Supplementary Figure S1. A3s are upregulated in EBV(+) NPC cell lines
RNA-seq data was downloaded from GSE54159 (1), and the RPKM values of APOBEC3B, 3F, 3H, were extracted. (1) Szeto CY, Lin CH, Choi SC, et al. Integrated mRNA and microRNA transcriptome sequencing characterizes sequence variants and mRNA-microRNA regulatory network in nasopharyngeal carcinoma model systems. FEBS Open Bio 2014; 4: 128-140.

Supplementary Figure S2. A3H haplotype of AdAH cells
The sequence of A3H gene, corresponding to amino acid residue 15, 18, 105, 121, and 178 are indicated.
Supplementary Figure S3.
A3s expression in influenza A virus-challenged, IRF7-deficient PBMC
Expression values of APOBEC3F, 3G, and 3B were extracted from GSE66486 (2).
(2) Ciancanelli MJ, Huang SX, Luthra P, et al. Infectious disease. Life-threatening influenza and impaired interferon amplification in human IRF7 deficiency. Science. 2015; 348: 448-53.
Supplementary Figure S5. 3D-PCR analysis of AdAH-LMP1 transductant for a nuclear gene, PIK3CA, and a mitochondrial ND2.

Total DNA from AdAH cells retrovirally transduced with neomycin resistant genes or LMP1, were subjected to 3D-PCR analysis targeting PIK3CA or ND2, as in Fig. 2. No CT indicates the lowest denaturation temperature at which the target sequence is amplified from the control plasmid containing no C-to-T mutation (4).

(4) Wakae K, Nishiyama T, Kondo S, et al. Keratinocyte differentiation induces APOBEC3A, 3B, and mitochondrial DNA hypermutation. Sci Rep. 2018; 8: 9745.

Supplementary Figure S4.
TES2 domain of LMP1 induces A3B expression, via NF-kB

Microarray data was downloaded from GSE29297 (3), and the expression levels of APOBEC3B, 3F, and 3G were extracted. The result is shown by the fold induction over 0hr.

(3) Gewurz BE, Mar JC, Padi M, et al. Canonical NF-kappaB activation is essential for Epstein-Barr virus latent membrane protein 1 TES2/CTAR2 gene regulation. J Virol. 2011; 85: 6764-73.
Supplementary Figure S6. 3D-PCR analysis of NPC specimens

(A) Total DNA from NPC tissues was subjected to 3D-PCR analysis targeting a host gene TP53, and a mitochondrial gene COI. For reference, the lowest temperature at which the gene was amplified from each control plasmid was indicated as dot lines (2). (B, C) The COI amplicons from a denaturing temperature of 84.5 °C or lower were sequenced (B), and the dinucleotide preference of G-to-A mutations was summarized (C). (D) Correlation between LMP1, histology, and COI hypermutation. (*P<0.05)
**Supplementary Figure S7.**
* LMP1 induces A3B expression in an EBV-replicating 293 cells

293-EBV cells (5) were transfected with pcDNA wildtype or dominant-negative(DN) LMP1, and were subjected to (A) Western blotting analysis, (B) RT-qPCR analysis, and (C) 3D-PCR analysis targeting COI. As for RT-qPCR, the mRNA level was quantified by the $2^{\Delta\Delta CT}$ method, and normalized by HPRT.

(5) Delecluse HJ, Hilsendegen T, Pich D, Zeidler R, Hammerschmidt W. Propagation and recovery of intact, infectious Epstein-Barr virus from prokaryotic to human cells. Proc Natl Acad Sci U S A. 1998; 95: 8245-50.

