RNA structure conservation and molecular epidemiology of Tick-borne encephalitis virus

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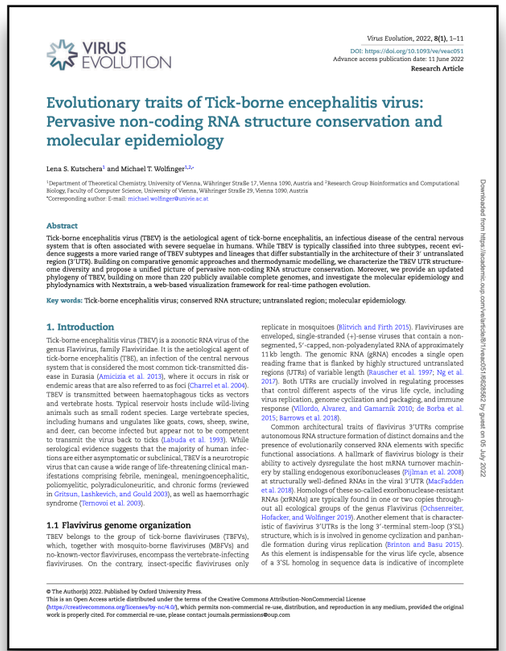

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Research Article

Evolutionary traits of Tick-borne encephalitis virus: Pervasive non-coding RNA structure conservation and molecular epidemiology

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Abstract

Tick-borne encephalitis virus (TBEV) is the aetiological agent of tick-borne encephalitis, an infectious disease of the central nervous system that is often associated with severe sequelae in humans. While TBEV is typically classified into three subtypes, recent evidence suggests a more varied range of TBEV subtypes and lineages that differ substantially in the architecture of their 3′ untranslated region (3′UTR). Building on comparative genomic approaches and thermodynamic modelling, we characterize the TBEV UTR structureome diversity and propose a unified picture of pervasive non-coding RNA structure conservation. Moreover, we provide an updated phylogeny of TBEV, building on more than 220 publicly available complete genomes, and investigate the molecular epidemiology and phylodynamics with Nextstrain, a web-based visualization framework for real-time pathogen evolution.

Key words: Tick-borne encephalitis virus; conserved RNA structure; untranslated region; molecular epidemiology.

