficult to extrapolate from present-day medical studies what the clinical impact of a pathogen would have been in the past, given different diets, disease burdens, and life expectancies, the virus has likely exhibited similar pathophysiological features. Consequently, our findings are consistent with the view that, although small HG communities could not sustain highly epidemic “crowd” diseases, they could maintain chronic infectious agents (35, 36).

#### **A replacement of HBV diversity occurred with the Neolithic transition in Europe**

Our data show that HBV remained widespread in Europe after the Neolithic transition (8-7 ka), with numerous strains recovered from early European farmers (EEF) across the continent (Figs. 3, S1; Data S1). Remarkably, all of these strains belong to a single HBV lineage that does not descend from previously observed Mesolithic strains (Figs. 2, 3, S2). We refer to this HBV lineage as the Western-Eurasian Neolithic-to-Bronze-Age (WENBA) lineage. This transition is also observable at a micro-scale in Grotta dell’Uzzo (Sicily), where HBV strains recovered from Neolithic individuals are unrelated to a Late Mesolithic strain identified at the same site (figs. S1, S2). This suggests that the HBV strains observed in EEFs were not acquired from local HGs in different areas, but were rather disseminated by EEFs themselves. While EEFs ultimately derived from early agricultural populations in the Near East (37, 38), the strain we retrieved from an Anatolian farmer dated to ~10 ka was not ancestral to the WENBA lineage (Fig. 2). Therefore, even if EEFs were indeed key in disseminating WENBA strains, whether

this lineage originated in Near Eastern centers of early agriculture or in another location along  
EEF's expansion routes remains to be determined. Furthermore, given the current sample  
availability for this period, a scenario in which the WENBA lineage would have originated and  
disseminated among European HGs shortly before the Neolithic transition cannot be  
5 completely excluded.

Later, we find WENBA HBV strains in two HGs from transitional Neolithic contexts in western  
Russia dated to ~7.2 and ~6.4 ka (JAZ001 and MUR007), as well as on both sides of the Greater  
Caucasus Mountain range and in Anatolia as early as ~5.6 ka (fig. S1). In general, phylogenetic  
relationships among HBV sublineages within the WENBA clade do not exhibit a strong  
10 geographical structure (fig. S2), nor do they seem to reflect the material culture or genetic  
profile of the individuals in which they were found (fig. S6). Furthermore, our phylodynamic  
reconstruction indicates that, after an initial growth phase, the transmission of WENBA HBV  
reached an equilibrium from ~7.5 to ~3.5 ka (fig. S7). Overall, this suggests that HBV strains  
disseminated by EEFs quickly spread throughout much of western Eurasia beyond the limits of  
15 the European agricultural expansion, where they became endemic and continued to circulate  
widely across different populations, for several thousand years. In particular, we do not observe  
significant changes in the HBV genetic landscape associated with the expansion of steppe-  
related ancestry that dramatically altered the genetic profile of Europeans from ~5 ka onward  
(37) (Figs. 2, S2; Data S1). Sexual and perinatal transmission have likely always been the major  
20 mechanisms of HBV infection in humans, but cultural practices involving contact with blood  
[e.g., tattooing (39)] or non-sexual violent interactions (40) could also have played a role in the  
spread of the virus in the past. In general, our findings attest to a degree of interconnectivity

among prehistoric populations of different origins, subsistence modes, and cultures that allowed for the dissemination of directly-transmitted pathogens.

### **The 2nd millennium BCE collapse of WENBA HBV**

5 Following the Early Neolithic (8-7 ka), the WENBA HBV lineage prevailed in most parts of western Eurasia for more than 4,000 years (Fig. 3). However, the latest occurrence of a WENBA strain in our dataset is dated to ~3.3 ka, after which this lineage is no longer observed (figs. S1, S2). In contrast, genotype A, which we first observe at the eastern edge of Europe and in the Near East between ~5 and ~3.5 ka, still appears after ~2.5 ka, by which time it had reached the Carpathian Basin in central Europe. Around the same date, we first observe  
10 genotype D in two individuals from the Italian Alps, as well as in various locations in the western steppe, before prevailing in large parts of Europe during the Medieval period. Thus, it seems that as most WENBA HBV lineages disappeared by the end of the 2nd millennium BCE, genotypes A and D subsequently spread from eastern reservoirs to eventually reach western regions that had previously only harbored WENBA strains (22).

