

Transcriptome-wide analysis of circRNA and RBP profiles and their molecular and clinical relevance for GBM

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ABSTRACT

Glioblastoma (GBM) is the most aggressive and lethal type of glioma, characterized by aberrant expression of non-coding RNAs including circular RNAs (circRNAs). They might impact cellular processes by interacting with other molecules – like microRNAs or RNA-binding proteins (RBPs). The diagnostic value of circRNAs and circRNAs/RBPs complexes is still largely unknown. To explore circRNAs and RBPs transcripts expression in GBM, we performed and further analyzed RNA-seq data from GBM patients' primary and recurrent tumor samples. We identified circRNAs differentially expressed in primary tumors, the circRNA progression markers in recurrent GBM samples as well as the expression profile of RBP transcripts. Subsequent analysis allowed us to generate a comprehensive catalog of circRNA-RBP interactions regarding both the RBPs sequestration by circRNA as well as the RBPs involvement in circRNA biogenesis. Furthermore, we demonstrated the clinical potential of circRNAs and RBPs in GBM and proposed them as the stratification markers in the de novo assembled tumor subtypes. Therefore, our transcriptome-wide study specified circRNA-RBP interactions that could play a significant regulatory role in gliomagenesis and GBM progression.

Keywords: circRNA/GBM/RBP/RNA-seq

1. Introduction

Gliomas are brain neoplasms originating from the glia and constitute the majority of all primary tumors in the central nervous system. They are classified into four grade groups, based on histological, genetic, and prognostic features. Low-grade gliomas (I and II grades) exhibit minor metastasis and recurrence potential, while high-grade gliomas (III and IV grades) present significant recurrence and progression prognosis [1]. Glioblastoma (GBM) - an IV-grade glioma is the most lethal, aggressive, and malignant among brain tumors in adults, with a median survival of 14.6 months post-treatment [2]. Current therapies, which are not curative, include radiotherapy and temozolomide-based chemotherapy [3]. Due to the lack of effective treatments, high internal molecular heterogeneity among GBM tissues, and high rate of recurrence, there is an urgent need to better understand the molecular basis of GBM and improve patient stratification, defining signatures useful as potential diagnostic and prognostic markers and most importantly to identify new therapeutic targets.

The most common molecular stratification parameter of GBM is the presence of mutations in isocitrate dehydrogenase - *IDH1* and *IDH2* genes. These mutations are most frequent in secondary GBM and predict a favorable disease outcome with prolonged median survival [4, 5]. An additional molecular classification of GBM comprises of 4 submolecular groups: proneural, classical, mesenchymal, and neural which are distinguished by specific gene expression patterns, mutations and associated with different tumor aggressiveness and prognosis for treatment response [6].

In recent years, non-coding RNAs (ncRNAs) and particularly circular RNAs (circRNAs) have gained attention as key players in cancer and potential therapeutic targets. CircRNAs are single-stranded RNA molecules produced by “back-splicing”, which joins a downstream 5' donor splice site and an upstream 3' acceptor splice site [7]. Due to their intrinsic resistance to exonuclease cleavage, circRNAs have a longer half-life in comparison to their linear counterparts making them promising cancer biomarkers [8-15].

Recent studies have highlighted the role of RNA binding proteins (RBPs) in the biogenesis and maintenance of circRNAs, influencing the transcriptome's molecular balance [16, 17]. CircRNAs can act also as miRNA and RBPs sponges potentially impacting gene expression and cellular pathways significantly [12, 18-24]. The interactions between circRNAs and RBPs rely on binding motifs and contextual features, such as secondary structure, flanking

nucleotide composition, or short non-sequential motifs [25]. Apart from the RBPs binding motifs, the biogenesis of circRNAs can be also facilitated by the presence of the complementary sequences in both flanking regions, like *Alu* elements [26]. Understanding nature and function of such interactions is crucial for understanding GBM, including tumor biology, progression, treatment response and survival rates [27-29].

In this study, we provide the comprehensive atlas of circRNAs and RBP transcripts differentially expressed in GBM. By utilizing deep total RNA-sequencing (RNA-seq) we established the expression profile of circRNAs and extensively studied their interaction with RBPs, including the potential impact on circRNA formation. First, we identified the differentially expressed circRNA in primary GBM patients' samples (GBM-PRM) as well as in the recurrent GBM samples (GBM-REC). We further experimentally validated the expression of selected circRNAs, their unique back-splice junction sequences and structures. Finally, based on the same dataset we have identified the profiles of RBPs transcripts expression in GBM. The study of circRNA and RBPs transcripts highlighted the potential binding sites within circRNAs and the RBPs possibly involved in circRNA biogenesis. Further analysis correlated circRNA and RBP expression with established GBM subtypes, leading to a new subtype classification that enhances patient stratification and identification of prognostic markers. Our global analysis pointed circRNAs significantly deregulated in GBM, offering new insights into potential diagnostic and therapeutic targets.

2. Results

2.1 circRNAs and RBPs transcripts are differentially expressed in GBM

2.1.1. Expression profile of circRNA in GBM

To define circRNA and RBPs mRNA expression profiles in primary (GBM-PRM, n=23) and recurrent GBM (GBM-REC, n=3) (Suppl. Tab. 1) in comparison to the healthy brain control (HB, n=52) (Suppl. Tab. 2), RNA sequencing was performed. Transcriptome sequencing approach was designed to simultaneously profile both circRNA and messenger RNA transcripts. We identified a total number of 29,141 circRNAs in all samples (Fig.1A) including more than 7,600 not previously annotated. The majority of identified circRNA were derived from exons (Suppl. Fig. 1A) and their length was similar among all analyzed samples with the median equal: 740, 631 and 555 nucleotides for HB, GBM-PRM and GBM-REC, respectively (Suppl. Fig. 1B-3D). The circRNA transcripts were distributed within all human chromosomes, including the chromosomes 1 and 2 particularly enriched in circRNAs (Suppl. Fig. 2). CircRNA expression profiles showed clear discrimination between GBM-PRM, GBM-REC and HB samples (Suppl. Fig. 3). The differential circRNA expression (DCE) analysis revealed 1270 circRNAs expressed between GBM-PRM and HB tissues with a log2 fold change in the range between -5.6 and 8.9 (adjusted p-value <0.05) where 1132 of circRNAs were downregulated and only 138 were upregulated (Fig. 1C). To search for circRNAs potentially involved in GBM progression we performed further DCE analysis between GBM-PRM and GBM-REC where we detected 3 differentially expressed circRNAs which were subsequently validated (Fig. 1D). To determine relationship between deregulated circRNAs and their linear counterparts we calculated the circular-to-linear ratio (CLR) based on the formula $[\text{circ} / (\text{circ} + \text{lin})]$. A CLR value >0.5 indicates that the number of circular RNA molecules is higher than the corresponding mRNA, while a CLR value <0.5 indicates the opposite. Interestingly, the obtained results showed that in the most cases the number of circRNAs was higher than that the number of their parental linear counterparts

(CLR>0.5). Moreover, both circular and linear molecules were frequently upregulated, indicating a positive correlation between their expression levels (Fig. 1E, upper right quadrant of the figure).

To have a better insight into the role of differentially expressed circRNAs, we performed Gene Set Enrichment Analysis (GSEA) on their linear counterparts. The analysis revealed 22 GO terms with negative enrichment scores with most of them related to the neurotransmitter secretion, transport and regulation of their levels, signal release from synapse or ion transport. Although no enriched KEGG terms were found below adjusted p-value threshold (0.05), it is worth to note, that without multiple test correction among 13 enriched KEGG terms like ‘Neuroactive ligand-receptor interaction’, ‘Synaptic vesicle cycle’ and ‘Glutamatergic synapse’ were identified with negative enrichment scores (Suppl. Fig. 4).

Obtained results thus clearly indicate global deregulation of circRNAs in GBM, which may suggest their role in processes related to the development of this tumor type.

2.1.2. Expression profile of RBPs transcript in GBM

As mentioned previously, RBPs play a pivotal role in circRNA biogenesis, thus they might be involved in regulating the balance between the expression of circRNAs and their linear counterparts. Therefore, we performed the analysis of the expression profile of RBP transcripts based on RNA-seq obtained from the same data set. We have identified 1420 RBP transcripts in HB, 1436 in GBM-PRM, and 1430 in GBM-REC samples (Fig. 1F). Differential gene expression (DGE) analysis of RBPs transcripts resulted in the finding that 817 from 1542 known human RBPs [30] are characterized by the significantly altered expression in GBM-PRM (469 up- and 348 downregulated) with a log2 fold change in the range between -4.8 and 4.7 (Fig. 1G, Suppl. Fig. 5).

2.2 Characteristics and validation of circRNAs dysregulated in GBM-PRM and GBM-REC

The DCE analysis revealed a list of differentially expressed circRNA among GBM-PRM and HB samples and indicated their possible involvement in processes related to GBM development. The potential progression markers were additionally identified by the comparative expression analysis between GBM-PRM and GBM-REC samples. 11 circRNAs were selected for further validation based on the list of mostly downregulated and upregulated molecules in GBM.

Based on the analysis of GBM-PRM versus HB control, we selected 4 downregulated circRNAs (circCADPS2, circEPB41L5, circUNC13C and circUSP45) and 4 upregulated ones (circARID1A, circGUSBP1, circPLOC2 and circVCAN). The DCE analysis between GBM-REC and GBM-PRM allowed us to distinguish 3 circRNAs specifically upregulated in recurrent samples: circEGFR, and 2 new, not previously annotated, circRNAs coming from *HLA-B* gene, and intergenic circRNA originating from chromosome 6p22.1 named for convenience as circInter6p22 (Suppl. Tab. 3).

Further comparison of circular to linear read ratio of selected circRNAs based on RNA-seq data, showed that in almost all cases the circular transcript is less abundant than the linear form in GBM, with the exception of VCAN circRNA transcript more expressed than its linear counterpart. Interestingly, we also perceived that the relation between circular and linear transcripts might differ between HB and GBM. For instance, circEPB41L5 is more abundant than its parental transcript in healthy brain, but this interplay is reversed in GBM where the linear form is more abundantly expressed (Fig. 2A-2B).

