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RES-231

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Impact of Epstein–Barr virus Genomic Alterations in Human Diseases and Oncogenesis

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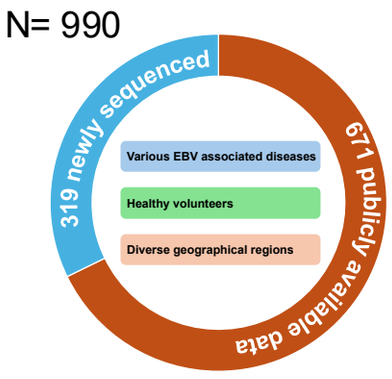
Background

- Epstein–Barr virus (EBV) infects over 90% of the global population and is implicated in a broad range of human pathologies, ranging from benign to various malignancies.
- Although its oncogenic potential is well established, the biological significance of EBV genomic alterations, particularly structural variants and mutations involved in immune evasion, remain still unclear.
- To address this, we comprehensively characterize EBV genomic variations across multiple disease contexts and evaluate their functional significance in oncogenesis.

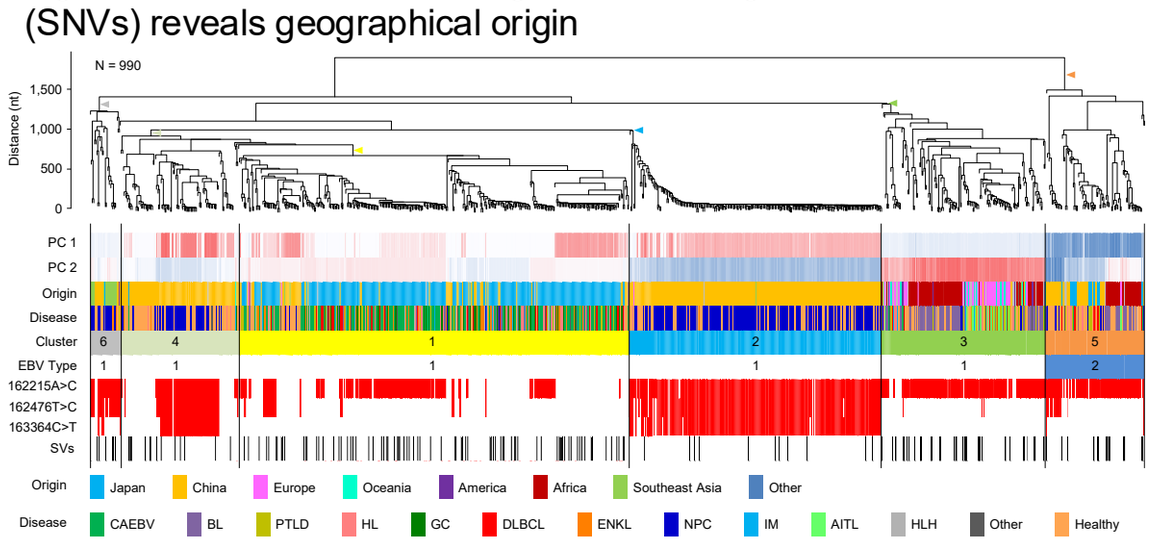
Methods



- Comprehensively analyzed 990 samples, consisting of 319 newly sequenced and 671 public data
- Target capture-based whole-genome sequencing was performed using custom baits for major EBV strains