15 The second half of the 2nd millennium BCE bears witness to major cultural shifts in the archaeological record in western Eurasia, including the sudden disappearance of tell settlements in the Carpathian Basin (41), the expansion of the Urnfield culture and the increase of military conflicts in large parts of Europe (42–45), the breakdown of the Terramare culture in northern Italy (46), and the so-called Late Bronze Age collapse of most state societies in the eastern  
20 Mediterranean region and Near East (47, 48). Some of these societal transformations could have been triggered by underlying phenomena such as climatic events (49) or the spread of epidemic diseases (50), and were likely associated with significant shifts in population



densities, trans-regional networks, and modes and scales of human mobility. The observed decline of WENBA HBV diversity, as well as our phylodynamic reconstruction (fig. S7), further point to important changes in epidemiological dynamics over large parts of western Eurasia during this period. However, while our data suggests that new lineages disseminated across Europe only later on, the lack of observations around 3 ka (Fig. 3) could reflect sampling biases related to the widespread adoption of cremation practices around that time (42–44), rather than a decrease of HBV prevalence. Searching for the virus in a large number of systematically dated samples across this period could help to better characterize the process that ultimately led to the renewal of western Eurasian HBV diversity after the end of the 2nd millennium BCE.

### **Recent re-emergence of the WENBA HBV lineage**

The majority of HBV strains circulating in western Eurasia today belong to genotypes A and D (3, 4), thus only reflecting a relatively recent part of the phylogeographic history of this virus. However, our results show that despite the seemingly complete disappearance of WENBA HBV strains around the end of the 2nd millennium BCE, one lineage descending from this clade has, in fact, persisted to the present. The latter gave rise to a group of modern strains classified as genotype G (Figs. 2, S2), a rare, recently described genotype for which the biology is poorly understood (51). First discovered in patients from France and the United States, genotype G was later found in other parts of Europe, the Americas, and in Asia, making its geographic origin unclear (52). Despite its wide distribution, genotype G exhibits remarkably low genetic diversity (53), suggesting a recent re-emergence after thousands of years of low-level persistence. Furthermore, genotype G has mostly been found in HIV-positive patients, and phylodynamic patterns have pointed to a sharp increase of its dissemination co-occurring

with the HIV pandemic, possibly associated with highly sexually active groups and injection drug users (52).

Genotype G has sometimes been referred to as “aberrant” due to its unique genomic features: a 36-nt insertion near the 5’ end of the core gene and two nonsense mutations in the pre-core region (51, 54). These changes inhibit production of the immunotolerogen e antigen (HBeAg), which appears essential for the establishment of a persistent HBV infection, and alter the structure of the HBV core protein, which may impair packaging and replication of the viral genetic material (54, 55). This likely explains why, in the vast majority of cases, genotype G occurs in co-infections with other HBV genotypes, which can provide the HBeAg and core protein production functions lacking in genotype G (54–56). We identified similar insertions and stop codons in 14 ancient HBV genomes ranging in age between ~7 and 3.5 ka, which form the WENBA subclade from which genotype G descends (fig. S8). Additionally, most of these ancient genomes were found in individuals showing signs of infections with several HBV variants [fig. S8; Data S2; (22)]. In fact, cases of mixed infection were exclusively found in individuals carrying WENBA HBV strains, among which they were very frequent (22/83 individuals, likely underestimating the true frequency). In all cases, both major and minor strains appeared to belong to the WENBA lineage, and sequencing data were partially supporting a ~40-bp insertion at the 5’ end of the core gene (table S3; Data S1).

Therefore, while genotype G is considered rare today, it seems that the co-transmission of its ancestral form together with another HBeAg+ WENBA strain was a common epidemiological feature of HBV between ~7.5 and 3.5 ka. On the other hand, it may appear surprising that this functionally-limited variant specifically persisted until today while the rest of the WENBA HBV diversity seemingly went extinct. Virologic studies indicate that genotype G tends to

outcompete HBeAg-producing strains during late HBV infection stages following anti-HBeAg seroconversion (56–58). It is tempting to speculate a link between these short-term selection patterns and the survival of this lineage over thousands of years, but the latter might also be related to less deterministic factors. One of the closest Bronze Age ancestors of genotype G was recovered at the archaeological site of Shagara in the eastern European forest zone (SGR003; figs. S1, S2), a location where the nowadays-widespread genotype A was already circulating (SGR004). Of note, genotype A is the most common genotype found with genotype G in mixed infections today (55, 57). The discovery of ancestral forms of both genotypes at the same archaeological site, albeit from different individuals and time periods, may indicate that this viral association had already formed during prehistory in eastern Europe.