In order to confirm the circular structure of the identified molecules, the RNase R treatment was performed (Suppl. Fig. 6). The obtained data clearly support the RNase R resistance and high RNA stability of the verified circRNA molecules. Subsequently, we used the same 8 GBM-PRM samples that were utilized in RNA-seq, to validate the RNA-seq results with RT-qPCR. Overall, we confirmed previous results of selected upregulated and downregulated circRNAs. Regarding downregulated circRNAs, we observed simultaneous downregulation of their linear transcripts with one exception – circEPB41L5 in which the linear form was upregulated in GBM-PRM (Fig. 2C). Among all upregulated candidates VCAN was distinguished as the most upregulated one (Fig. 2D). Regarding circular RNAs upregulated in GBM-REC in comparison to GBM-PRM, we noted the upregulation of circRNAs expression in comparison to their linear counterparts, with a strikingly elevated level of circEGFR reaching ~12000-fold change (Fig. 2E). Comparison of RNA-seq results with RT-qPCR supported obtained data in most cases (Fig. 2H). We also verified the correlation of the expression of circular and linear transcripts in analyzed samples and confirmed the significant positive correlation for UNC13C ($r=0.997$, $p\text{-value}<0.001$), VCAN ($r=0.6957$, $p\text{-value}=0.05533$) in GBM-PRM vs. HB. Regarding circRNAs upregulated in GBM-REC we have also noticed high positive correlation between circular and linear isoforms for EGFR ($r=0.9175$, $p\text{-value}=0.003587$) and HLA-B ($r=0.8896$, $p\text{-value}=0.007315$) (Fig. 2I).

2.3 Interplay between circRNAs and RBPs

It is already known that RBPs regulate circRNAs biogenesis via binding to flanking introns and thus promote back-splicing process. They can also be sequestered by circRNAs acting as molecular sponges making them direct interactors in molecular processes. This interplay could be significant for the function of both circRNAs and RBPs, therefore we aimed to comprehensively investigate the interplay between those molecules [17, 31-34]

2.3.1 RBPs might be sequestered by circRNAs

In the first step, we verified potential probability of circRNAs to sequester RBPs. To examine which differentially expressed RBPs are able to bind to deregulated circRNAs, we calculated k-mers ($k=6$) enrichment in differentially expressed circRNAs in GBM-PRM vs. HB (both up- and downregulated) and compared them to each binding motif's position in RBPs. 6-mers enriched in differentially expressed circRNAs were mapped to the RBPs binding sites determined either by eCLIP or by RNA-bind and RNA-seq data [35]. As a result, we have obtained the list of 38 RBPs differentially expressed in GBM-PRM compared to HB tissue. We observed very distinct sequence patterns for RBP motifs enriched exclusively in downregulated vs upregulated circRNA. Namely, motifs enriched in downregulated circRNA were U-rich, whereas those for upregulated ones contained a lot of G and C nucleotides (Fig. 3, Suppl. Fig. 7). This observation indicated a distinct difference in the recognition sites of upregulated and downregulated circRNAs which might explain the discrimination mechanism between the binding of both types of molecules.

2.3.2 RBPs are correlated with circRNAs and their host gene expression

Next, we calculated correlation coefficients between the expression of previously identified differentially expressed RBPs and deregulated circRNA. We observed that expression levels of some RBPs significantly correlates with the expression levels of several hundred differentially expressed circRNAs (Fig. 4A, Suppl. Fig. 8). The vast majority exhibited a positive correlation, notably, the ELAV and CPEB families, which were downregulated in

GBM (Fig. 4A, marked as red bars). Conversely, ZFP36, RBM47, PTBP1, RBM5S and SF3B4 mostly showed negative correlation with circRNAs (Fig. 4A, marked as green bars). Then, we assessed whether the expression of these RBPs correlates with expression of circRNAs' linear counterparts. For this purpose, we used the subset of circRNAs parental mRNAs and calculated coefficients. Furthermore, we confirmed whether the correlation with RBPs have the same or opposite direction considering simultaneously circRNAs and mRNAs. Most of them showed the same direction of correlation in both circRNAs and corresponding mRNAs (Fig. 4B). Interestingly, RBPs positively correlated with circRNA expression (Fig. 4A marked as red bars) also showed positive correlation with mRNA expression in ~50% of cases. In contrast, RBPs with expression negatively correlated with circRNAs (ZFP36, PTBP1, RBM47, RBMS2 and SF3B4) mostly did not show significant correlation with mRNA expression. Moreover, we investigated which of the deregulated RBPs might be associated with circRNAs subjected to validation. We observed that there are RBPs with altered expression levels which correlates with the expression level of selected circRNAs - regarding upregulated circARID1A and circGUSP1 there were over 20 positively correlated RBPs (Fig. 4C).

2.3.3 RBPs might bind with flanking regions thus impact circRNAs biogenesis

As mentioned before, RBPs are important players in the circRNA biogenesis [17, 33, 34]. To identify the RBPs potentially involved in circRNAs biogenesis, we analyzed RBP 6-mers binding motifs enriched in flanking introns (up to 1000 nt upstream and downstream from the backsplice junction) of differentially expressed circRNAs in GBM vs. HB. We identified 14 differentially expressed RBP genes with binding motifs in the flanking introns across all the analyzed samples (Figure 5A). Correlation analysis between RBPs and circRNAs expression in GBM samples highlighted significant correlation with CPEB3, ELAVL2, ELAVL3, and KHDRBS2 showing a strong positive correlation with both up- and downregulated circRNAs - except one - ELAVL3 which correlated only with downregulated circRNAs. We also noted RBPs with a strong negative correlation with the expression level of upregulated circRNAs like IGF2BP2, and IGF2BP3. In search of potential circularization enhancers, we identified lowly expressed RBPs, which showed positive correlation with downregulated circRNAs (Fig. 5B-5C). CPEB3 was highly correlated with circRLF ($\rho = >0.8$), circLRBA ($\rho = 0.7$) and selected before as one of the most downregulated circRNAs in GBM - circEPB41L5 ($\rho = 0.65$) (Fig. 5B), while KHDRBS2 showed strong positive correlation with circLRBA ($\rho >0.8$) and circVMP1 ($\rho = 0.7$). These findings might indicate RBPs exclusively involved in the regulation of circRNAs biogenesis.

2.3.4 RBPs could both impact circRNAs expression and be sequestered by them

We further investigated whether differentially expressed RBPs could both influence circRNAs biogenesis and be sequestered by the same circRNAs. We found a common set of 10 RBPs: CPEB3, ELAVL2, ELAVL3, KHDRBS2, RBM41, RBM47, RBMS2, SF3B4, TIA1, ZFP36 with motifs enriched in both - flanking introns and total sequence of circRNAs (Fig. 6A, Suppl. Fig. 9). Additionally, we calculated motif frequencies for these RBPs in the 100 nt regions encompassing the junction site (5' boundary and 3' boundary) and we defined intron-exon and exon-intron boundaries (Fig. 6B). For most RBPs, we observe similar motif frequencies in introns, boundaries and circRNA. However, an increased number of binding

sites was observed in the sequence covering the 5' boundary region for the CPEB3 protein. A similar dependence was noted in the case of the SF3B4, which was additionally characterized by an increased frequency of motifs in the 3' boundary of the circRNA (Fig. 6C). Altogether, it suggests that RBPs might play a dual role- both influence circRNAs biogenesis and at the same time be regulated by these molecules.

2.4 Combinatorial analysis of RBPs and circRNAs expression profiles suggest new patient stratification criteria

2.4.1 CircRNA expression is related to the GBM subtypes

We utilized the list of 840 genes from the TCGA GBM dataset and literature [6] as it provides the knowledge for unifying GBM transcriptomic and genomic data allowing for GBM molecular stratification into 4 molecular subtypes: classical, mesenchymal, proneural and neural. The provided framework allowed us to cluster the analyzed 23 GBM study samples into classical (5 samples), mesenchymal (8), neural (5), and proneural (5) (Fig. 7A). Then we determined the presence of different circRNAs in each of the individual molecular subtypes (Fig. 7B). We identified 54 differentially expressed circRNAs in the neural subtype versus other subtypes, where circERC1 and circMLIP were characterized by the highest expression levels (Fig. 7C, Suppl. Tab. 4). The data show the high similarity of the neural subtype to the HB samples. Interestingly, we further distinguished overexpressed circCOL4A1 and circCOL1A2 which were upregulated in the mesenchymal subtype (Suppl. Tab. 5). Moreover, in this subtype, we observed decreased expression of circRBM39 and circRIMS2. Noteworthy, we did not find any circRNAs related exclusively to the classical and proneural subtypes.

2.4.2 RBPs in GBM can be used as the new potential stratification markers

To assess also the clinical value of RBPs in GBM we aimed to identify RBP-based signatures for patient stratification. At first, we subset RBPs able to discretize patients into two clusters according to their expression with no significant association with GBM molecular subtypes. We identified RBPs that cluster GBM samples into two or more groups (Suppl. Tab. 6). Next, we focused on RBPs whose expression in at least one of these newly defined clusters was differentially expressed in comparison to HB samples. We observed a prevalent upregulation of RBPs in the novel subgroups of patients (Fig. 7D). The overall expression of these RBPs was able to separate GBMs from HB samples, with the clusterization of patients in two major newly identified subgroups, independent from the GBM molecular subtypes. We were also looking for RBPs potentially related to the previously mentioned known 4 molecular subtypes and established that there are 41 of them (Suppl. Fig. 5). From these RBPs, we found 7 with motifs enriched in differentially expressed circRNA and/or flanking sequences (CPEB1, CPEB3, ELAVL2, ELAVL3, IGF2BP3, RBM47, RBM6) (Fig. 7E, highlighted in red). RBM47 was highly expressed in mesenchymal, RBM6 in classical, and IGF2BP3 in classical and proneural subtypes (Fig. 7E). Majority (6) of 7 selected RBPs further cluster GBM samples into 2 newly defined groups (Fig. 7F) and ELAVL3 cluster GBM samples into 3 groups (Fig. 7G). Thus, RBPs expression profile might be taken into consideration as an additional factor stratifying individual GBM tumors, which could enrich the current division.

2.4.3 RBPs expression correlates with the overall survival rates of GBM patients

Finally, we checked the differentially expressed RBPs and their correlation with the overall survival rates (OVS) of GBM patients. We utilized available data from TCGA GBM dataset. We selected patients with high or low expression of the given RBPs and found that 30 RBPs differentially expressed in our 23 GBM samples were significantly correlated with OVS in the TCGA GBM cohort (Suppl. Fig. 10A - upregulated RBPs, 10B - downregulated ones). 22 of them were previously shown to be brain tumor markers, correlated with disease outcome or response to the treatment (Suppl. Tab. 7).

3. Discussion and future perspectives

In our study, we conducted an extensive RNA-seq screen focusing on circRNA and RBP expression profiles as well as their interactions. We detected circRNAs differentially expressed in GBM primary tumors, identified the circRNA progression markers in GBM recurrent ones, as well as we established the expression profile of RBP transcripts. Further analysis enabled us to generate a comprehensive catalog of circRNA-RBP interactions including the sequestration of RBPs by circRNA and their involvement in circRNA biogenesis. Additionally, we demonstrated also the clinical potential of circRNAs and RBPs in GBM and identified them as the stratification markers in the *de novo* assembled tumor subtypes.