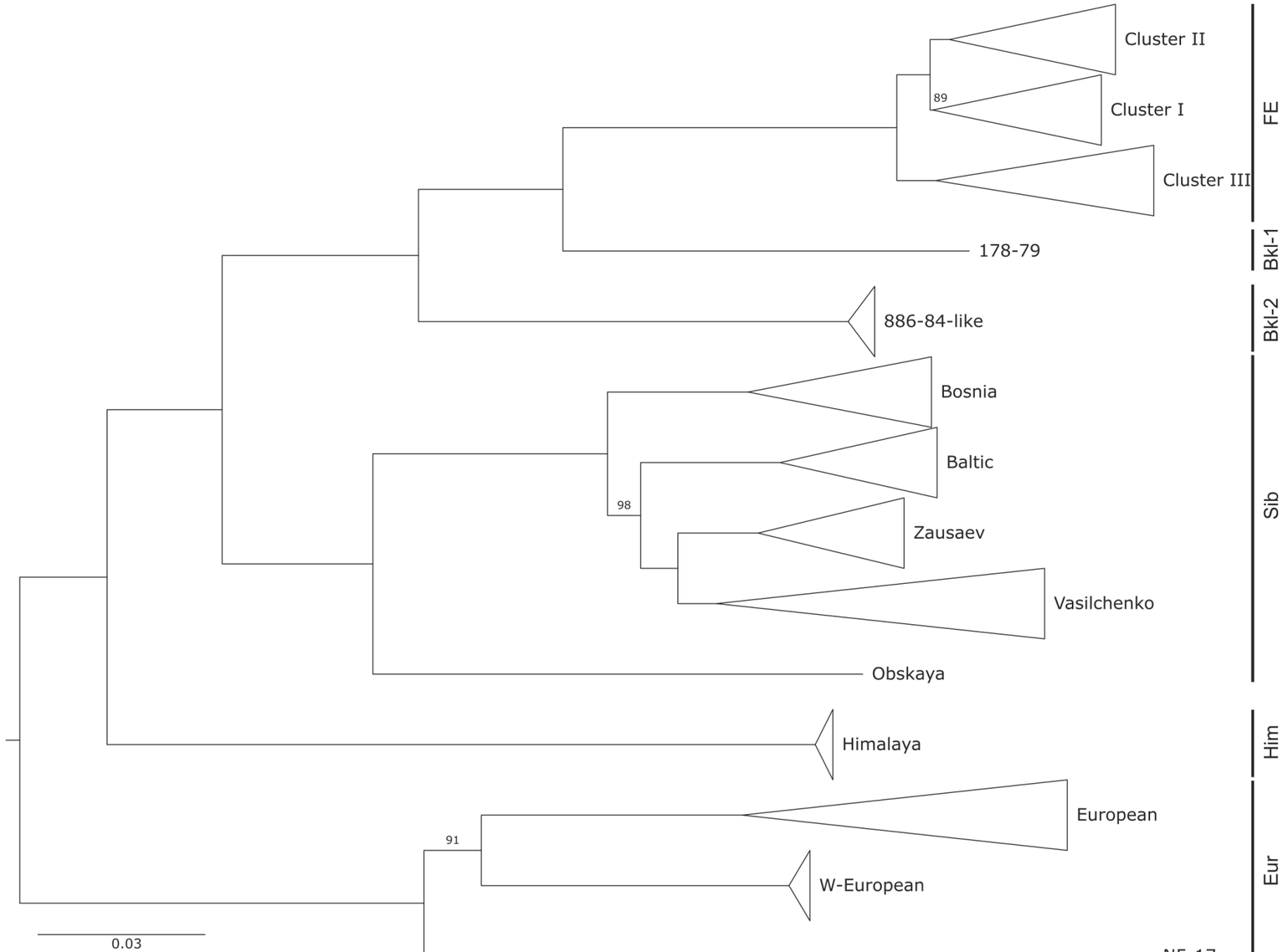
1. Introduction

Tick-borne encephalitis virus (TBEV) is a zoonotic RNA virus of the genus Flavivirus, family Flaviviridae. It is the aetiological agent of tick-borne encephalitis (TBE), an infection of the central nervous system that is considered the most common tick-transmitted disease in Eurasia (Amicizia et al. 2013), where it occurs in risk or endemic areas that are also referred to as foci (Charrel et al. 2004). TBEV is transmitted between haematophagous ticks as vectors and vertebrate hosts. Typical reservoir hosts include wild-living animals such as small rodent species. Large vertebrate species, including humans and ungulates like goats, cows, sheep, swine, and deer, can become infected but appear not to be competent to transmit the virus back to ticks (Labuda et al. 1993). While serological evidence suggests that the majority of human infections are either asymptomatic or subclinical, TBEV is a neurotropic virus that can cause a wide range of life-threatening clinical manifestations comprising febrile, meningeal, meningoencephalitic, poliomyelitic, polyradiculoneuritic, and chronic forms (reviewed in Gritsun, Lashkevich, and Gould 2003), as well as haemorrhagic syndrome (Ternovoi et al. 2003).

1.1 Flavivirus genome organization

TBEV belongs to the group of tick-borne flaviviruses (TBFVs), which, together with mosquito-borne flaviviruses (MBFVs) and no-known-vector flaviviruses, encompass the vertebrate-infecting flaviviruses. On the contrary, insect-specific flaviviruses only replicate in mosquitoes (Blitvich and Firth 2015). Flaviviruses are enveloped, single-stranded (+)-sense viruses that contain a non-segmented, 5′-capped, non-polyadenylated RNA of approximately 11 kb length. The genomic RNA (gRNA) encodes a single open reading frame that is flanked by highly structured untranslated regions (UTRs) of variable length (Rauscher et al. 1997; Ng et al. 2017). Both UTRs are crucially involved in regulating processes that control different aspects of the virus life cycle, including virus replication, genome cyclization and packaging, and immune response (Villordo, Alvarez, and Gamarnik 2010; de Borba et al. 2015; Barrows et al. 2018).