## Conclusions

This study demonstrates the value of large-scale paleogenomic analyses for studying the phylogeographic history of HBV. DNA-enrichment allowed us to reconstruct large proportions of over one hundred ancient HBV genomes from a variety of skeletal tissues, opening important possibilities for future paleovirologic studies. We show that HBV was already widely present in humans during the early Holocene, and that its phylogeographic history reflects several well-known human migrations and demographic events, including the expansion of First American populations in the Americas and the Neolithic transition in Europe, but not others, such as later Bronze Age steppe ancestry expansions. Furthermore, our results reveal patterns that were not expected on the basis of human genetic and archaeological data alone, such as the near complete renewal of western Eurasian HBV diversity around the end of the 2nd millennium BCE. These findings highlight that the reconstruction of ancient viral diversity has great potential to contribute to our understanding of human history.

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## Supplementary Materials

Materials and Methods

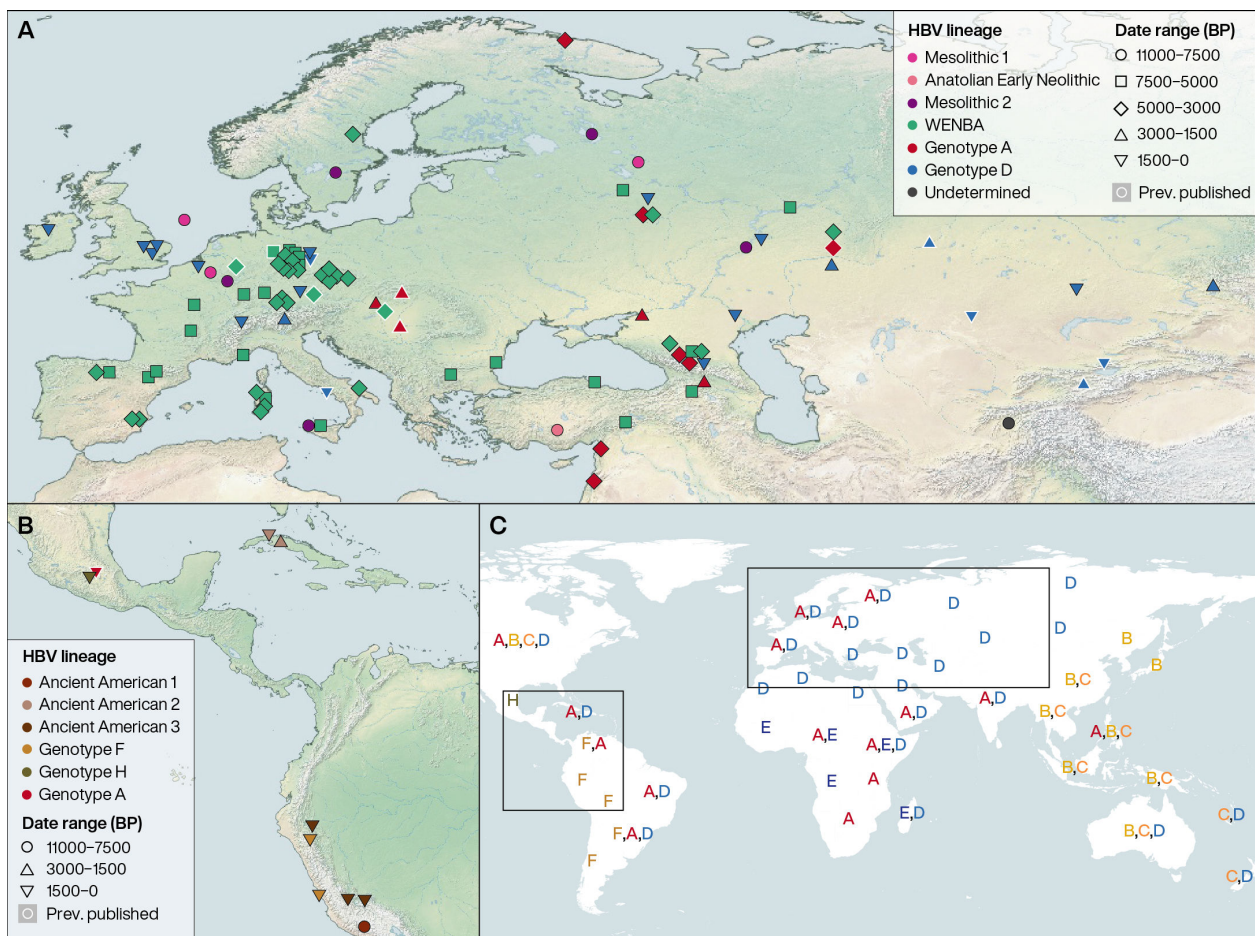
Supplementary Text

Figs. S1 to S10

Tables S1 to S5

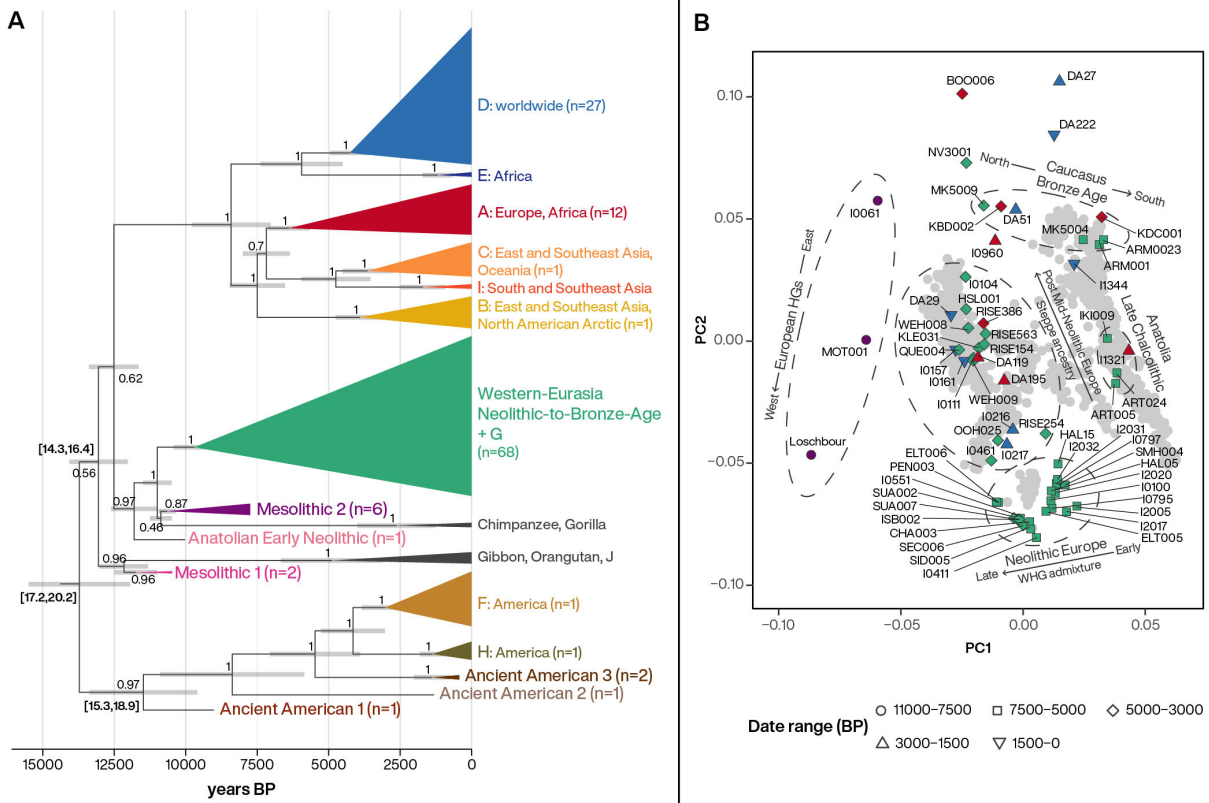
References (59–254)