Given that GBM is an aggressive, therapy-resistant brain tumor with high inter- and intra-tumoral diversity, there is an urgent need to understand the transcriptome profile of this tumor type to find new, distinctive molecular biomarkers and therapeutic targets for GBM. Due to their high stability and brain-specific expression pattern, circRNAs are considered remarkably interesting as potential cancer molecular signatures [36-38]. Additionally, their role in cancer-related processes namely proliferation, migration, invasion, and apoptosis in GBM have already been studied and verified [39]. Most of the studies concerning circRNA in GBM are focused on a single or a few molecules and their specific mechanism of action with only a few studies attended to high-throughput circRNA profiling in GBM [40-43]. One study reported up to now the GBM patients-derived data being however focused on general cancer-related mechanisms. The findings reveal that certain circRNAs are deregulated across multiple types of cancers, including GBM, esophageal squamous cell carcinoma, lung adenocarcinoma, thyroid cancer, colorectal cancer, gastric cancer, and hepatocellular carcinoma. Despite these observations, the study does not solely focus on GBM, nor validates the obtained results. Additionally, it did not provide any description of the complex network of interactions and dependencies between circRNAs, their linear counterparts, and RBPs in glioblastoma [44].

In our study, we identified 1270 circRNAs differentially expressed in GBM-PRM samples compared to HB controls with almost 90% being downregulated. This pattern aligns with previously published circRNA profiles in different cancer types, including GBM, indicating a potential competition in biogenesis between circRNAs and mRNAs utilized for the protein synthesis - essential for proliferating tumor cells [43, 45-48]. Further, common downregulation of circRNAs observed in cancer cells can be caused by their extensive proliferation. This could dilute the concentration of stable circRNAs as previously suggested [45, 49]. It is also supported by the opposite phenomena, namely the accumulation of circRNA in the non-proliferating aging mouse brain, mainly composed of post-mitotic cells [50]. Similar trends can be observed in *D. melanogaster* and *C. elegans* aging models [51, 52]. On the contrary, in T-cell acute lymphoblastic leukemia (T-ALL) the majority of deregulated circRNAs showed increased expression in comparison to normal thymocytes

[53]. Tumor cells display a high rate of transcription, especially in aggressive cancers like GBM, while the increased incidence of back-splicing happens rather when co-transcriptional processing activities are inhibited or slowed down [54, 55]. This agrees with our analysis, where circRNA downregulation is in most cases independent of changes in their linear counterparts which suggests no impairment in the transcription process but rather the involvement of back-splicing.

Prior research has demonstrated that dysregulation of circRNAs might exert oncogenic functions in GBM, both downregulated in high-grade glioma circBRAF and upregulated in GBM circPITX1 are associated with poor patients' prognosis [43, 56]. In our study, among downregulated circRNAs, circEBP41L5 was detected as the most decreased one in GBM and displays the biggest discrepancy between the expression of linear and circular transcripts. In the literature, circEBP41L5 is described as a GBM suppressor what acts through miR-19a sponging, thus it could serve as a prognostic or therapeutic molecule for new clinical approaches [57]. Remaining downregulated circRNAs might act as suppressors and require further studies to better understand the mechanism underlying GBM.

In the remaining 10% of upregulated circRNA in GBM, the most upregulated appeared to be circVCAN which high expression is observed also in gastric cancer [58] and radioresistant glioma tissues [59]. The knockdown of these circRNAs resulted in the inhibition of cell proliferation, migration, and invasion, and accelerated apoptosis by regulating miR-587 [58] and miR-1183 [59]. Another validated differentially expressed circRNA with elevated expression levels in our GBM tissues – circPLOD2 was also found upregulated in GBM in a previous study [60]. This finding indicates an immense potential of circPLOD2 as a biomarker of GBM. CircPLOD2 has also been described as a promoter of tumorigenesis and recurrence biomarker in colon cancer. [61, 62]. It is also frequently upregulated under hypoxia conditions in HeLa and MCF-7 cancer cell lines which mimic oxygen-deprived core of tumor mass [63]. There are no literature reports on selected circARID1A and circGUSPB1 which are overexpressed in GBM. The mRNA of *ARID1A* gene emerged as a cancer suppressor in different cancers. The absence of ARID1A in cancer can lead to widespread dysregulation of gene expression in cancer initiation, promotion, and progression [64, 65]. We also tried to distinguish potential molecular markers of GBM progression based on our analysis. 3 circRNAs: circEGFR, circHLA-B, circInter6p22 were found differentially expressed between GBM-PRM and GBM-REC tissue samples. The most overexpressed candidate, particularly in GBM-REC tumors, is circEGFR. CircEGFR is derived from the EGFR gene which is a well-established oncogene in various cancers [66, 67]. In contrast, circEFGR was also found as an inhibitor of the malignant progression of glioma by regulating the levels of miR-183-5p and TUSC2 [68]. Since there are different circEGFR isoforms originating from different genomic locations, the isoform defined in the mentioned report (hsa_circ_0080223) shows downregulation in tumor tissues, however circEGFR regarding our research (hsa_circ_0080229) is upregulated. Another study, consistent with our findings, indicates that hsa_circ_0080229 upregulates the expression of murine double minute-2 (MDM2) and promotes glioma tumorigenesis and invasion via the miR-1827 sponging mechanism [69]. This proposes that the expression of circEGFR is increasing with tumor progression. Our results, although observed in a depleted group of samples and should be interpreted with caution, supported this hypothesis and it could be intriguing to further examine additional glioma tissues of different histopathological grades in the future.

Previous studies revealed that the expression pattern of circRNAs and their circularization are significantly affected by RBPs which bind to the specific motifs in pre-mRNA [17, 34]. We observed significant changes in the expression of ~half of annotated human RBPome in GBM, which suggests that some of the changes in circRNA expression may be caused by disruption of their biogenesis. Moreover, these direct interactions of circRNAs with RBPs can substantially affect molecular processes [70]. Additionally, circRNAs can act as protein sponges, decoys that regulate protein accessibility in cell compartments, and also as scaffolds that allow protein-protein interactions mediating both circRNA and RBP functions [33]. Based on these findings, we decided to analyze the transcriptome of RBPs which could potentially interact with our deregulated circRNAs. In our data, recognition motifs for 38 RBPs are enriched in differentially expressed circRNAs. In our study, upregulated circRNAs are mostly motifs enriched in G and C in differentially expressed RBPs. It was shown that RBPs enriched in G-rich motifs might be splicing activators, that might potentially explain the upregulation of circRNAs to which they bind [25]. On the other hand, downregulated circRNAs are in U-rich motifs. It was previously shown that U-rich motifs correlate with higher mRNA decay rates [71]. Further analyses showed that ELAV families, downregulated in GBM, are correlated with the highest number of downregulated circRNAs. ELAVL proteins recognize AU-rich elements in the 3' UTRs of gene transcripts and thereby regulate gene expression post-transcriptionally stabilizing mRNA to avoid degradation [72]. It was also shown that circularizing exons were significantly more enriched with RBP binding sites compared to non-circularizing exons [17]. In our study, we found 14 RBP binding motifs enriched in flanking introns of differentially expressed circRNAs with the most promising HNRNPD and ZFP36 significantly correlated with highly expressed circRNAs. In our study, ELAVL2 and ELAVL3 showed a positive correlation with circRNAs enriched in flanking introns with the highest frequency in a region covering 100 nt upstream from the 5' backsplice junction end. These observations indicate specific circRNA-RBP interactions that might be directly involved in the circRNA processing.

Another protein family that might impact circRNAs expression is CPEB. Both CPEB1 and CPEB3 are downregulated in GBM with U-rich motifs enriched in downregulated circRNAs and show the highest number of positive correlated downregulated circRNAs including validated by us circEPB41L5. We showed, that KHDRBS2 predicted to be involved in alternative splicing [73] is the most downregulated RBPs in GBM and highly correlated with exosome-transmitted circVMP1 which facilitates the progression and cisplatin resistance of non-small cell lung cancer [74] and promotes glycolysis and disease progression in colorectal cancer [75].

Besides the transcriptome-wide characterization of circRNAs and RBPs in GBM and their putative interactions, we extend our analysis to determine differentially expressed circRNAs and RBPs specific for known molecular GBM subtypes. GBM is a heterogeneous disease that can be classified into four known molecular subtypes according to mutation landscape and gene expression pattern [6].

According to the circRNA expression pattern, the neural subtype was the most similar to the healthy brain samples. The RBPs expression analysis revealed the high expression levels of CPEB and ELAVL families in neural GBM samples which are generally downregulated in GBM ([76, 77]. These findings confirm earlier reports that the neural subtype may be non-tumor margins contamination [78-80].

Among GBM subtypes, the mesenchymal one is known as the most aggressive, invasive, and resistant to treatment [81]. We found further that both circCOL4A1 and circCOL1A2 are highly expressed in this subtype. Moreover, circCOL1A2 was previously described as upregulated in gastric cancer enhancing the migration and invasion properties [82] and also promoting angiogenesis in diabetic retinopathy [83, 84], which can make circCOL1A2 a relevant marker of mesenchymal GBM subtype. For the first time, we managed to distinguish new GBM groups based on RBP expression patterns, independent of known molecular subtypes. As mentioned before, potentially involved in circRNAs biogenesis CPEB and ELAVL families stratify GBM into 2 or 3 groups. Altogether, both CPEB and ELAVL families appear to have an impact on the circRNAs.

In conclusion, we provided a comprehensive global-scale analysis of circRNAs and RBPs in glioblastoma based on the patient-derived samples.

Specifically, we established a list of circRNAs differentially expressed in primary GBM tumors, the circRNA progression markers in recurrent GBM samples, but also, indicated a global deregulation of RBP transcripts. Selected circRNAs were further verified experimentally by the qRT-PCR method. Subsequent analysis allowed us to generate a comprehensive catalog of circRNA-RBP interactions regarding both the RBPs sequestration by circRNA as well as the RBPs involvement in circRNA biogenesis. Furthermore, we demonstrated the clinical potential of circRNAs and RBPs in GBM and proposed them as the stratification markers in the de novo assembled tumor subtypes. Moreover, our findings suggest that both circRNAs and RBPs might be considered as clinical markers and tumor-subtyping factors in the future. The list of potential functions of distinct circRNAs as well as the circRNA-RBP interactions is long and their regulatory functions are complex. The mechanism of action and the mutual dependencies await still further in-depth investigation. However, with our comprehensive study, we provide a foundation for future research into the molecular mechanisms and clinical implications of circRNAs and RBPs interactions in glioblastoma.

4. Materials and Methods

4.1 Patients' sample collection

Tumor tissues (n=26; Suppl. Tab. 1) were collected from GBM patients up to one hour after tumor excision. The material was obtained from the Department and Clinic of Neurosurgery and Neurotraumatology of the University of Medical Sciences in Poznan (Poland) and from the Department of Neurosurgery of Multidisciplinary City Hospital in Poznan (Poland). Prior to the surgery, the approval by the Bioethics Council of the Poznan University of Medical Science (Nr. 46/13) and the donors' consent had been obtained. Four commercial samples (purchased from Ambion, Clontech and Takara companies) of pooled human brain (HB) total RNAs were used as healthy brain controls (Suppl. Tab. 2).

