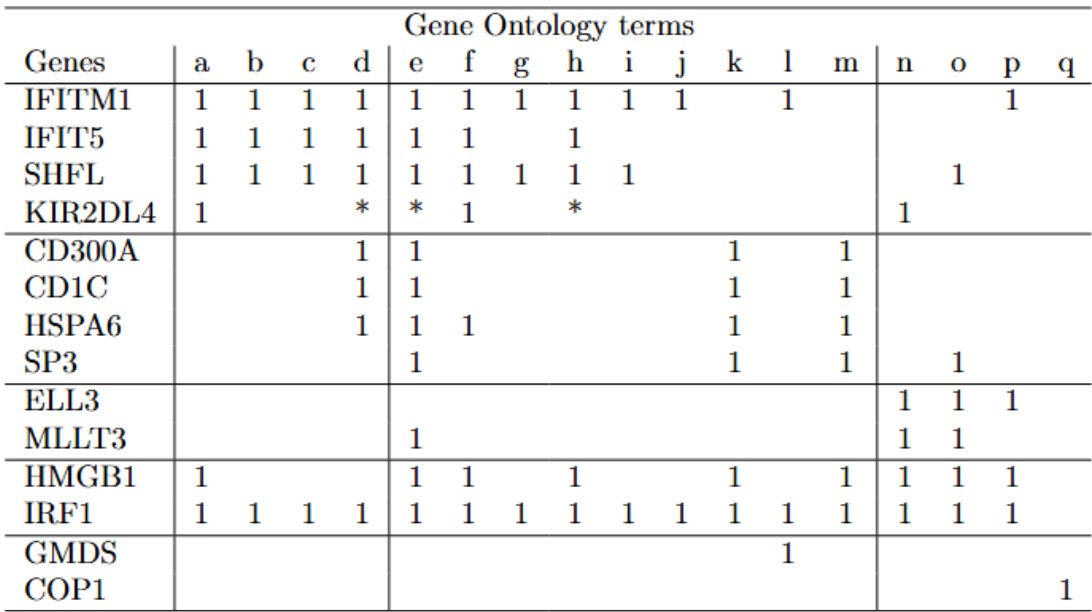
## **Supplementary Materials**

# Supplementary Tables

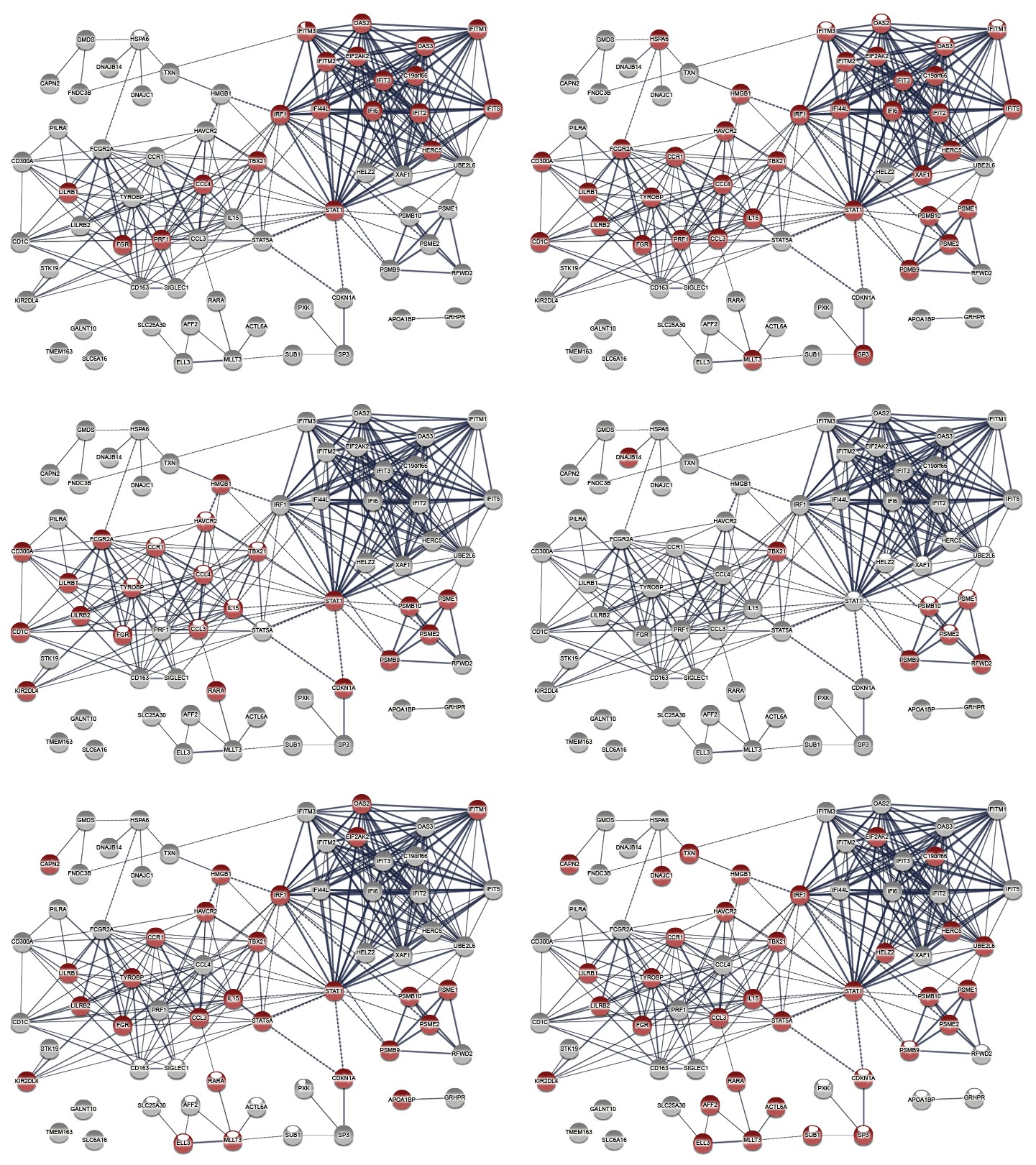
**Table S1**: Markers identified by three feature selection methods (RAFS, Boruta, and MDFS).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Gene | Marker | In RAFS | In Boruta | In MDFS |
| IFIT5 | 203595\_s\_at | 0 | 1 | 1 |
| 203596\_s\_at | 1 | 1 | 1 |
| IFITM1 | 201601\_x\_at | 1 | 1 | 1 |
| 214022\_s\_at | 1 | 1 | 1 |
| CD300A | 209933\_s\_at | 1 | 1 | 1 |
| 217078\_s\_at | 0 | 1 | 1 |
| CD1C | 205987\_at | 1 | 1 | 1 |
| SP3\* | 213168\_at | 1 | 1 | 1 |
| 229217\_at | 0 | 0 | ? |
| 232709\_at | 0 | 0 | ? |