Common architectural traits of flavivirus 3′UTRs comprise autonomous RNA structure formation of distinct domains and the presence of evolutionarily conserved RNA elements with specific functional associations. A hallmark of flavivirus biology is their ability to actively dysregulate the host mRNA turnover machinery by stalling endogenous exoribonucleases (Pijlman et al. 2008) at structurally well-defined RNAs in the viral 3′UTR (MacFadden et al. 2018). Homologs of these so-called exoribonuclease-resistant RNAs (xrRNAs) are typically found in one or two copies throughout all ecological groups of the genus Flavivirus (Ochsenreiter, Hofacker, and Wolfinger 2019). Another element that is characteristic of flavivirus 3′UTRs is the long 3′-terminal stem-loop (3′SL) structure, which is is involved in genome cyclization and packaging formation during virus replication (Brinton and Basu 2015). As this element is indispensable for the virus life cycle, absence of a 3′SL homolog in sequence data is indicative of incomplete



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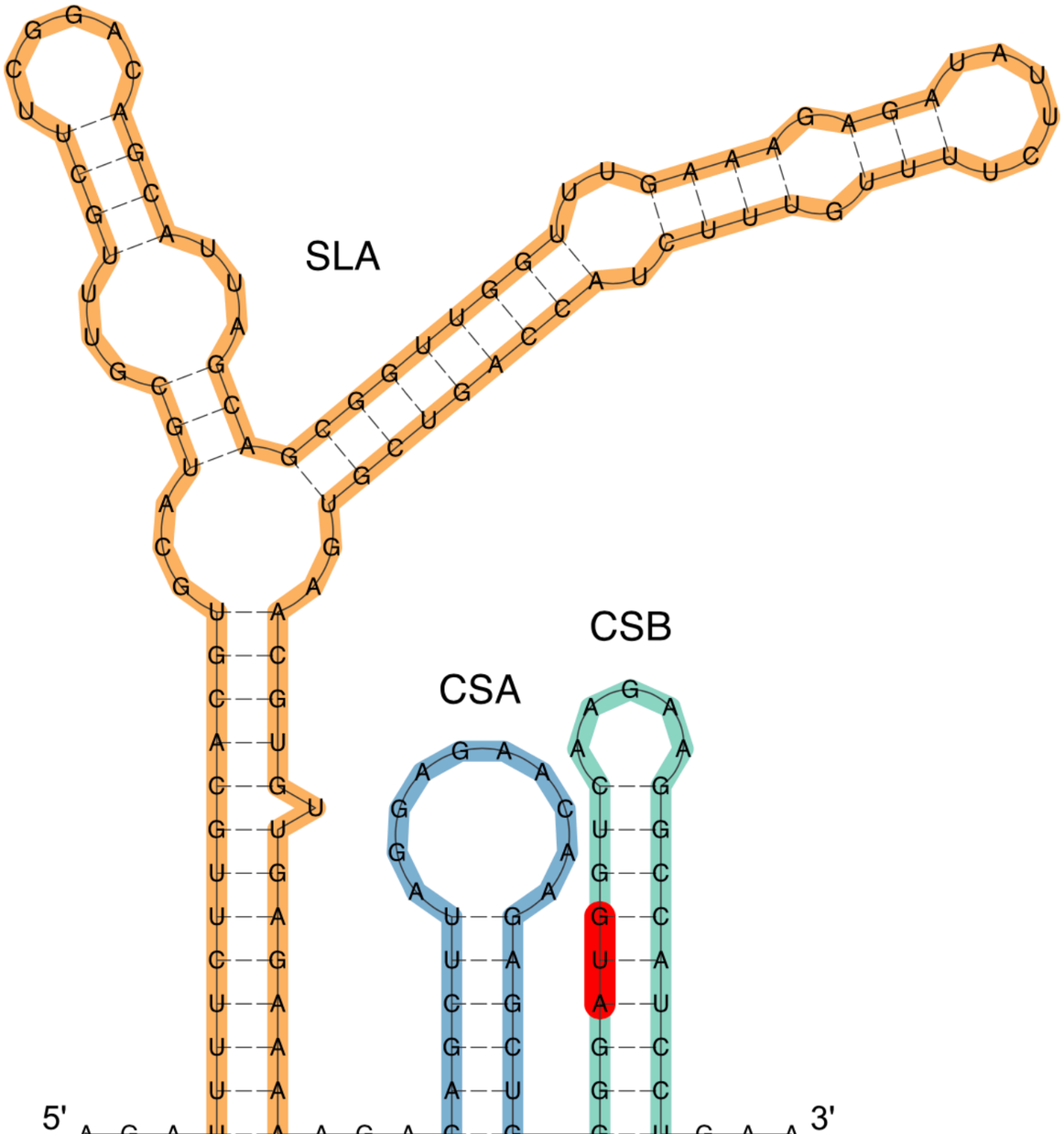