4.2 RNA extraction and quality check

Total RNA extraction from GBM patient tissue was performed using TRIzol reagent (Invitrogen) according to the manufacturer's protocol. RNA samples have been subjected to DNase I treatment using a ready-to-use DNA-free™ DNA Removal Kit reagents following the manufacturer's protocol (Ambion). The quality of purified RNA was measured by NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific) followed by agarose gel electrophoresis. RNA integrity was verified on Agilent Bioanalyzer 2100 (Agilent

Technologies). RNA samples with RNA Integrity Number (RIN) at least 7.4 were used for library preparation and RNA-seq analysis (Suppl. Fig. 11, 12).

4.3 Library preparation and RNA sequencing

300 ng of total RNA were ribosomal RNA-depleted using RNase H [23]. Ribosomal RNA-depleted libraries were constructed using Illumina's TruSeq Total RNA Library Prep Kit. Adaptor ligations were performed according to manufacturer's instructions and cDNA fragments were amplified in RT-qPCR for 8-15 cycles. After the purification with AMPure XP beads, the DNA concentration was measured with Qubit (Thermo Fisher Scientific) and the fragments length were defined with Screen Tape Assay Agilent D1000, 4200 Tape Station System. RNA sequencing was performed using Illumina Hi-seq 4000, average of ~73 million of 150 paired-end reads per sample.

4.4 circRNAs identification

Quality control of raw sequencing reads was done with FastQC (<https://www.bioinformatics.babraham.ac.uk/projects/fastqc/>). Next, the adapters were removed using Trimmomatic [85], version 0.38 with the following parameters ILLUMINACLIP:2:30:10 SLIDINGWINDOW:10:25 MINLEN:35. After adapter trimming, a second quality check with FastQC was performed. A genomic index was created for GRCh37 human genome obtained from Gencode using Burrows-Wheeler aligner [86], version 0.7.17 (bwa -bwtsw). Then, reads were mapped with the following parameters: bwa-mem -T 19. CircRNAs were detected from alignment files with CIRI [87], version 2.0.6 using default parameters. CircRNAs annotation and differential expression analysis was performed using circMeta R package [88]. The edgeR [89] method was used for differential expression (DE) analysis. Heatmaps were prepared using the pheatmap R package and data normalized using Trimmed Mean of M-values (TMM) method from edgeR R package [89].

Gene Set Enrichment Analysis (GSEA), including Gene Ontology (GO) and Kyoto Encyclopedia of Genes & Genomes (KEGG) was performed using clusterProfiler R package [90] and IDs for linear transcripts ranked by circRNA log2 fold change between GBM and HB samples. In case of multiple circRNAs originating from one gene, mean log2 fold change was used. For both GO and KEGG, the following set of parameters was used: nPerm = 10000, minGSSize = 3, maxGSSize = 800, pvalueCutoff = 0.05, pAdjustMethod = "fdr".

Data were visualized using the ggplot2 R package. Most of the analysis was done in R 4.1.3, except for KEGG enrichment for GSEA, which was prepared in R 3.6.1.

4.5 RBPs identification

To identify RBPs differentially expressed between HB and GBM samples, trimmed reads were mapped to the human genome (GRCh37 v30 from Gencode) using Burrows-Wheeler aligner [86], version 0.7.17, followed by mapping sequencing reads to genomic features using featureCounts function from Rsubread package with useMetaFeatures option and without counting multimapping and multi-overlapping reads. Differential gene expression analysis was performed using edgeR glmQLFTest [89]. RBPs were selected from differentially expressed genes based on the human RBP list, obtained from Gerstberger et al., 2014 [30].

4.6 circRNAs-RBPs interactions

To identify putative RBPs binding sites in differentially expressed circRNA, first, circRNA sequences were extracted using FcircSEC [91] followed by k-mer enrichment analysis

between differentially expressed and non-differentially expressed circRNAs. K-mer enrichment analysis was performed with $k = 6$, using `kmer_compare` function from the FeatureReachR package. Then 6-mers enriched in differentially expressed circRNAs were mapped to the RBPs binding sites determined either by eCLIP [35] or by RNA bind and Seq experiments [25], using `estimate_motif_from_kmer` function from FeatureReachR and CISBP RNA_hs or RBNS position weighted matrices lists, respectively. Significantly enriched RBP binding motifs (adjusted p value < 0.1) were visualized using `ggseqlogo` R package [92]. Analysis was then repeated for circRNA flanking regions (1000 nt flanks).

Correlation of expression of RBPs, which were differentially expressed between HB and GBM samples, and their binding motifs enriched in differentially expressed circRNA, was estimated with differentially expressed circRNA expression using `cor.test` function from R with Spearman rank correlation option. The Upset plot was prepared using the UpSetR package [93].

4.7 GBM subtypes analysis based on circRNAs

Raw sequencing data were subjected to the quality check using FastQC tool. The adaptors were trimmed and the reads were filtered to eliminate the low-sequencing-quality bases using Trimmomatic [85]. Furthermore, the RNA-seq reads were mapped to the human reference transcriptome (ENSEMBLE V.102) to quantify the expression level of the transcripts. The transcript-level estimates were summarized and associated with the gene IDs for gene-level analysis using `tximport` [94]. For the samples categorization we used genes indicated in TCGA GBM dataset and other genes that have been found to be significant for GBM molecular subtyping including *SLC12A5*, *SYT1*, *GABRA1*, *NEFL*, *CDKN1A*, *NF1*, *MET*, *PDGFRA*, *BOP1*, *ILR4* were included. CircRNAs differentially expressed within the subtypes were identified using circMeta R package [88] with edgeR [89] method for differential circRNAs expression (DCE).

4.8 GBM samples stratification based on RBPs expression

GBM samples stratification according to RBPs expression changes was performed using the CircIMPACT workflow [95]. At first, we subset RBPs able to discretize patients into two clusters according to their expression with no significant association with GBM molecular subtypes (χ^2 test, p-value > 0.01). We clustered patients in novel subgroups linked by common RBPs pattern expression. The unsupervised clustering was performed using the k-means algorithm with euclidean distance and automatic selection of the optimal number of k clusters of patients using the silhouette index. Finally, we tested which RBPs reach significant estimates of the expression changes between previously defined clusters (one-way ANOVA test p-values ≤ 0.05). After correction for multiple tests, the RBPs with significant expression variation were used to compose the list of discriminant RBPs for the corresponding sample clustering.

4.9 Survival analysis

Survival analysis was performed on the GBM dataset from TCGA. Log2 transformed HTseq counts were downloaded using UCSC Xena tool [96]. Log2 transformation was reversed and raw reads were normalized using TMM method from edgeR R library [89]. Then differentially expressed RBPs were selected (listed in Suppl. Tab. 8) and for each RBP quartile normalization was applied. Samples belonging to Q1 were marked as 'low', Q2 and Q3 - 'medium' and Q4 - 'high'. Survival analysis was performed using survival and survminer R libraries between samples with 'low' and 'high' expression levels. Log-rank

(Mantel-Haenszel) test was used to assess statistical significance (p value < 0.05). Data were visualized using `ggsurvplot` function from `survminer` library.

4.10 Reverse transcription and quantitative RT-qPCR

The reverse transcription reaction was proceeded using the Transcriptor High Fidelity cDNA Synthesis Kit (Roche) according to the manufacturer's protocol. 500 ng of total RNA extracted from patient-derived tissues was used. The real-time qPCR reaction was performed using the CFX Connect Real-Time PCR Detection System (Bio-Rad) on the 96-well plates recommended by the manufacturer. Each sample was run in three technical replicates. RT-qPCR analysis was performed with LightCycler® 480 SYBR Green I Master (Roche) and primers designed using the Primer-BLAST tool [97] and purchased from Thermo Fisher Scientific. Primers' sequences are listed in the Suppl. Tab. 9. The expression level of the studied genes was calculated in CFX Maestro 2.0 software. Hypoxanthine phosphoribosyltransferase (*HPRT*) was used as an endogenous control for calculating the expression levels of selected genes. As control, commercially available RNA from HB tissues was used (Suppl. Tab. 2).

4.11 RNase R treatment

2 μ g of total RNA were treated with 4U of RNase R (Lucigen) at 37°C for 5 or 10 minutes in case of downregulated and at 37°C for 30 minutes for upregulated circRNAs followed by 20 minutes at 65°C. Next, total RNA was purified using NucAway Spin Columns (Invitrogen) and reverse transcribed with the Transcriptor High Fidelity cDNA Synthesis Kit (Roche) according to the manufacturer's protocol. Then, PCR was performed with 35 cycles (15s denaturation at 95°C followed by 30s at the optimum annealing temperature for each pair of primers (Suppl. Tab. 9) and 20s extension) with a prior 3-minute denaturation. The depletion of linear RNA was confirmed by running the PCR products on agarose gel.

4.12 Statistical analysis of the results

Each experiment was performed in three biological replicates including three technical replicates each. Statistical significance of the differences observed in experimental data was calculated in R, using `t-test (stat_compare_means function)`. P-values are presented in plots.

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6. Authors Contribution

Conceptualization, JLL, ZZ, MPS, KK, JOM, AG and KR; Sample collection, RP, and AMB; Formal analysis, JLL, ZZ, MPS, JOM, AG, KK, AB, MZ, JK, AR-W and KR; Investigation, JLL, ZZ, MPS, KK, AG, AB and KR; Methodology, JLL, ZZ, MPS, AB, SB, AR-W and MZ; Resources, KR, NR; Supervision, KR; Funding acquisition, KR; Visualization, MPS, AB; Writing - original draft, JLL, ZZ, MPS, JOM; Writing - review & editing, JLL, ZZ, MPS, JOM, AG, KK, AB, SB, AR-W, and KR. All authors have read and approved the final version of the manuscript.

7. Conflict of Interest

The authors declare no conflict of interest.

8. Funding

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9. Ethics approval and consent to participate

The GBM samples ($n = 26$) were obtained from the Clinic of Neurosurgery and Neurotraumatology, Karol Marcinkowski University of Medical Sciences in Poznan, Poland, and Department of Neurosurgery, Jozef Strus Hospital in Poznan, Poland during 2015-2020 based on the approval from the Ethical Committee (Nr. 46/13), and individuals signed an informed consent form.

10. Data availability

Sequencing data have been deposited in NCBI GEO repository under accession code GSE196695. Scripts used for data analysis and processed data are available at https://github.com/MSajek/GBM_circs.