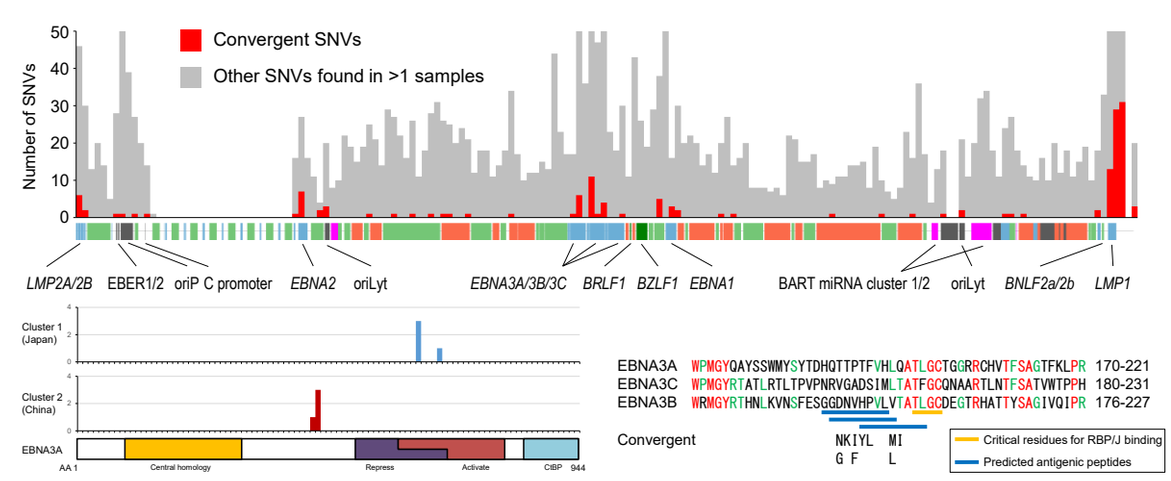
Results

Figure 1. Hierarchical clustering based on single nucleotide variations (SNVs) reveals geographical origin



- Hierarchical clustering of EBV genomes revealed six SNV-based clusters mainly defined by geographical origins.
- Clusters 1, 2, 4, 6: Predominantly from Asia.
- Cluster 3: Largely from Africa, Europe, and the Americas.
- Clusters 2 & 4: Included endemic NPC patients and healthy volunteers, linked to NPC-related SNVs.

Figure 2. Convergent mutations and immune pressure on *EBNA3B* epitope



- Convergent mutations are frequent in *EBNA2, EBNA3B, and LMP1*, reflecting immune-mediated selective pressure.
- A novel *EBNA3B* epitope (aa 198–206) was identified as a recurrent hotspot in Japanese samples, with strong binding to HLA-B*35:01, one of the most common HLAs in the Japanese population.
- Findings suggest host-specific immune selection shaping EBV evolution.