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**Supplementary Figure S8.**
* Colony formation assay and migration assay of A3B overexpressing AdAH cells

AdAH cells were transfected with a CRISPR activation plasmid for A3B, (A,B) A3B overexpression was validated by RT-qPCR (A) and Western blotting analysis (B). (C) 3D-PCR analysis targeting COI. (D, E) Colony assay and migration assay. As for RT-qPCR, the mRNA level was quantified by the $2^{\Delta\Delta CT}$ method, and normalized by HPRT.
Supplementary Figure S9. The hypothesis of accumulating host gene mutation, induced by LMP1-APOBEC axis.
### Supplementary Table S1: Primers used in this study

| Primer Name | Assay          | Figures                                      | Target Genes         | Orientation | Sequence                                                                 | Reference                                      |
|-------------|----------------|----------------------------------------------|----------------------|-------------|--------------------------------------------------------------------------|-----------------------------------------------|
| COI, outer  | 3D-PCR         | Figs. 2 and 3, and Supplementary Fig. S3     | COI, outer           | F           | GCCGTGGACTATTCTCTACAACACACAAA                                              | this study                                    |
|             |                |                                              |                      | R           | GGAGGGTTATATTGAGATAGGGTGTGAGAAA                                            |                                               |
| COI, inner  |                |                                              | COI, inner           | F           | GTATACGCTACAGCCATGATGTTGTTA                                               |                                               |
|             |                |                                              |                      | R           | GAGGAGACACTCGTGAGTGAAGGTGA                                                |                                               |
| ND2, outer  |                |                                              | ND2, outer           | F           | ATAGCAGTTCTACCAGACAAACCCTAACACAAA                                          |                                               |
|             |                |                                              |                      | R           | GGAGGATAGGAATAGGCTGAATGGCTGAATGA                                         |                                               |
| ND2, inner  |                |                                              | ND2, inner           | F           | ACCGCAATCTCAGCTACTGAGTTAAA                                                 |                                               |
|             |                |                                              |                      | R           | GGGAGTGAATAAGGTATCTGAGACGCTAGGCTGAA                                       |                                               |
| TP53, outer |                |                                              | TP53, outer          | F           | GAGTGCAACTTAAGCTTCCAAGAAAGGACAAA                                         |                                               |
|             |                |                                              |                      | R           | GCTGGTGTGTGGCCAGTCTAGGGA                                                   |                                               |
| TP53, inner |                |                                              | TP53, inner          | F           | TTTCTTTTCTTCTTCCTGAGTGTTAAA                                                |                                               |
|             |                |                                              |                      | R           | AAGGTTGATAAAAAGGTATCTGAGCTAGGCTAA                                         |                                               |
| PK3CA, outer|                |                                              | PK3CA, outer         | F           | GGTTCTTTCTTCCTGCAGTT                                                     |                                               |
|             |                |                                              |                      | R           | GTGCCAATCACCACATGTA                                                       |                                               |
| PK3CA, inner|                |                                              | PK3CA, inner         | F           | GCTTTTTCTGTGAAATCTGCTG                                                    |                                               |
|             |                |                                              |                      | R           | GCTGAGATCAGCCAAATTGAGTT                                                    |                                               |
| A3A         | RT-qPCR        | Fig.1, Fig. S4                               | A3A, A3A             | F           | AATGCCATTTGAAAGGCAATA                                                     |                                               |
|             |                |                                              |                      | R           | CAAAGAGAAGGCAAGAGGCTCA                                                    |                                               |
| A3B         |                |                                              | A3B, A3B             | F           | TTTGAGGCGAGGTATTTCA                                                       |                                               |
|             |                |                                              |                      | R           | CAGAGATGCTGAGGTCAGCA                                                      |                                               |
| A3C         |                |                                              | A3C, A3C             | F           | CAACGATCGAAGCAAGAAGT                                                      |                                               |
|             |                |                                              |                      | R           | TATGTCGTCAGAAGAAGC                                                        |                                               |
| A3D         |                |                                              | A3D, A3D             | F           | ACCGCAATCTCAGCTGAATC                                                     |                                               |
|             |                |                                              |                      | R           | GCTGACCGAAATTTGGA                                                        |                                               |
| A3F         |                |                                              | A3F, A3F             | F           | GAAACAGAGCAAGCCAGGCT                                                       |                                               |
|             |                |                                              |                      | R           | GAAATGGGCCCTTGATGAAGA                                                     |                                               |
| A3G         |                |                                              | A3G, A3G             | F           | GCTGAGGAGACGCAGACGTA                                                     |                                               |
|             |                |                                              |                      | R           | GAGAGAAGCCAGACGCTG                                                       |                                               |
| A3H         |                |                                              | A3H, A3H             | F           | CCCGCCTGACTACACATG                                                       |                                               |
|             |                |                                              |                      | R           | GGTTGGAAGAAAAGGCGGG                                                       |                                               |
| HPRT1       |                |                                              | HPRT1, HPRT1         | F           | GCTCTGCTGAGTATTAGT                                                        |                                               |
|             |                |                                              |                      | R           | CGAGCAAGACGTCTGATGTA                                                      |                                               |
| A2          |                |                                              | A2, A2               | F           | CACAGGCCTCAGCTGAA                                                        |                                               |
|             |                |                                              |                      | R           | AAGCGGCTGGATGCTG                                                          |                                               |
| LMP1        |                |                                              | LMP1, LMP1           | F           | CCCTTTGTATACCTCTGAGTACGCA                                                 |                                               |
|             |                |                                              |                      | R           | ACCCGAGAGATAGAAAGCCAGCAAG                                                  |                                               |
| A15 and 18  | A3H haplotyping| Supplementary Fig. S2                        | A15 and 18           | F           | GCTGACTCTCAGAGACGCTCCTCTCTCTTT                                              |                                               |
|             |                |                                              |                      | R           | CGTCGCGAAGAGAGGCTGAGTGTGGS                                               |                                               |
| A105 and 121|                |                                              | A105 and 121         | F           | AATCGAGACCTCAGCCAGGCGCTGCTCTG                                              |                                               |
|             |                |                                              |                      | R           | TGGGAGCCATGACCTCACCAGGG                                                  |                                               |
| A178        |                |                                              | A178, A178           | F           | CTGCTGAGACACTGAGCTGCTGCCC                                                  |                                               |
|             |                |                                              |                      | R           | GCAGTGCGGAGAGGTGAAGTGTGAGCTGGT                                             |                                               |
### Supplementary Table S2: Antibodies used in this study

