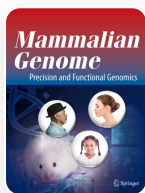


Genomic-microbial coevolution in human development: chromosome 2 fusion, and human accelerated regions

Published: 21 April 2026

Volume 37, article number 59 (2026) [Cite this article](#)



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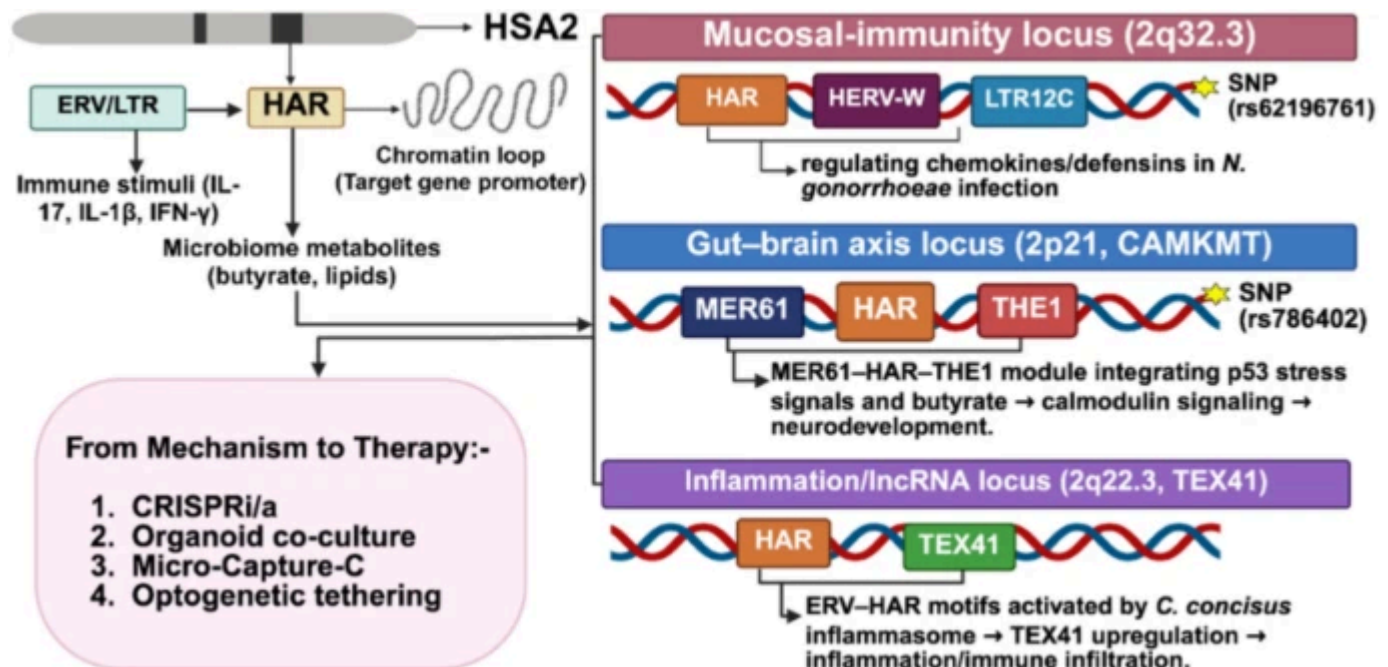
Abstract

Human-specific traits arise from a confluence of genomic and ecological innovations. A unique telomere-to-telomere fusion of ancestral ape chromosomes produced human chromosome 2 (HSA2), reorganizing the genome and its regulatory landscape. In parallel, hundreds of Human Accelerated Regions (HARs), conserved elements with human-specific sequence changes, became developmental enhancers, and ancient retroviral insertions, namely, endogenous retroviruses (ERVs), were co-opted into promoters and enhancers. Here, we integrate comparative genomics, epigenomics, and host-microbiome co-evolution to propose a unified framework linking these factors to human evolution. We posit that the chromosome 2 fusion reshaped 3D genome architecture and gene regulation. HAR and endogenous retroviral sequences formed composite regulatory modules that drove innovations in cortex development, limb patterning, and immune function. Moreover, host-microbiome co-evolution is woven into this framework, with

examples of microbiota-responsive HAR-ERV circuits influencing mucosal immunity, gut-brain signaling, and inflammation.

Graphical abstract

An integrative model from HSA2 fusion to tunable ERV-HAR circuits and microbiome-conditioned outputs. Ideogram of HSA2 marking the fusion junction and conserved TAD scaffold, with local loop retargeting near the break, anchored by the classic hallmarks of the 2q13 telomere-to-telomere fusion and the remnant inactivated centromere framing a substrate for regulatory rewiring. An ERV LTR as a stimulus-responsive input (IFN/ $\text{IL-1}\beta$, SCFAs, lipids), a HAR as a human-specific tuner (amplitude/timing), and a 3D loop to a target promoter. Right, three chr-2 vignettes (2q32.3 mucosal immunity; 2p21 CAMKMT; 2q22.3 TEX41) summarize predicted pathways. Microbial co-diversification and selection pulses motivating Micro-Capture-C/HiChIP enhancer-promoter maps, organoid co-culture challenges, CRISPRi/a and base editing of HAR/LTR motifs, and optogenetic loop tethering (LADL), culminating in a therapeutic dial to modulate inducible ERV-HAR modules in infection and autoimmunity



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Data availability

No datasets were generated or analysed during the current study.

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Acknowledgements

We thank the University Grants Commission (UGC), the Government of India, and the Department of Science and Technology Innovation in Science Pursuit for Inspired Research (DST INSPIRE) for providing financial support in the form of a fellowship to SS, and MS respectively. We acknowledge Anusandhan National Research Foundation (ANRF) for funding through the PAIR scheme (File No: ANRF/PAIR/2025/000018/PAIR-A(G)). PT

is supported by grants from the Italian Ministry of University and Research (PRIN2022) and Lega Italiana per la lotta contro tumori (LILT). The funding bodies do not have a role in study design and manuscript preparation. We appreciate our lab colleagues for their consistent discussions and advice. We acknowledge the Indian Institute of Technology Indore for providing support in the form of facilities.

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Ethics declarations

Competing interests

The authors declare no competing interests.

Additional information

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About this article

Cite this article

Singh, S., Shahadab, M., Sachin, K. *et al.* Genomic–microbial coevolution in human development: chromosome 2 fusion, and human accelerated regions. *Mamm Genome* **37**, 59 (2026). <https://doi.org/10.1007/s00335-026-10228-1>

Received

14 December 2025

Accepted

06 April 2026

Published

21 April 2026

Version of record

21 April 2026

DOI

<https://doi.org/10.1007/s00335-026-10228-1>

Keywords

[Chromosome-2 \(HSA2\)](#)

[Human accelerated regions \(HARs\)](#)

[Endogenous retroviruses \(ERVs\)](#)

[Host-microbiome co-evolution](#)

[Gut-brain axis](#)