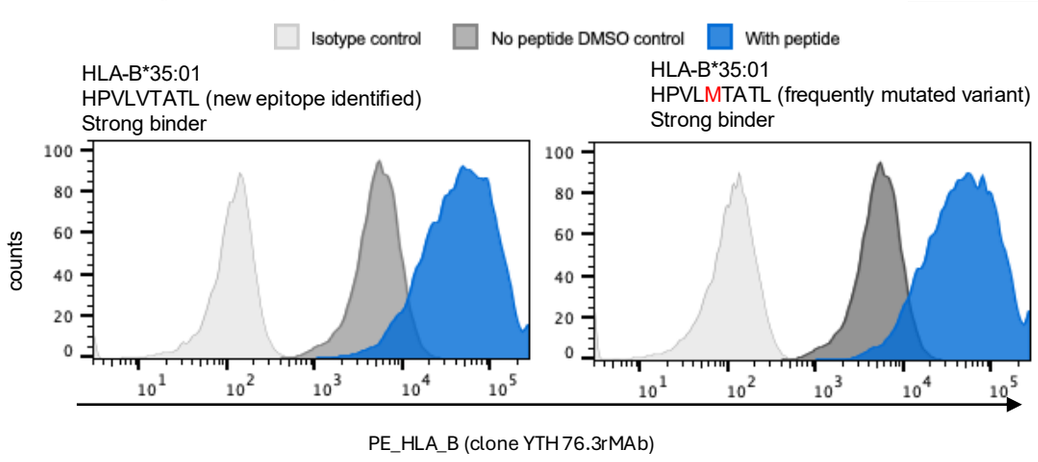
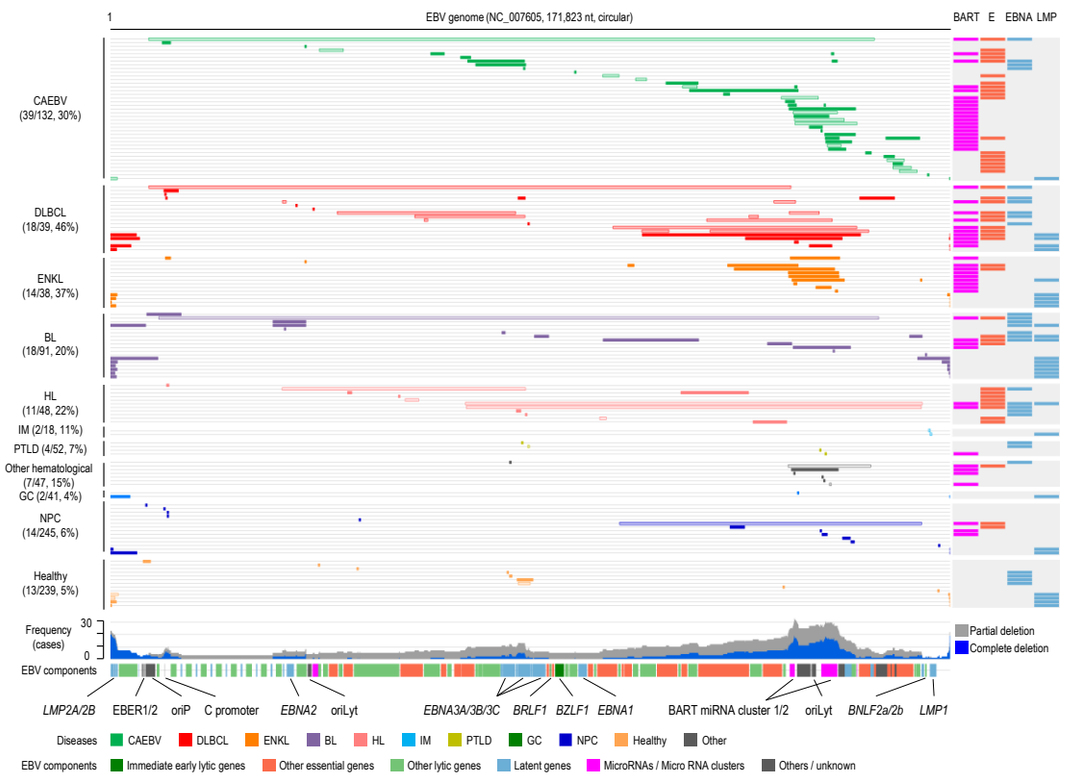