| assay | Figures | target | origin | reference |
|-------|---------|--------|--------|-----------|
| WB    | Figs.1 and 3 | A3B | serum from a rabbit immunized with A3AB peptide, CDEHSQALSGRLRLAQNLQGN | Kondo et al. Oncogene 2017  
Wakae et al. Sci Rep. 2018 |
|       |         | A3D | sigma, HPA055116 | |
|       |         | A3F | serum from a rabbit immunized with A3F peptide, CFVYNDEPFKPKWKLKYN | Seishima et al. Sci. Rep. 2018 |
|       |         | A3G | serum from a rabbit immunized with A3G peptide, CQDLSGRLRLAQNLQEN | Kitamura et al. Plos Pathogens 2013  
Wang et al. J. Virol. 2014  
Seishima et al. Sci. Rep. 2018 |
|       |         | A3H | sigma, HPA021492 | Seishima et al. Sci. Rep. 2018 |
|       |         | LMP1 | abcam, ab78113 | |
|       |         | HA | invivogen, #ab-hatag | |
|       |         | FLAG | Sigma, F3165 | |
|       |         | GAPDH | Sigma Aldrich, G9545 | |
| IHC   | Figs.1 and 4 | LMP1 | Dako, M0897 | |
|       |         | A3B | Abcam, ab184990 | Kondo et al. Oncogene 2017  
Seishima et al. Sci. Rep. 2018 |
|       |         | A3F | abnova, H00200316-A01 | |
|       |         | A3G | serum from a rabbit immunized with A3G peptide, CQDLSGRLRLAQNLQEN | |