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Figures legends:

Figure 1. Overview of the identified circRNAs and RBPs in GBM. **A.** Venn diagram illustrates an overlap between circRNAs that were found expressed in analyzed GBM-PRM, GBM-REC tissues and HB control. **B.** Distribution of novel and annotated circRNAs in selected samples. **C.** Volcano plot of differentially expressed circRNAs and mRNAs in GBM-PRM vs HB. The blue and red dots indicate downregulated and upregulated circRNAs, respectively. **D.** Volcano plot of differentially expressed circRNAs in GBM-REC vs GBM-PRM. The blue and red dots indicate downregulated and upregulated circRNAs, respectively. **E.** The graph presents the circular-to-linear ratio (CLR) of circRNAs and their linear counterparts. The log₂FC of circRNAs is marked on the X-axis, and the log₂FC values of the corresponding mRNAs are marked on the Y-axis. **F.** Venn diagram illustrates an overlap between RBPs expressed in analyzed GBM-PRM, GBM-REC tissues, and HB control. **G.** Volcano plot of differentially expressed RBPs in GBM-PRM vs HB. The blue and red dots indicate downregulated and upregulated circRNAs, respectively.

Figure 2. Expression of selected circRNA dysregulated in GBM and their linear counterparts. **A.** Boxplots illustrating the ratio of circular to linear RNA expression levels in RNA-seq analysis for analyzed transcripts dysregulated in GBM-PRM in comparison to HB. **B.** Boxplots illustrating the ratio of circular to linear RNA expression levels in RNA-seq analysis for analyzed transcripts dysregulated in GBM-REC in comparison to GBM-PRM. **C.** qRT-PCR results of circular and linear RNA expression levels of selected downregulated gene candidates in GBM-PRM normalized to HB control. Dashed horizontal lines on panels A-C indicates HB expression level. **D.** qRT-PCR results of circular and linear RNA expression levels of selected upregulated gene candidates in GBM-PRM normalized to HB control. Dashed horizontal lines on panels A-C indicates HB expression level. **E.** qRT-PCR results of circular and linear expression level of selected upregulated gene candidates in GBM-REC normalized to GBM-PRM. Dashed horizontal line indicates the expression level in GBM-PRM. **F.** Log₂ fold change comparison of selected circRNAs dysregulated in GBM-PRM based on qRT-PCR and RNA-seq analysis. **G.** Log₂ fold change comparison of selected circRNAs dysregulated in GBM-REC based on qRT-PCR and RNA-seq analysis. **H.** Pearson correlation of validated circRNAs and their linear counterparts dysregulated in GBM-PRM. **I.** Pearson correlation of validated circRNAs and their linear counterparts dysregulated in GBM-REC.

Figure 3. Differentially expressed RBPs with motifs enriched in differentially expressed circRNAs. **A.** Upregulated RBPs with motifs enriched in upregulated circRNAs. **B.** Downregulated RBPs with motifs enriched in upregulated circRNAs. **C.** Upregulated RBPs with motifs enriched in downregulated circRNAs. **D.** Downregulated RBPs with motifs enriched in downregulated circRNAs. Sequence logos represent motifs enriched in circRNAs.

Figure 4. Expression of RBPs is correlated with circRNA and circRNA host genes expression. **A.** Counts of circRNA significantly correlated with differentially expressed RBPs. **B.** Comparison of correlation direction between RBPs (from figure A) and circRNAs vs RBPs and circRNAs linear counterparts. RBPs highlighted as blue show the same direction of correlation and RBPs highlighted as red show opposite direction. **C.** Correlation of the expression level of selected validated circRNAs with the expression level of dysregulated RBPs.

Figure 5. RBPs with motifs enriched in introns flanking circRNAs are correlated with circRNA expression. **A.** Heatmap of correlation (ρ) between 14 RBPs with enriched motifs flanking backsplice junction of circRNAs differentially expressed in GBM vs HB. Only significant correlations (p values < 0.05) were reported. For each RBP number of positively and negatively correlated circRNAs were added in the upper bound of the heatmap. **B-C.** CBEP3 and KHDRBS2 normalized expression distribution in HB and GBM. For each RBP, correlated circRNAs are reported in terms of: I. average normalized expression in GBM samples; II. average circular to linear proportion (CLR) in GBM; III. log2fold change comparing circRNA expression in GBM vs HB and IV. correlation entity with the RBP - CBEP3 and KHDRBS2, respectively.

Figure 6. RBP motifs enriched in flanking introns and circRNA itself. **A.** Venn plot showing overlap between RBPs with motifs enriched in flanking introns and in total sequence of circRNA. **B.** Schematic representation of circRNA with 5' and 3' flanking introns (1000 nt upstream from the 5' backsplice junction end, 1000 nt downstream from the 3' backsplice junction end) and 5' and 3' boundaries (50 nt from intron and 50 nt from circRNA sequence). **C.** Normalized frequency of enriched motifs in RBPs within regions shown in panel B.

Supplementary tables legends:

Supplementary Table 1. The characteristics of GBM tissue donors, who donated their tissue to the study. P – primary GBM, R – recurrent GBM; Classification of Malignant Tumors (TNM) according to Union for International Cancer Control (UICC) - T1, T2, T3, T4 represent size and/or extension of the primary tumor; RNA Integrity Number (RIN); samples subjected to experimental validation marked in blue.

Supplementary Table 2. The characteristics of HB controls used in the study. RNA Integrity Number (RIN).

Supplementary Table 3. Characteristics of the circular and linear transcripts subjected to the validation. ns – no statistical significance for $p \geq 0.05$.

Supplementary Table 4. CircRNAs differentially expressed in neural subtype versus other subtypes.

Supplementary Table 5. CircRNAs differentially expressed in mesenchymal subtype versus other subtypes.

Supplementary Table 6. Differentially expressed RBPs used for stratification of GBM samples into different groups.

Supplementary Table 7. RBPs shown to be brain tumor markers, correlated with disease outcome or response to treatment.

Supplementary Table 8. Differentially expressed RBPs used for survival analysis.

Supplementary Table 9. List of the primers used in the qPCR validation and RNase R treatment experiment.

Figures legends:

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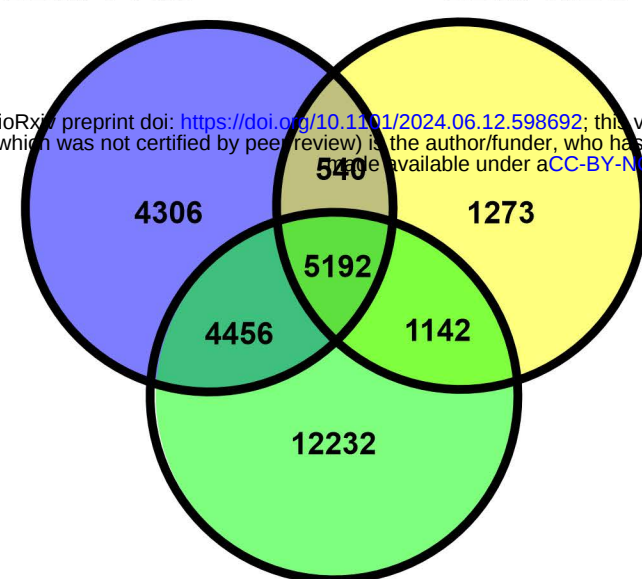
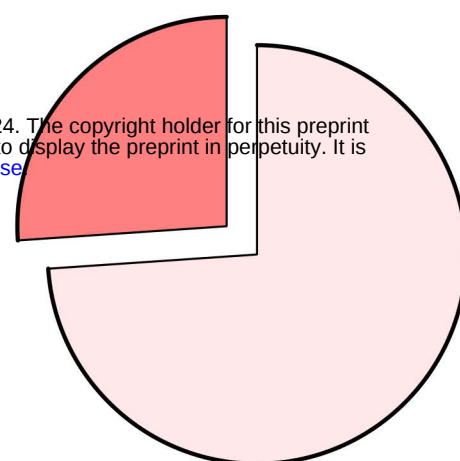
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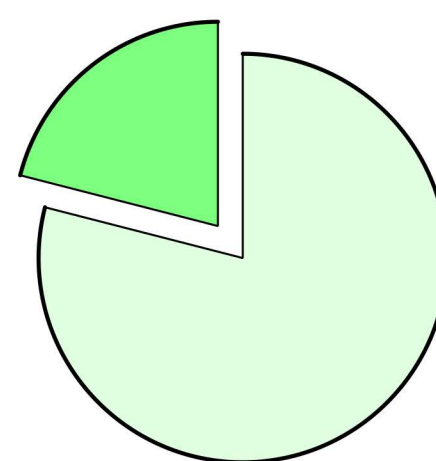
Figure 7. Representation of a subtype-specific circRNA and RBPs clustering GBM into new subtypes. **A.** Heatmap presenting subtype classification of the GBM samples used in the study. **B.** Venn diagram shows the number of the identified circRNAs in detected GBM subtypes. **C.** Comparison of selected circRNA up- and downregulated in mesenchymal and upregulated in neural subtypes. **D.** Log2 fold changes of 214 differentially expressed RBPs that can be used for patients' stratification. **E.** Heatmap showing mean expression differences between 41 RBPs within samples belonging to distinct GBM subtypes. RBPs highlighted red contain binding motifs enriched in differentially expressed circRNA sequences/flanking regions. **F.** RBPs clustering GBM samples into 2 groups with motifs enriched in differentially expressed circRNA sequences/flanking regions. **G.** ELAVL3 clusters GBM samples into 3 groups and has binding motifs enriched in differentially expressed circRNA sequences/flanking regions.

A**GBM-PRM** **GBM-REC**

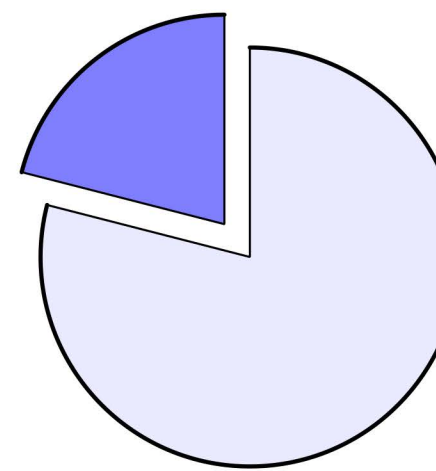
bioRxiv preprint doi: <https://doi.org/10.1101/2024.06.12.598692>; this version posted June 14, 2024. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

**B****all datasets****Total = 29141**

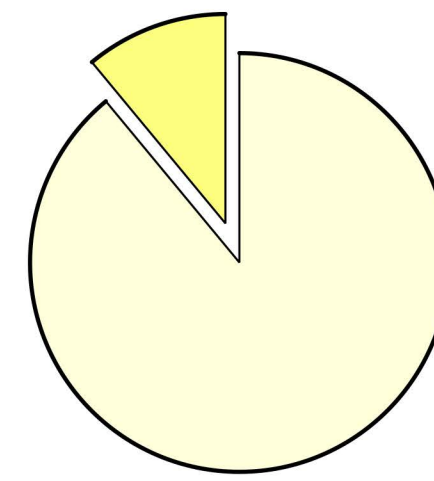
74% annotated circRNAs
26% novel circRNAs