| 238035\_at | 0 | 0 | ? |
| SLC6A16 | 219820\_at | 1 | 1 | 1 |
| HSPA6 | 117\_at | 1 | 1 | 1 |
| HSPA7 | 213418\_at | 0 | 1 | 1 |
| KIR2DL4 | 211245\_x\_at | 1 | 1 | 1 |
| 208426\_x\_at | 0 | 1 | 1 |
| 211242\_x\_at | 0 | 1 | 1 |
| GRHPR | 201347\_x\_at | 1 | 1 | 1 |
| 214864\_s\_at | 1 | 1 | 1 |
| 216308\_x\_at | 1 | 1 | 1 |
| TMEM163 | 1552626\_a\_at | 1 | 1 | 1 |
| 223503\_at | 0 | 1 | 1 |
| COP1\* | 1552617\_a\_at | 1 | 0 | 1 |
| 234950\_s\_at | 0 | 0 | ? |
| SHFL | 1555491\_a\_at | 1 | 1 | 1 |
| 218429\_s\_at | 0 | 1 | 1 |
| 53720\_at | 0 | 1 | 1 |
| MLLT3 | 1569652\_at | 1 | 1 | 1 |
| 204918\_s\_at | 1 | 1 | 1 |
| 204917\_s\_at | 0 | 1 | 1 |