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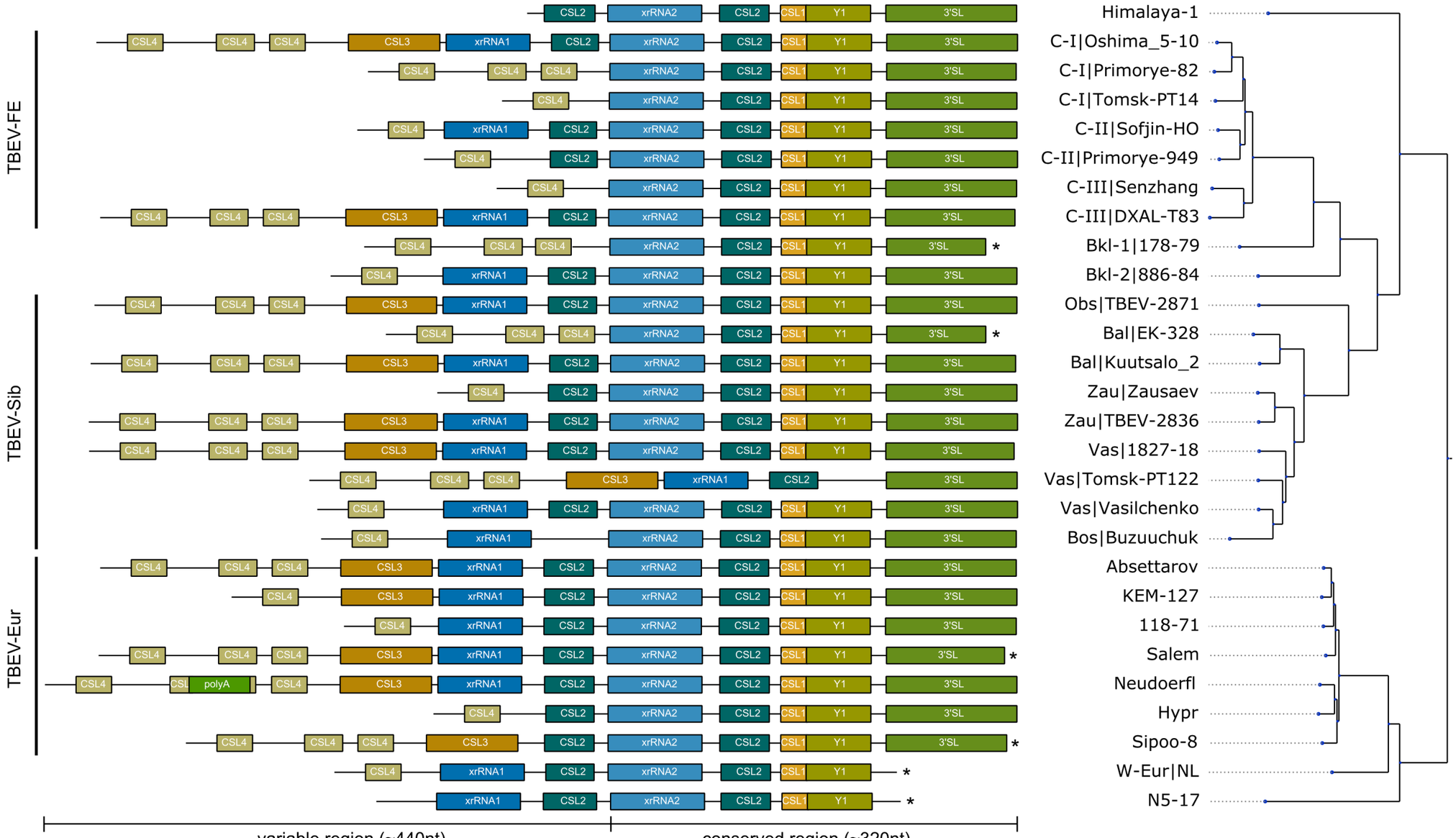