HB**Total = 23122**

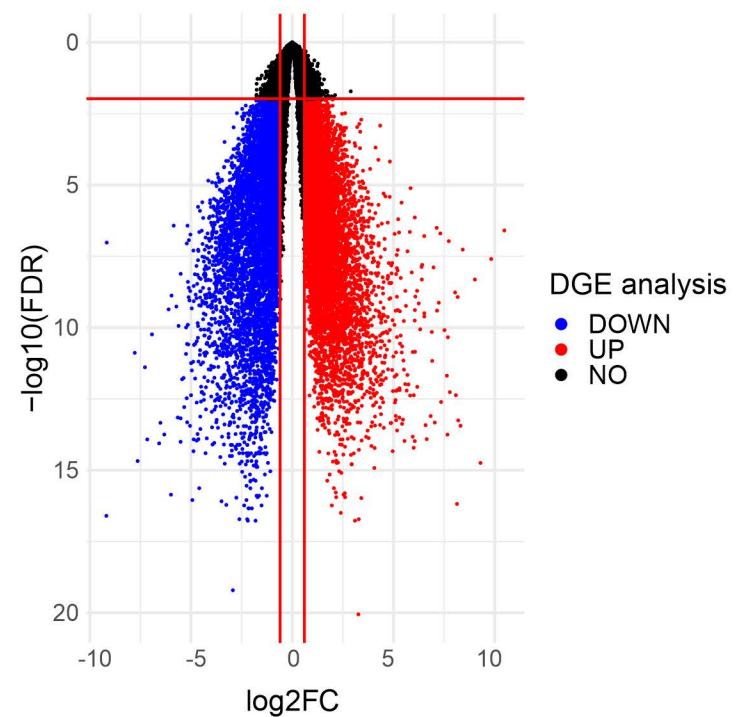
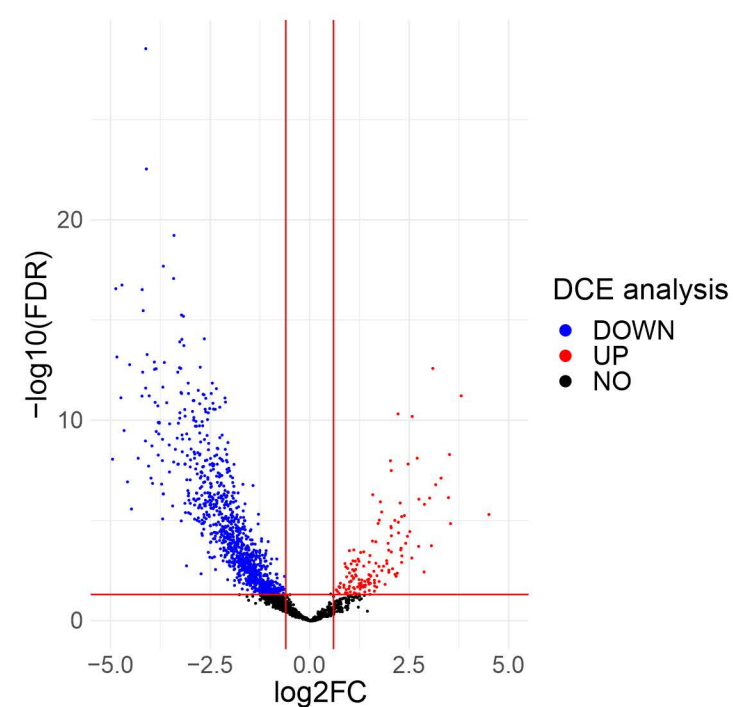
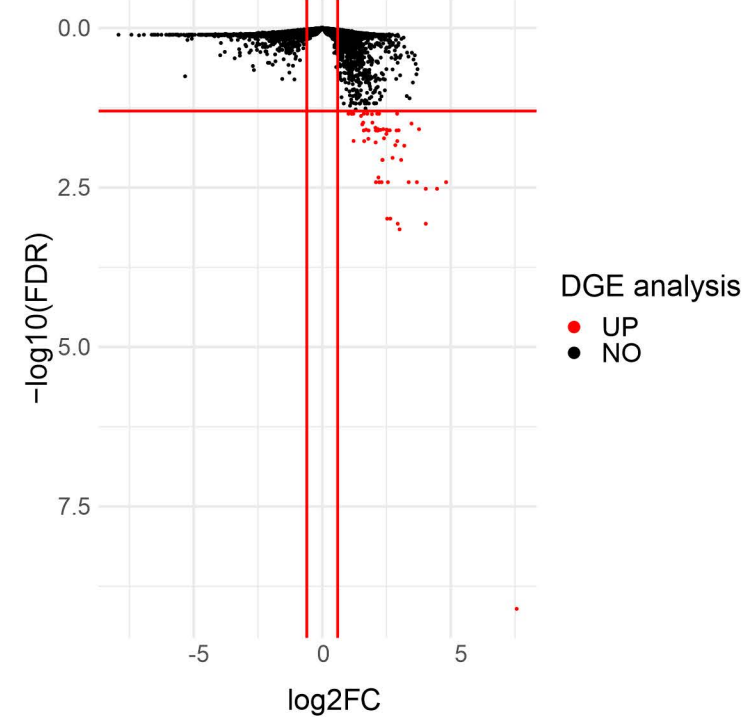
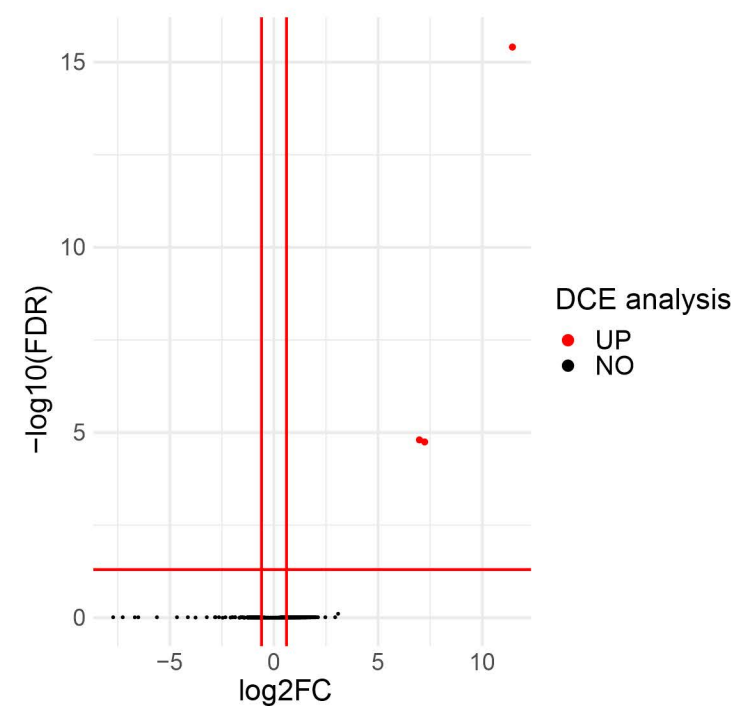
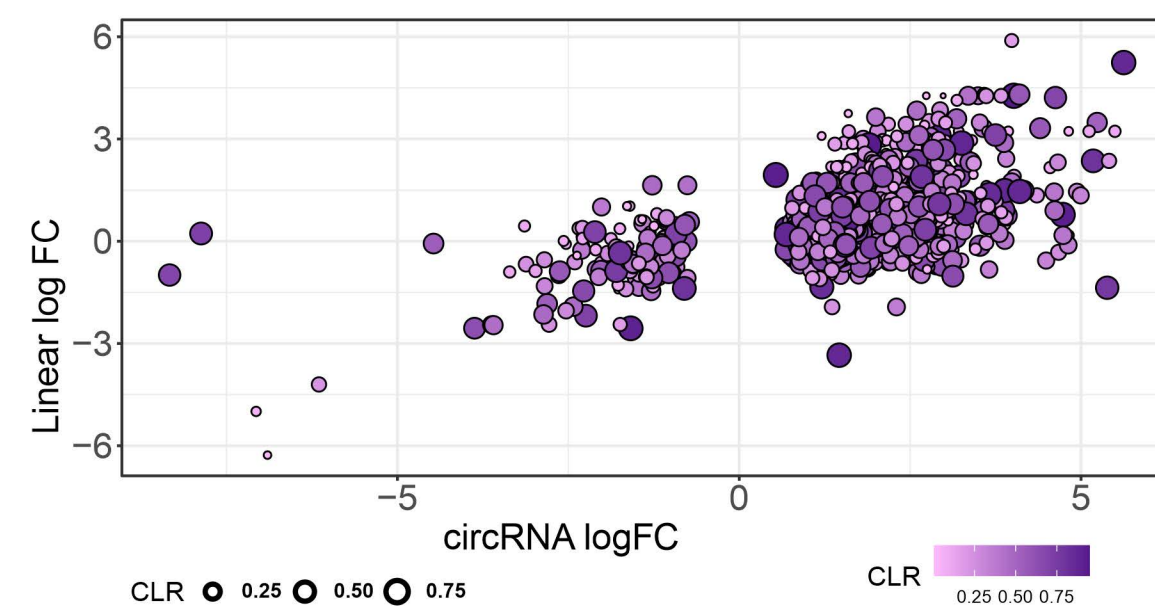
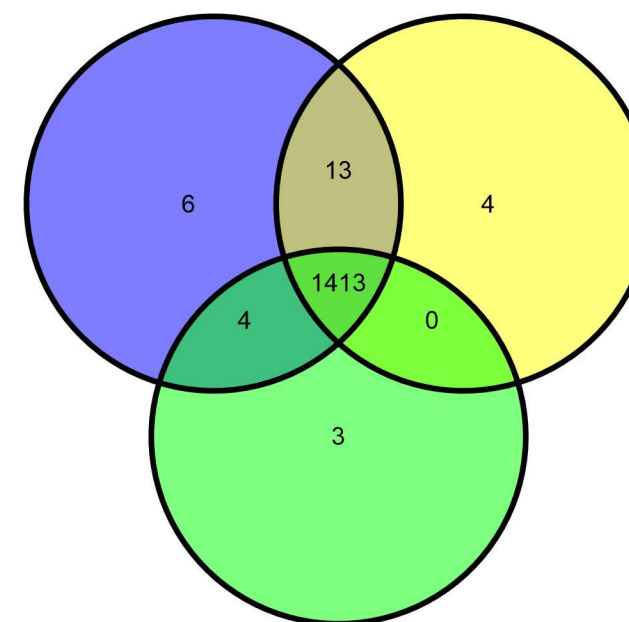
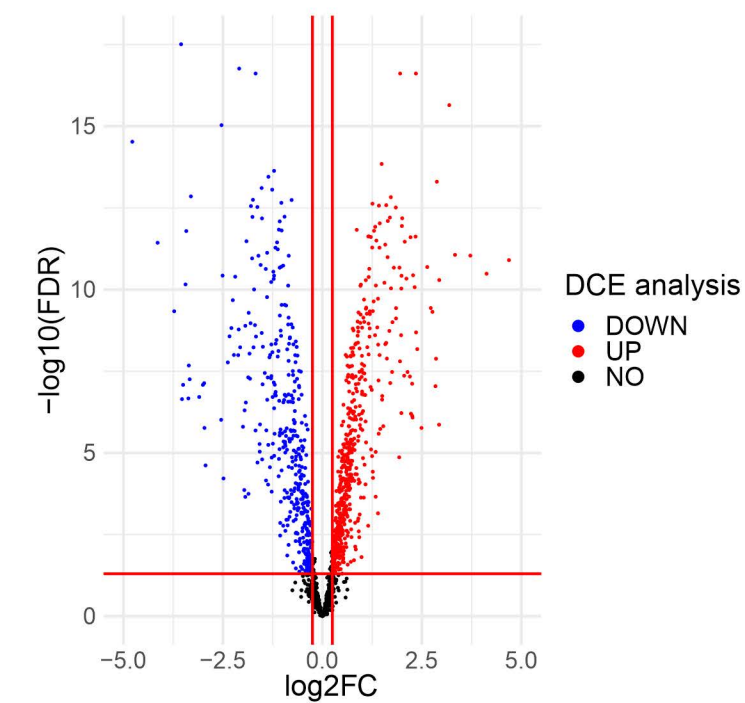
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21% novel circRNAs