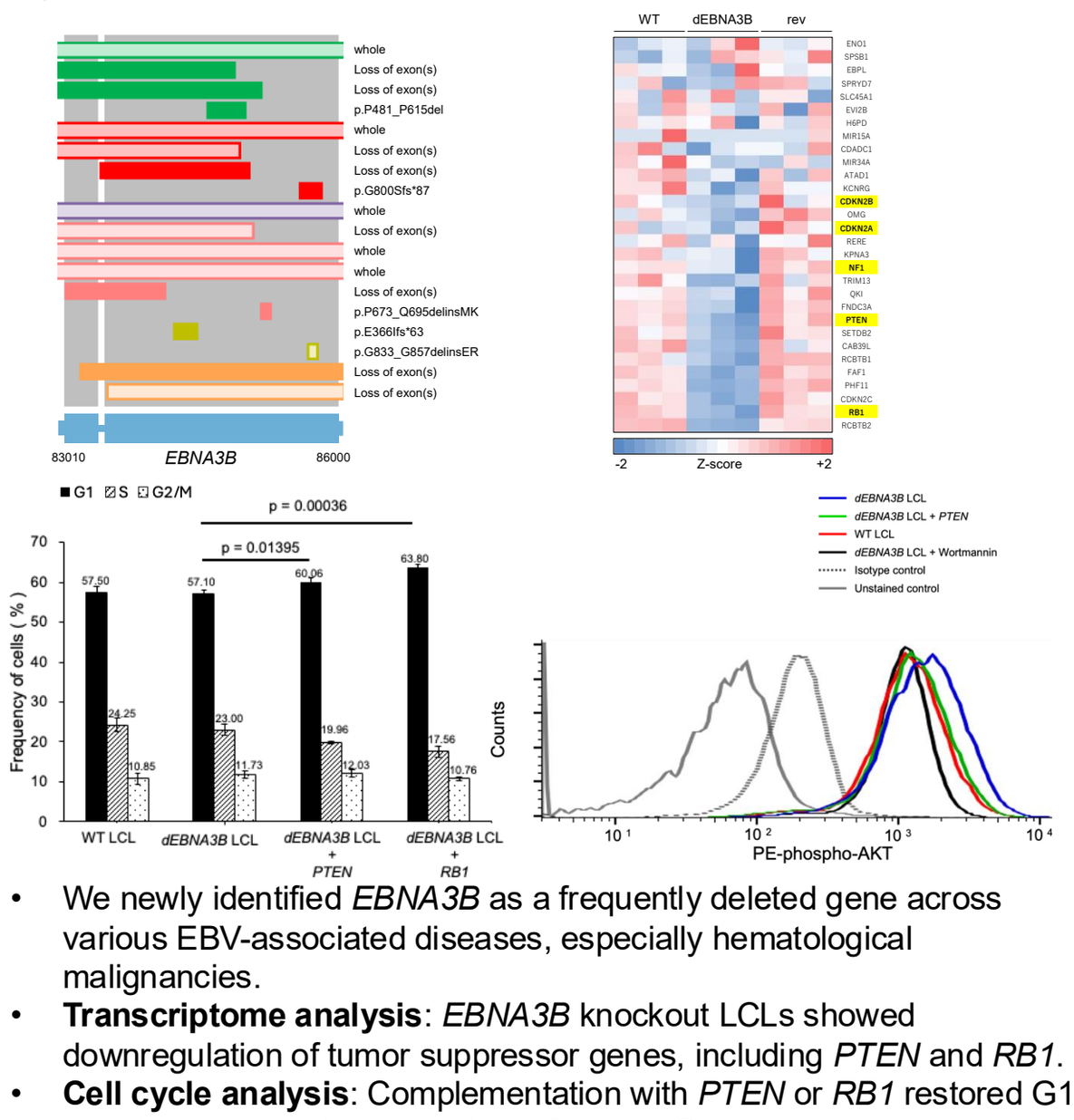
Figure 3. Intragenic deletions across various diseases



CAEBV = Chronic active EBV infection
PTLD= Post-transplant lymphoprolifirative disorder
DLBCL= Diffuse Large B cell lymphoma
GC= Gastric carcinoma.
ENKL= extranodal NK/T-cell lymphoma.
NPC= Nasopharyngeal carcinoma.
BL= Burkitt lymphoma
HL= Hodgkin's lymphoma

- Comprehensive overview of intragenic deletions (>50 bases) identified across diverse diseases.
- Frequent deletion in **CAEBV & hematological malignancies** (22–47%).
- Less common in **PTLD, IM, epithelial tumors (GC, NPC), and healthy controls** (4–11%).
- Most recurrently affected region: ***BART* miRNA clusters (1/2)**

Figure 4. EBNA3B deletion and tumor suppressor function



- We newly identified *EBNA3B* as a frequently deleted gene across various EBV-associated diseases, especially hematological malignancies.
- **Transcriptome analysis**: *EBNA3B* knockout LCLs showed downregulation of tumor suppressor genes, including *PTEN* and *RB1*.
- **Cell cycle analysis**: Complementation with *PTEN* or *RB1* restored G1 arrest, increasing the proportion of cells in G1 phase and slowing proliferation - a hallmark of tumor suppressor activity, since it prevents uncontrolled cell cycle progression.
- **Phospho-AKT assays**: Loss of *EBNA3B* led to higher AKT activation; rescue with *PTEN* or PI3K inhibitor (Wortmannin) reduced phosphorylation, confirming pathway specificity.
- Collectively, these findings establish *EBNA3B* as a viral tumor suppressor.

Conclusions

- Our study reveals EBV genomic alterations reflect immune pressure and disease context.
- A novel EBNA3B epitope highlights immune-driven evolution, while deletions support its tumor suppressive and therapeutic relevance.

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