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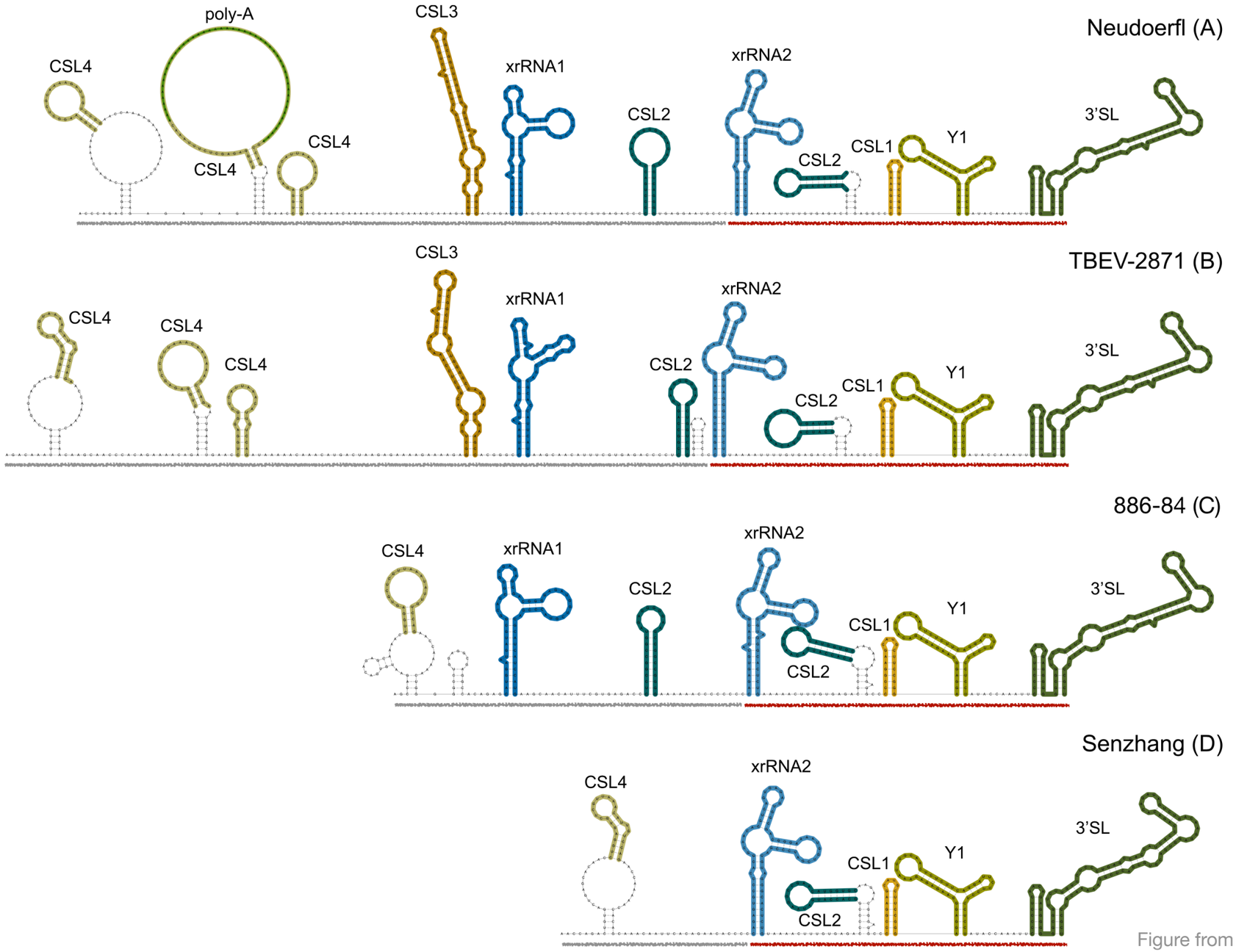