GBM-PRM**Total = 14548**

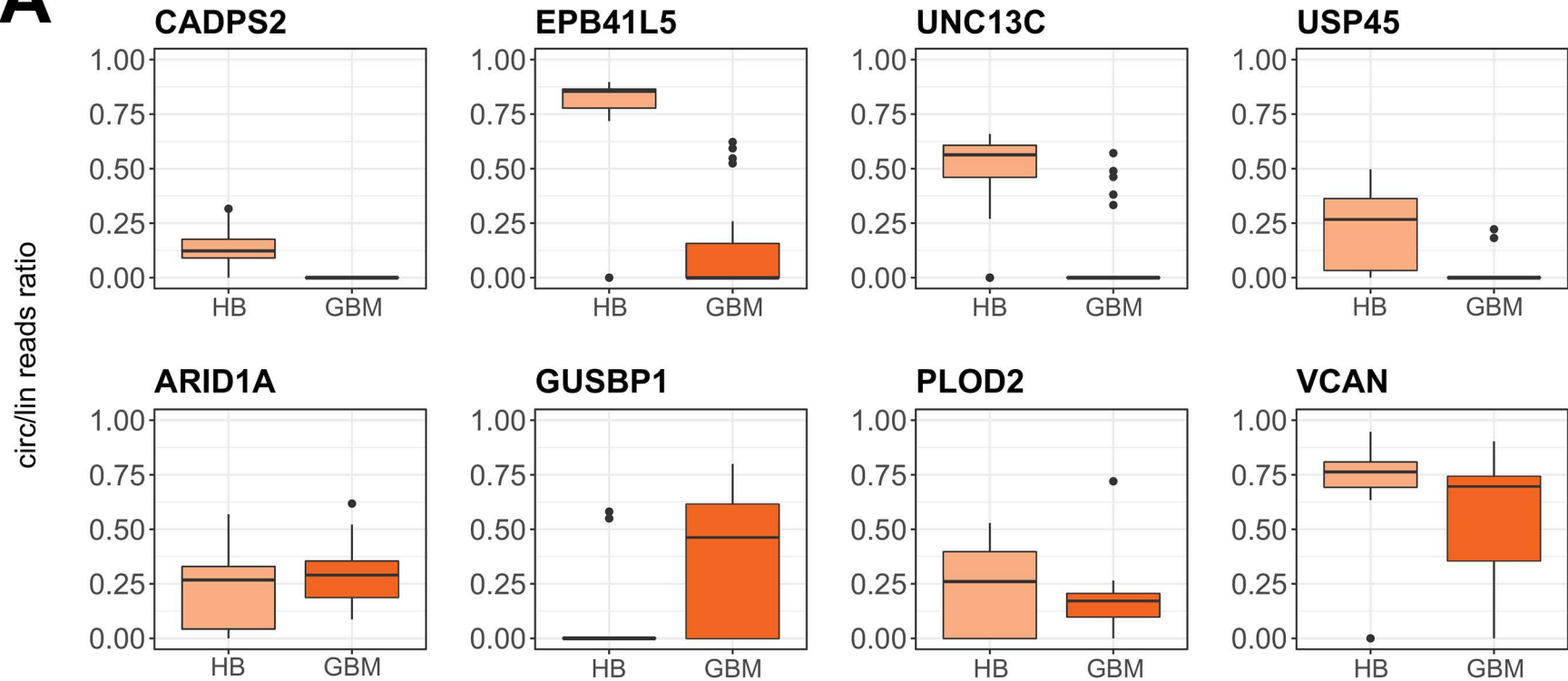
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21% novel circRNAs

GBM-REC**Total = 8147**

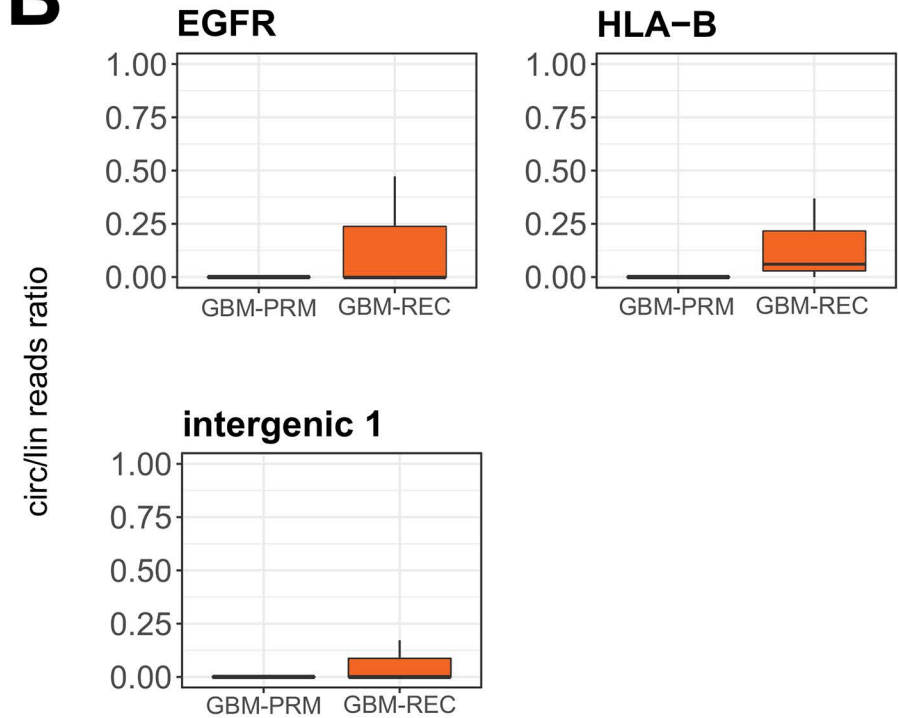
89% annotated circRNAs
11% novel circRNAs