| IRF1-AS1 | 1564276\_at | 1 | 1 | 1 |
| 230405\_at | 0 | 1 | 1 |
| 232253\_at | 0 | 1 | 1 |
| HMGB1 | 200679\_x\_at | 0 | 0 | ? |
| 200680\_x\_at | 0 | 0 | ? |
| 214938\_x\_at | 0 | 0 | ? |
| 224731\_at | 0 | 1 | 1 |
| 224734\_at | 1 | 1 | 1 |
| ELL3 | 219517\_at | 1 | 1 | 1 |
|  | 219518\_s\_at | 0 | 1 | 1 |
| GMDS | 204875\_s\_at | 1 | 1 | 1 |
|  | 214106\_s\_at | 1 | 1 | 1 |
| GALNT10 | 207357\_s\_at | 0 | 1 | 1 |
| 212256\_at | 0 | 1 | 1 |
| 230906\_at | 0 | 0 | ? |
|  | 235292\_at |  | 1 | 1 |
|  | 220879\_at |  | 1 | 1 |

**Table S3**. Selected Gene Ontology terms and their associations with seed proteins in the columns.For each Gene Ontology (GO) term, the number of proteins in the network associated with that term and statistical significance levels is shown using the following scheme: \*\*\*\*\*p *<* 10−15, \*\*\*\*p *<* 10−12, \*\*\*p *<* 10−9, \*\*p *<* 10−6, \*p *<* 10−3. a: GO:0006952 – defense response, 34∗∗∗∗∗; b: GO:0009615 – response to virus, 21∗∗∗∗∗; c: GO:0051607 – defense response to virus, 18∗∗∗∗∗; d: GO:0006955 – immune response, 34∗∗∗∗∗; e: GO:0002376 – immune system process, 40∗∗∗∗; f: GO:0006950 – response to stress, 45∗∗∗∗; g: GO:0034340 – response to type I interferon, 12∗∗∗∗; h: GO:0045087 – innate immune response, 23∗∗∗∗; i: GO:0034097 – response to cytokine, 27∗∗∗∗; j: GO:0019221 – cytokine-mediated signaling pathway, 22∗∗∗∗; k: GO:0060337 – type I interferon signaling pathway, 11∗∗∗; l: GO:0007166 – cell surface receptor signaling pathway, 29∗∗∗; m: GO:0045321 – leukocyte activation, 17∗∗; n: GO:0050793 – regulation of developmental processes, 28∗∗; o: GO:0010468 – regulation of gene expression, 35∗; p: GO:0045595 – regulation of cell differentiation, 20∗; q: GO:0043161 – proteasome-mediated ubiquitin-dependent protein catabolic process, 7 *<* 0*.*01. Associations identified by STRING are denoted by 1, associations inferred from analysis of the literature are denoted by \*.

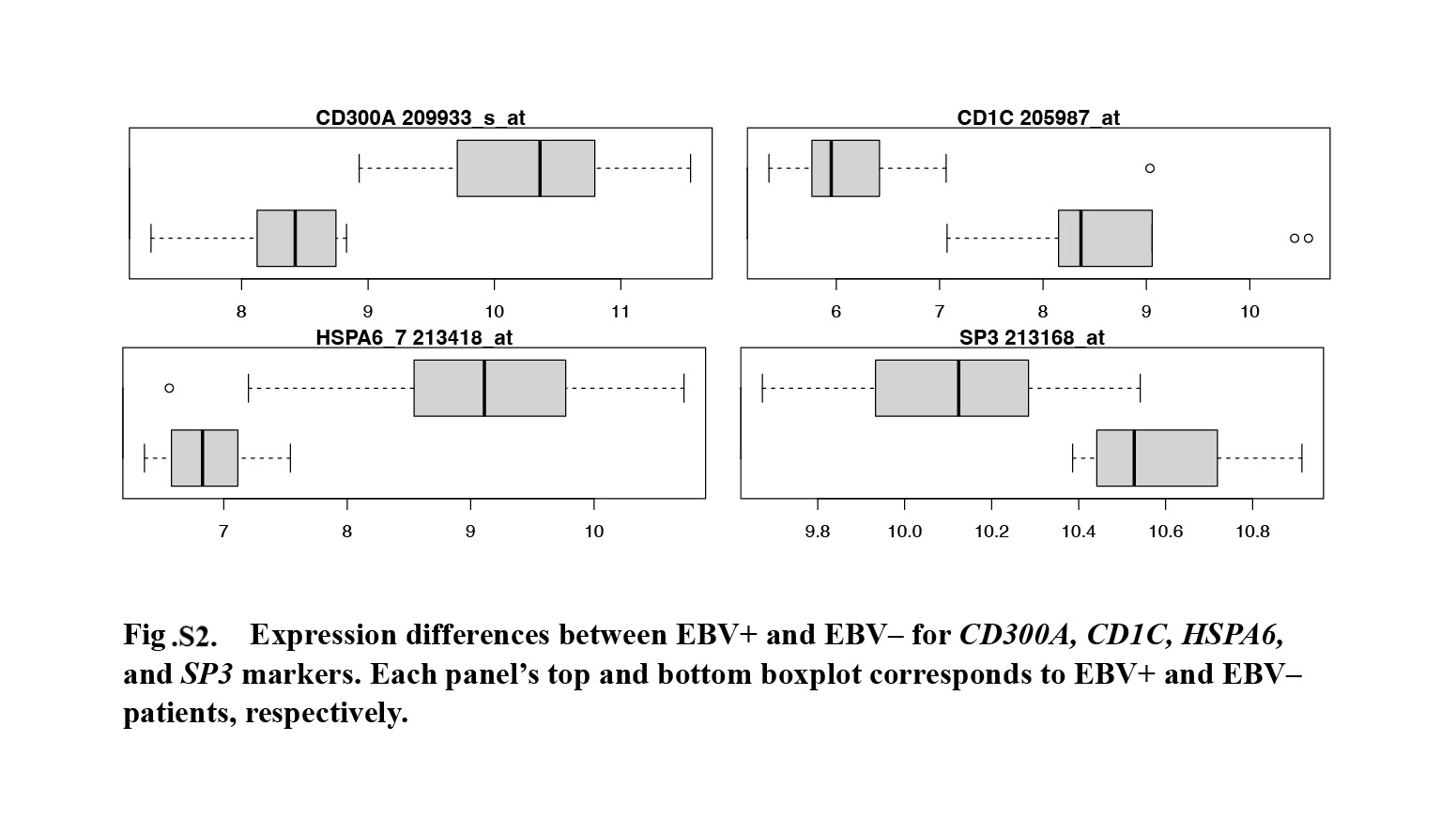