5 Data S1 to S4



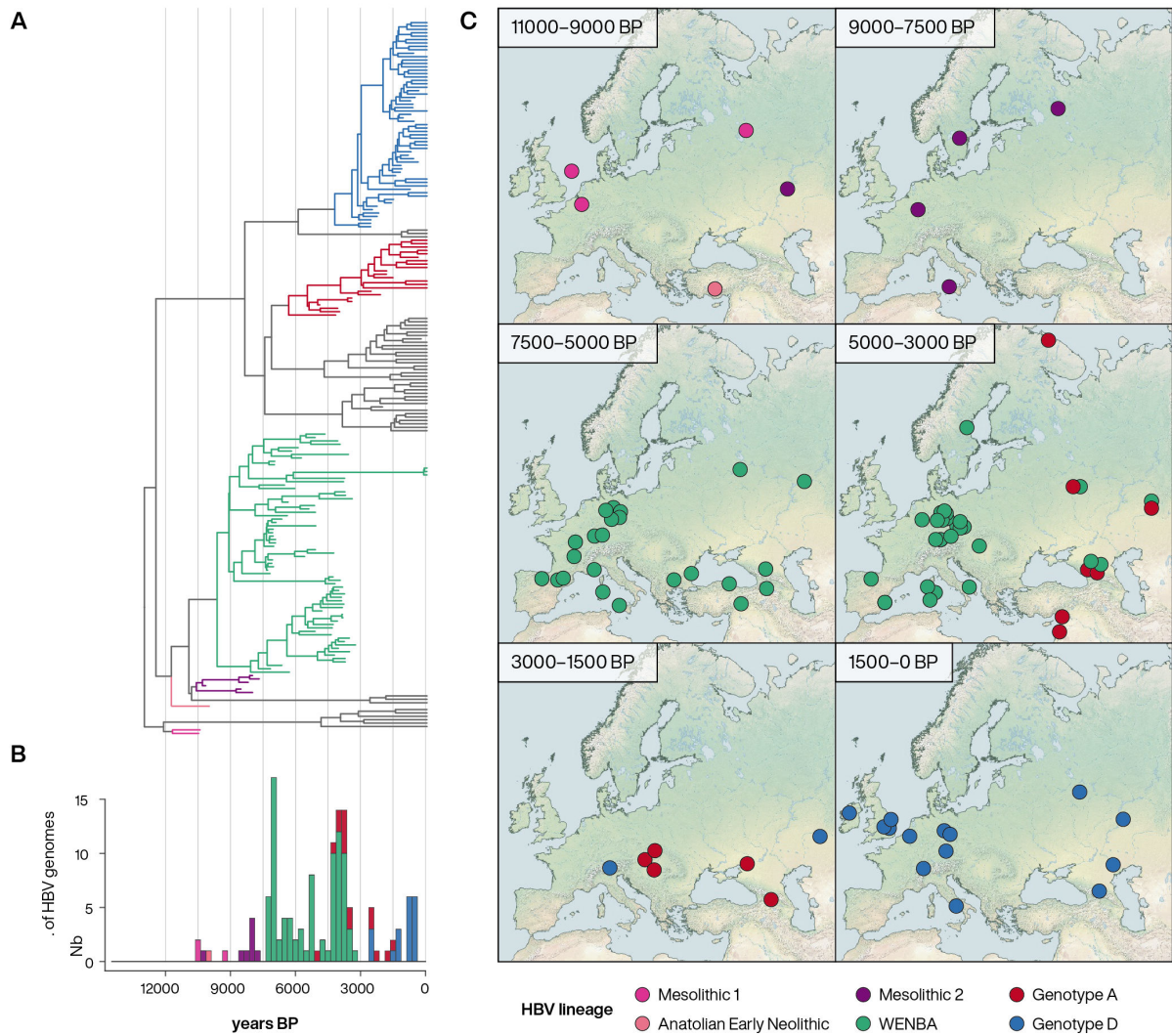
**Fig. 1: Geographic location, time period, and lineage of ancient HBV genomes from (A) Eurasia and (B) the Americas. (C) Main distribution of present-day HBV genotypes [adapted from (4), (14)].**





**Fig. 2. HBV phylogeny and genetic profile of infected individuals.** (A) Time-calibrated phylogenetic tree of HBV obtained using a skyline coalescent tree prior and a lognormal relaxed clock. Main clades were collapsed and annotated with their typical present-day geographic location and the number of ancient genomes they contain. Posterior node supports and date estimates (grey bars, indicating 95%HPD) are reported. Additional time-intervals written on deep nodes are 95% HPD estimates obtained with a time-dependent rate model. (B) Principal components analysis plot of modern and ancient western Eurasians summarizing the genetic variation of a subset of individuals for which human genetic data was available. Individuals are colored according to the lineage of the HBV strain they carried, as in the tree.

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**Fig. 3. Spatiotemporal distribution of ancient western Eurasian HBV strains. (A)** Time-calibrated phylogenetic tree (Eurasian branch). Lineages containing ancient HBV genomes are colored. **(B)** Histogram showing the number of recovered ancient HBV genomes belonging to each lineage through time. **(C)** Geographic distribution of ancient HBV genomes within different time-periods, colored by lineage.

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