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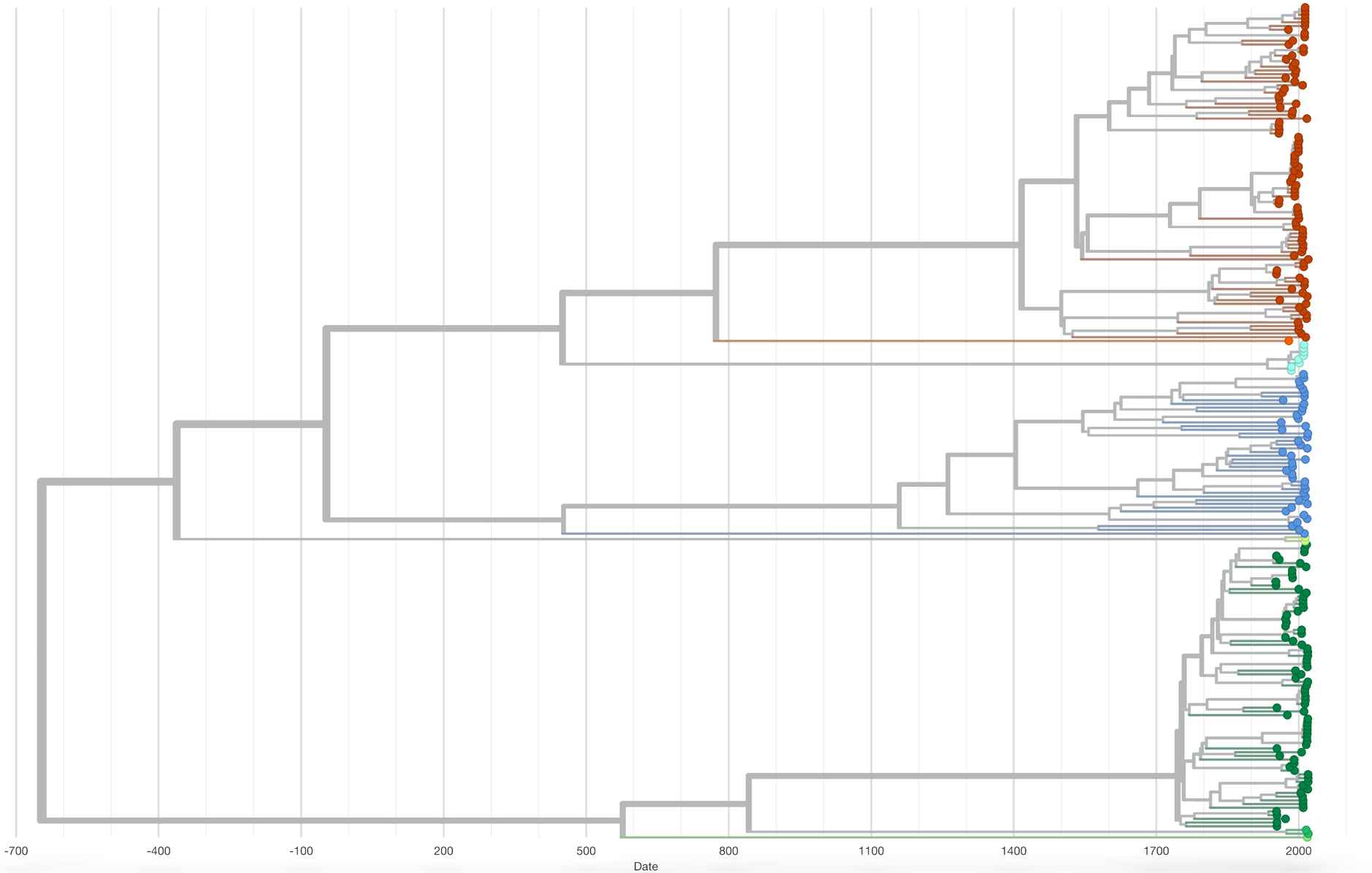

