## Population-Scale 3D Genomics of EBV Infection in B Lymphocytes

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## **Background**

Epstein-Barr virus (EBV) is a member of the herpesvirus family, one of the most common human viruses, and the first human oncogenic virus to be discovered. Infecting more than 90% of adults worldwide it establishes a lifelong infection in B lymphocytes and epithelial cells. In most individuals, EBV infection occurs during childhood and remains asymptomatic or causes mild illness. However, when acquired later in life, it can lead to infectious mononucleosis, characterized by fever, sore throat, and lymph node swelling. EBV has a unique ability to persist in the body by alternating between latent and lytic phases, allowing it to evade immune surveillance and remain dormant for years.

Beyond acute infection, EBV plays a significant role in the development of several diseases, including various cancers and autoimmune disorders. It is strongly linked to malignancies such as Burkitt lymphoma, nasopharyngeal carcinoma, and certain types of Hodgkin and non-Hodgkin lymphomas. EBV's contribution to cancer arises from its capacity to drive uncontrolled B cell proliferation, alter immune signaling, and influence epigenetic and transcriptional regulation. The virus has also been implicated in autoimmune diseases such as multiple sclerosis and systemic lupus erythematosus, where chronic immune activation and molecular mimicry may play a role.

The outcome and severity of EBV infection can vary considerably among populations due to genetic, environmental, and mmunological factors. For example, nasopharyngeal carcinoma is endemic in Southeast Asia, while Burkitt lymphoma is most prevalent in sub-Saharan Africa, often coexisting with malaria infection. These differences suggest that host genetics, co-infections, and regional environmental influences shape the immune response to EBV and modulate disease risk. Understanding these population-specific patterns is crucial for developing tailored prevention and treatment strategies for EBV-associated diseases.

## Using a multi-omics framework, we examine populationspecific responses to EBV infection across 24 populations:

Multi-omics data from lymphoblastoid cell lines (LCLs) generated by the Human

Pangenome Reference Consortium (HPRC), the 1000 Genomes Project Gambian in Western Division - Mandinka (GWD)

(GEUVADIS), and the ENCODE project, along with additional individual studies, are being integrated to investigate EBV-related immune regulation. In total, we are combining over 2,100 datasets, including Hi-C, RNA-seq, 5' CAGE, and ATAC-seq, to examine population-specific mechanisms underlying EBV response and latency control.

AITICAN ANDESTRY IN SOURIWES LOSA (NSBY) COMMINION IN Nigeria (ESN)

Luhya in Webuye, Kenya (LWK)

Mende in Sierra Leone (MSL)

Yoruba in Ibadan, Nigeria (YRI)

Colombian in Medellin, Colombia (CLM)

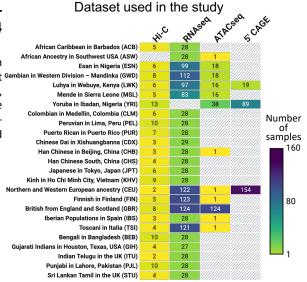
Peruvian in Lima, Peru (PEL)

Puerto Rican in Puerto Rico (PUR)

Chinese Dai in Xishuangbanna (CDX)

Han Chinese Dai in Xishuangbanna (CDX)





The site of EBV-human chromatin interactions are conserved within population but varies among

population

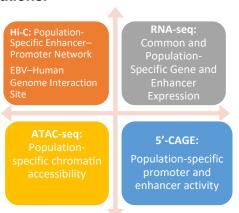
EBV-human chromatin interaction map in LCLs. Plot shows interactions between the Epstein-Barr virus genome and human chromosomes with line thickness proportional to the supporting population count

Fraction of individuals with interaction

0 0.25 0.5 0.75 1

0 0125	0.5 0.75
GO term	FDR
Embryonic Skeletal System Development (GO:0048706)	2.5E-04
Embryonic Skeletal System Morphogenesis (GO:0048704)	1.7E-03
Positive Regulation of Neuron Differentiation (GO:0045666)	3.7E-03
Embryonic Organ Morphogenesis (GO:0048562)	3.7E-03
Chordate Embryonic Development (GO:0043009)	1.3E-02
Enteroendocrine Cell Differentiation (GO:0035883)	1.5E-02
B Cell Activation (GO:0042113)	3.9E-02
Skeletal System Morphogenesis (GO:0048705)	3.9E-02
B Cell Differentiation (GO:0030183)	6.2E-02

A consolidated dataset providing a comprehensive resource for studying EBV infection dynamics across diverse populations.



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