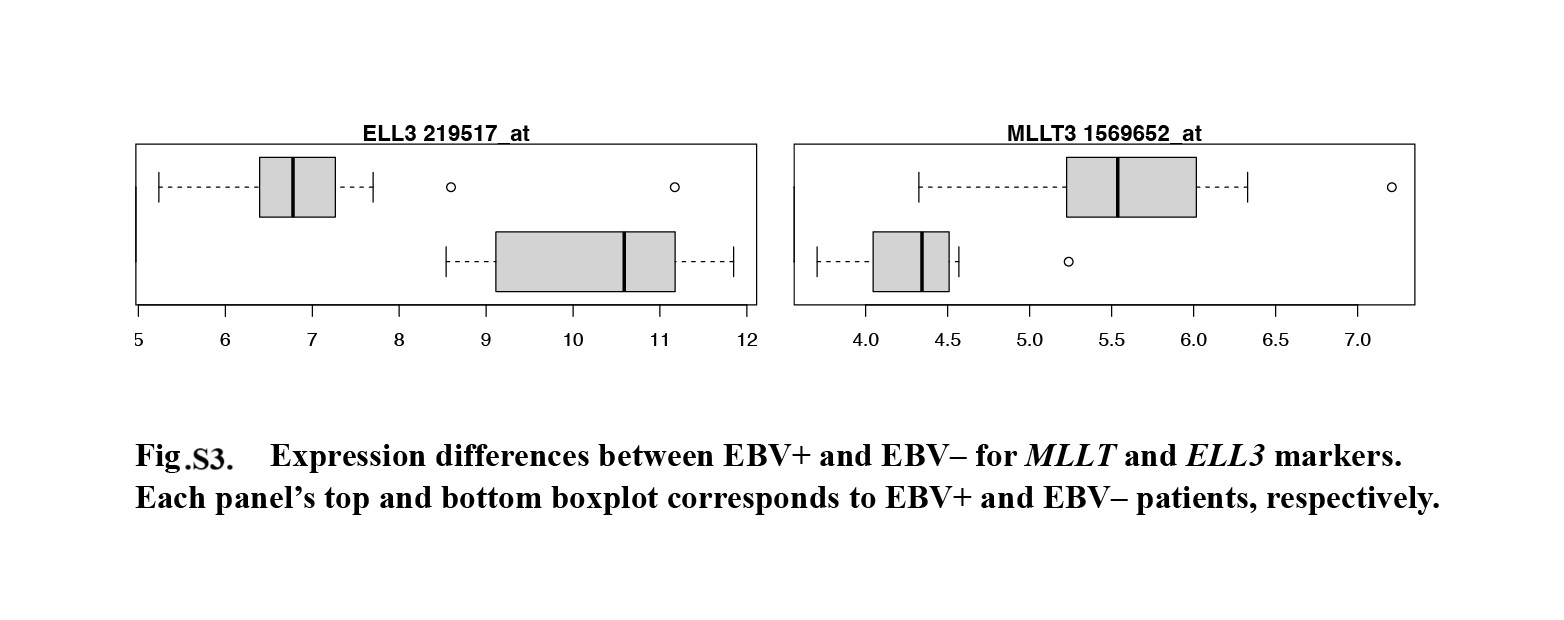
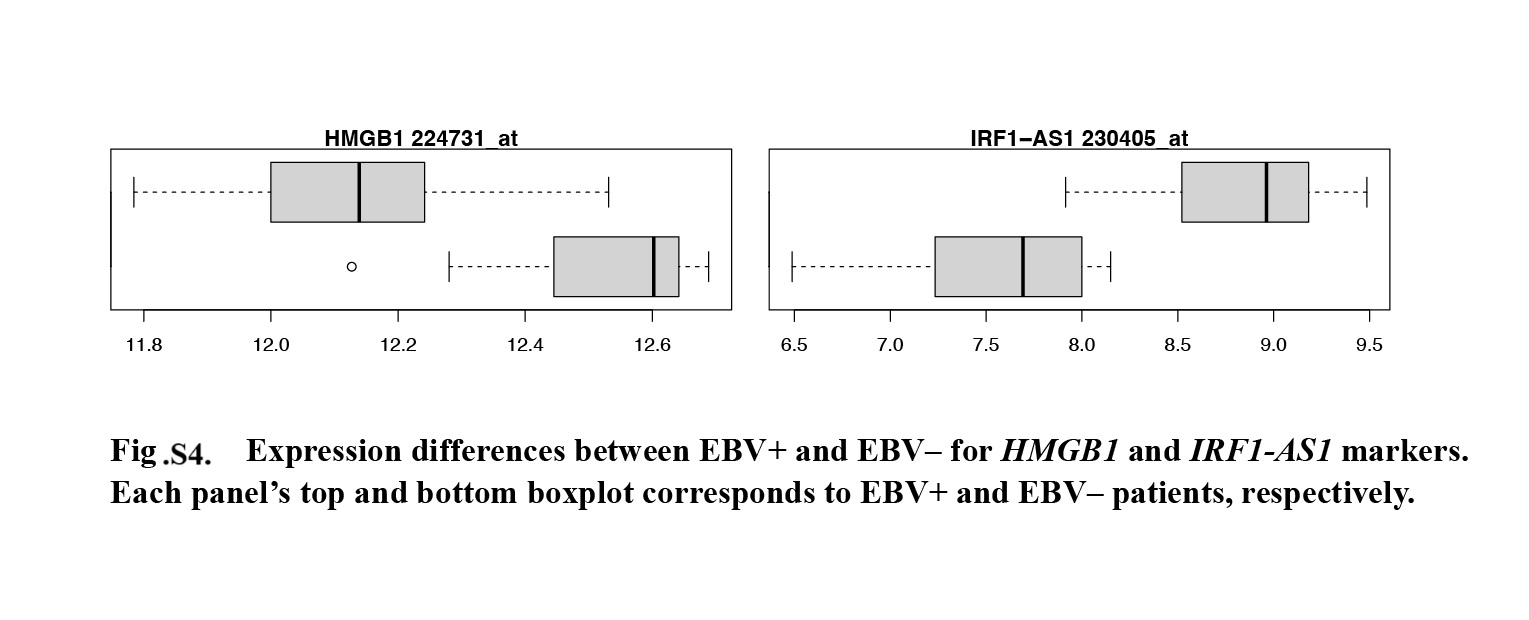


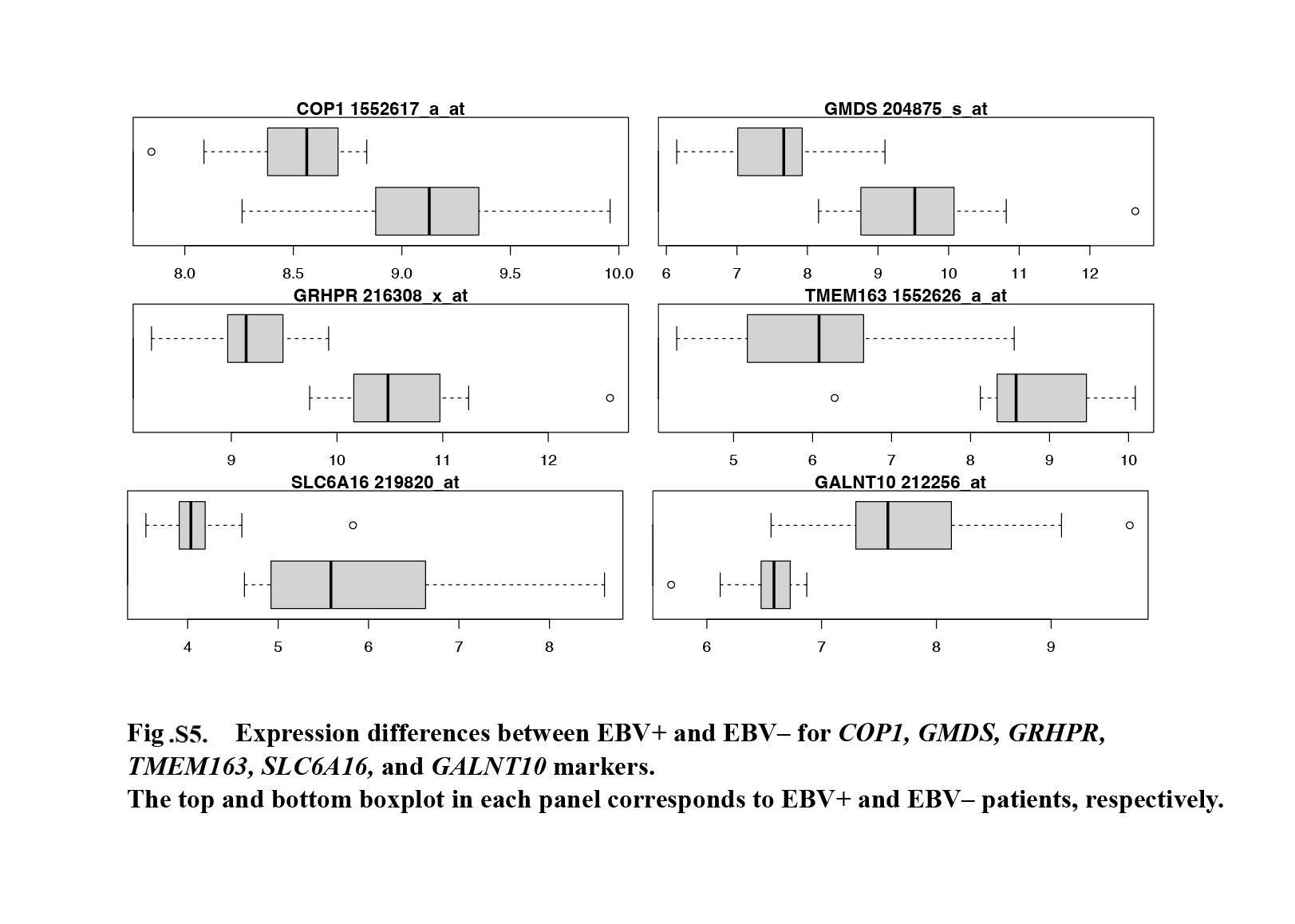
# Supplementary Figures



**Fig.S1.** Prominent Gene Ontology terms from the biological process hierarchy: top left – GO:0009615 (response to virus); top right – GO:0006955 (immune response); middle left GO:0002684 (positive regulation of the immune system process); middle right GO:0043161 – proteasome-mediated ubiquitin-dependent protein catabolic process; bottom left – GO:0050793 (regulation of developmental processes); bottom right – GO:0010468 (regulation of gene expression).