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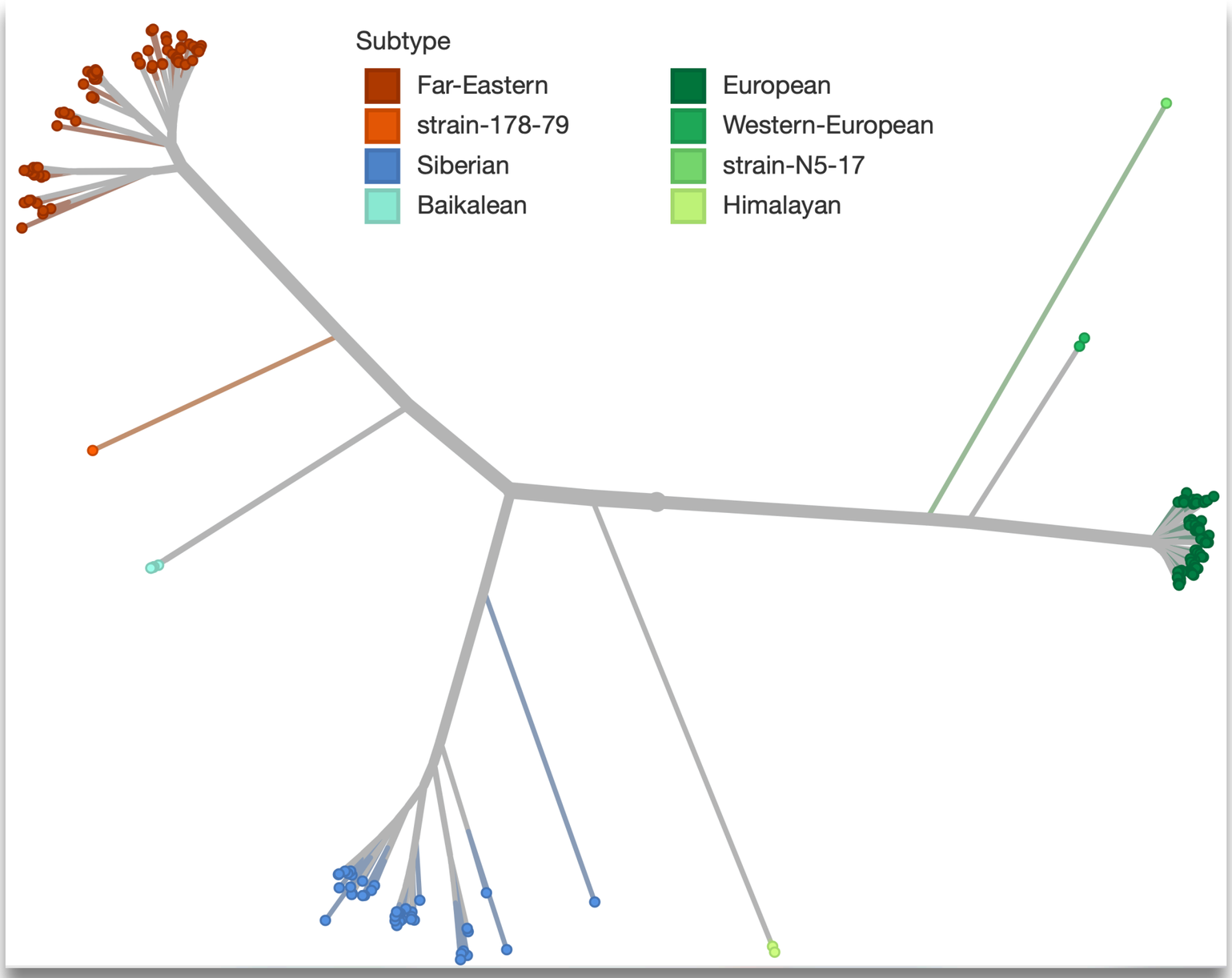