# Clusters of functionally related genes

Four clusters of genes differentially associated with the EBV status of PTLD patients were identified. The first cluster included genes, *IFITM1*, *SHFL*, *IFIT5*, and *KIR2DL4*. IFN-stimulated proteins such as *IFITM1* and *SHFL* exhibit antiviral activity (Smith et al., 2019). *IFITM1* may inhibit viral entry into the host cell cytoplasm (Narayana et al.,2015). *SHFL* can restrict expression of viral genes (Kinast et al. 2020; Rodriguez et al., 2019). The *IFIT5* mediates PPIs andcan modulate nuclear factor kappa B signaling (Zheng et al., 2015). The *KIR2DL4* plays important roles in the functional regulation of natural killer cells (Ding et al., 2022). The relationship of cluster #1 genes to immune responses could have been expected given our comparison of EBV+ and EBV– samples. However, three genes in this group, *IFIT5*, *IFITM1*,and *KIR2DL4*,are also associated with malignancy. The *IFITM1* is an oncogene involved in various cancers (Yu et al., 2011; Sari et al., 2011; Liu et al., 2019; Yan et al., 2019; Hatano et al.,2008; Chu et al., 2022). The *IFITM1* promotes tumor cell proliferation, inhibits cell death, and stimulates invasion and metastasis (Min et al., 2020). The *IFIT5* promotes the progression of renal, prostate, and bladder cancers (Liang et al.,2020; Lo et al., 2019, Huang et al., 2019). Due to the association with human papilloma virus oncogene E6, *IFIT5* may also be involved in the progression of oral squamous cell carcinoma (Pidugu et al., 2019). Another gene from the first cluster, *KIR2DL4*,is correlated with poor prognosis in non-small cell lung cancer (NSCLC) and with renal cell carcinoma development (Liang et al., 2020; He et al., 2016)

The second cluster included genes *CD300A*, *CD1C*, *HSPA6*,and *SP3*. The *CD300A* gene is a transmembrane glycoprotein in leukocytes that plays important roles in regulating their activation, proliferation, differentiation, and migration (Cao et al., 2021). High *CD300A* expression is associated with suppression of glioblastoma, NSCLC, and breast cancer (Du et al., 2018; Tang et al., 2018; Chen et al.,2023; Xu et al., 2023) and predicts poor survival in patients with acute myeloid leukemia (Xu et al.,2023). The *CD1C* is structurally related to class I major histocompatibility complex molecules but presents lipid and glycolipid antigens to T cells (Layre et al., 2014). The *CD1C* is a marker in cervical cancer (Uhlen et al., 2017)and cervical squamous cell carcinoma (Liu et al., 2020), and plays an antitumor role in NSCLS (Lu et al., 2019). The *HSPA6* is a heat shock protein family member involved in cell cycle regulation, hormone induction, and housekeeping (Song et al.2022; Hartl et al., 1996). The *HSPA6* upregulation after treatment of bladder and colorectal cancers correlates with tumor suppression (Safe et al., 2023). However, HSPA6 is a risk factor for early hepatocellular carcinoma recurrence and is related to its invasiveness and prognosis (Hedrick et al., 2016). The *SP3* is a transcription factor overexpressed in multiple tumors and is a negative prognostic factor for patient survival (Mansour et al., 2021).

The third cluster included genes *ELL3* and *MLLT3*. The *ELL3* plays an essential role in activating developmentally regulated genes by priming them to recruit the proper transcription initiation complex during cell differentiation (Lee et al., 2019). Interestingly, it both regulates and is regulated by p53protein, which is a key tumor suppressor (Kabra et al. 2022). The *MLLT3* regulates human hematopoietic stem cell self-renewal and engraftment (Kang et al.,2013).

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