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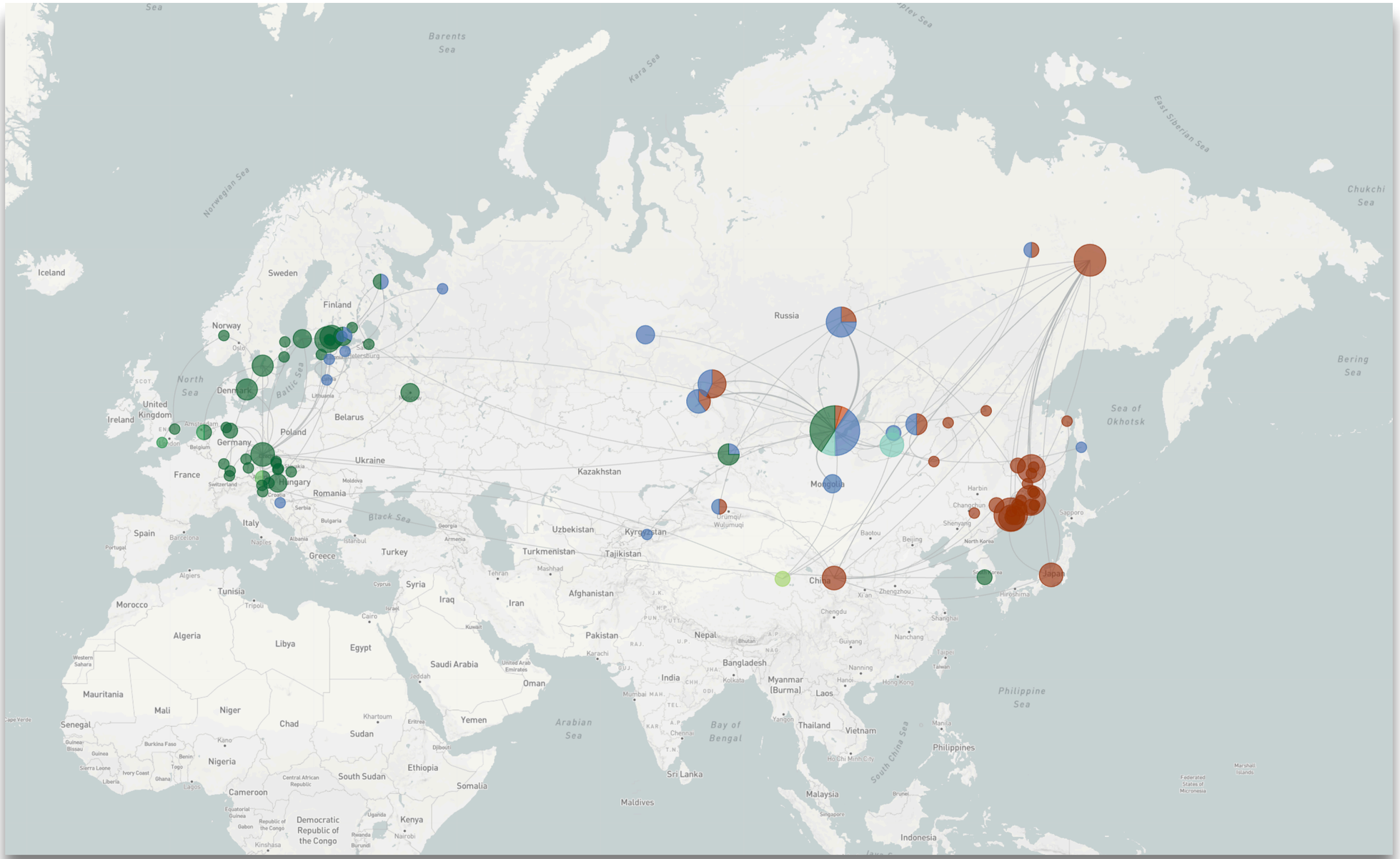

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