C**GBM-PRM vs HB****D****GBM-REC vs GBM-PRM****E****HB vs GBM-PRM****F****GBM-PRM** **GBM-REC****G****GBM-PRM vs HB**

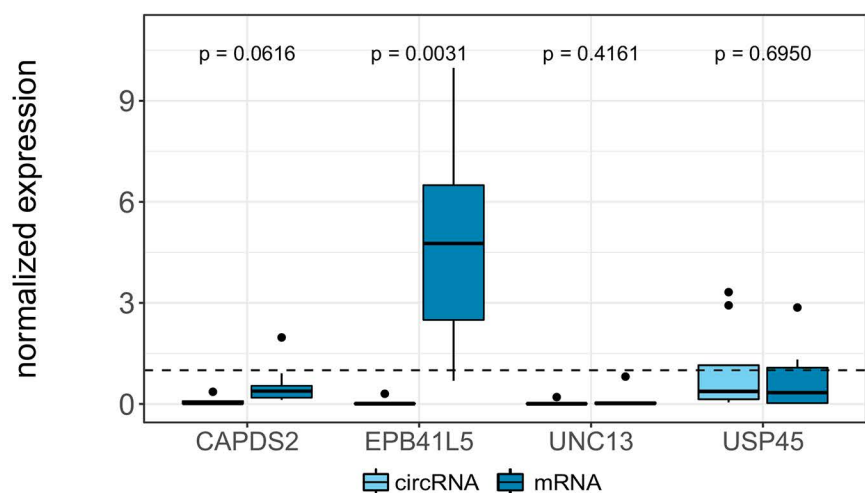
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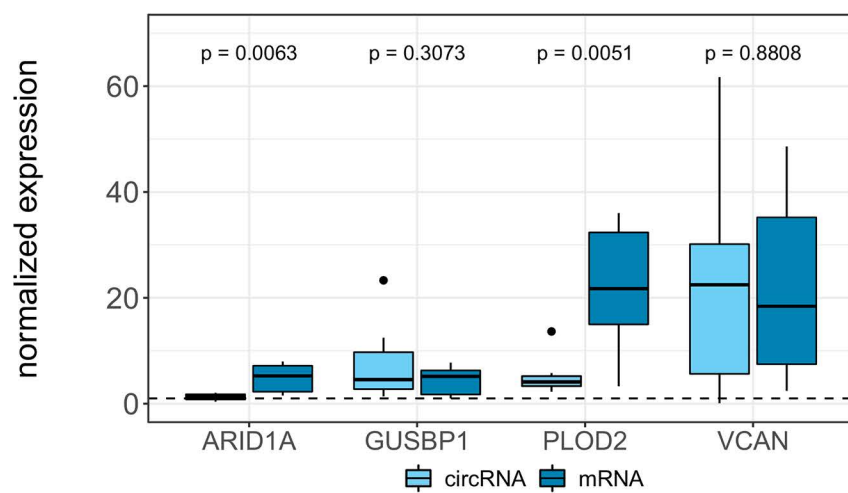
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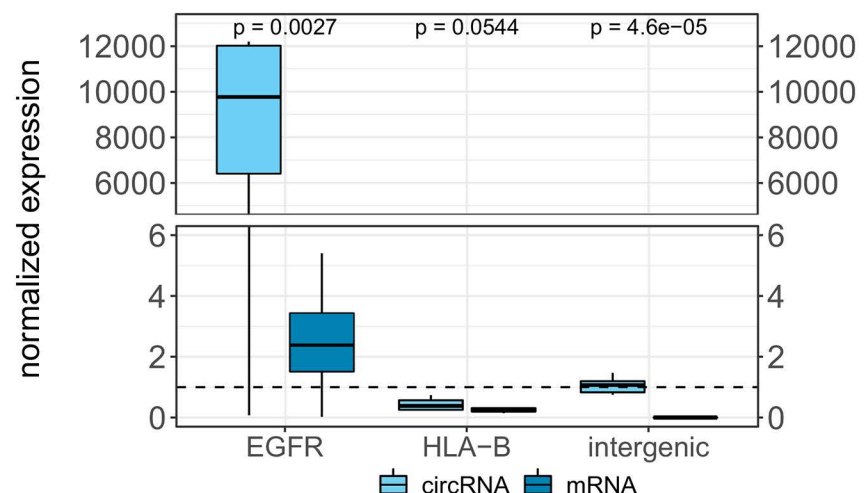
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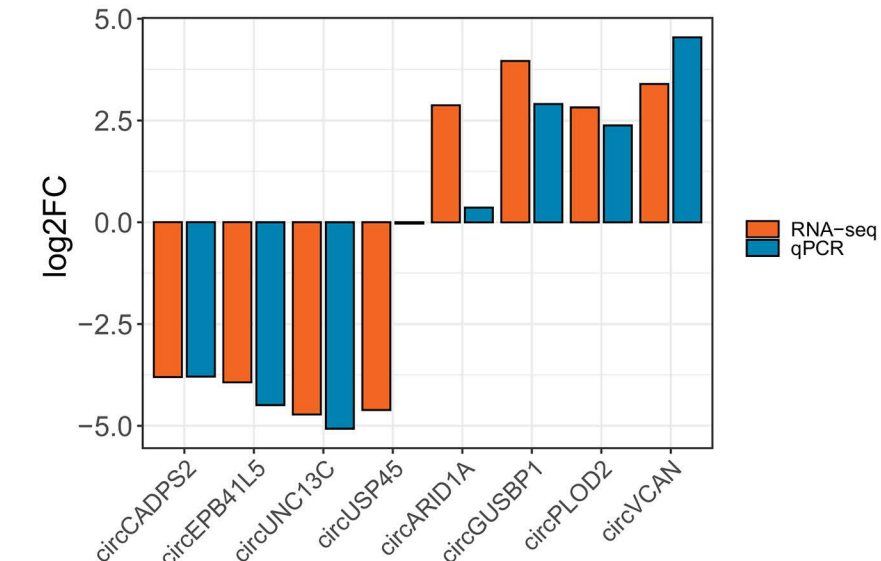
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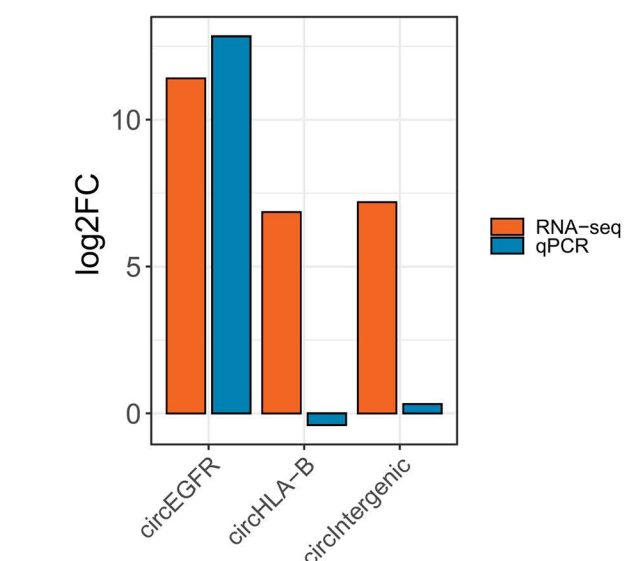
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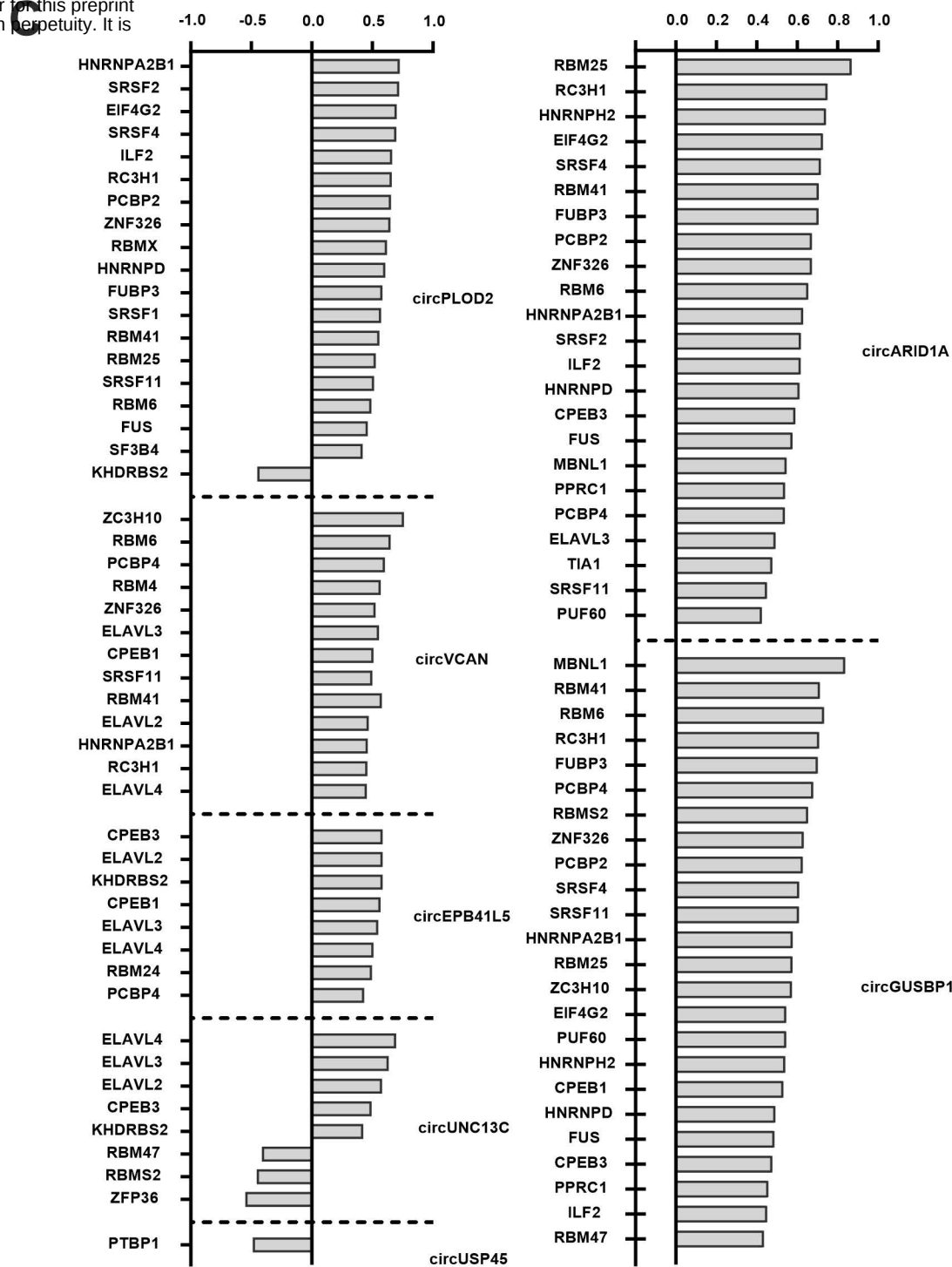
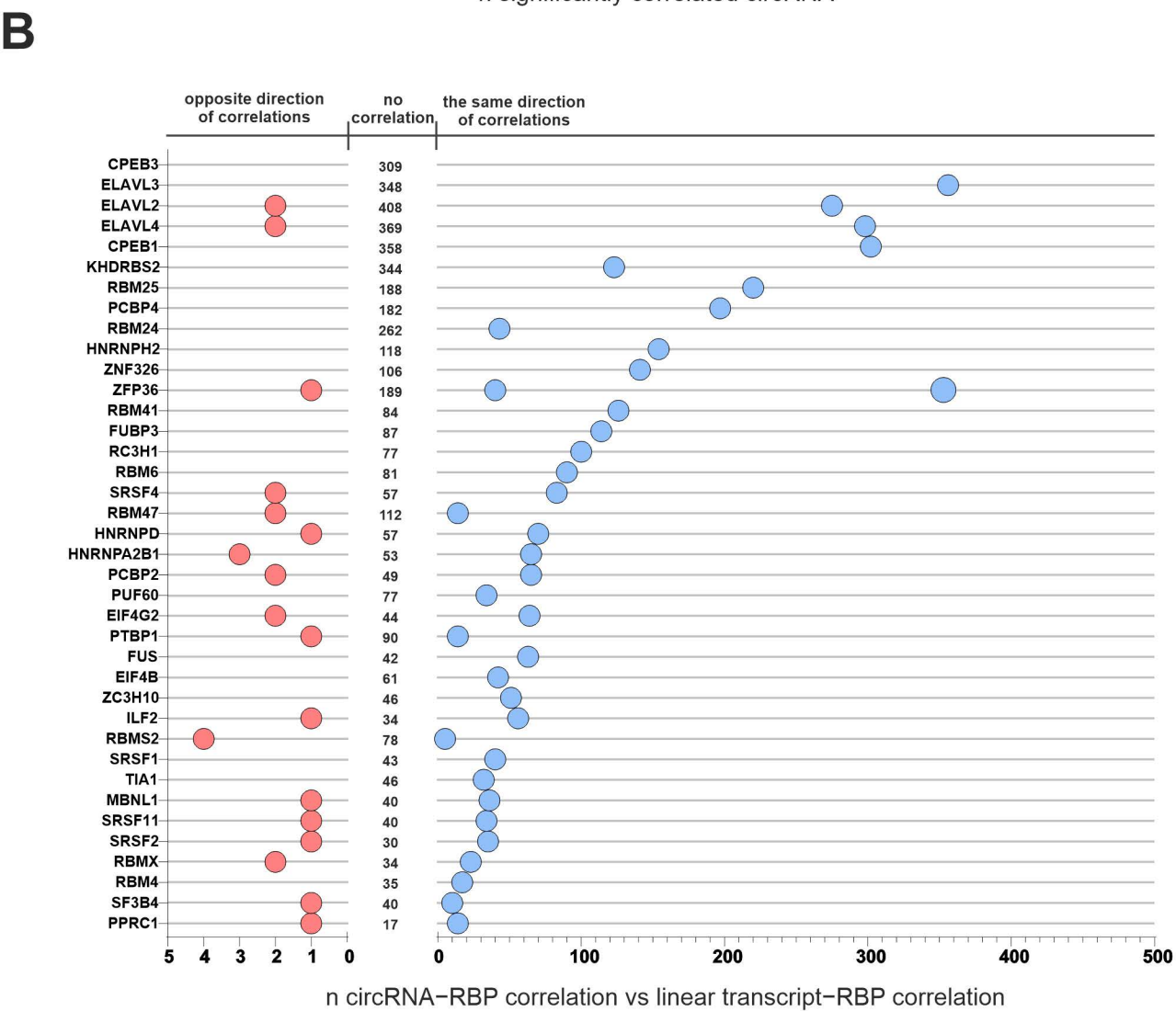
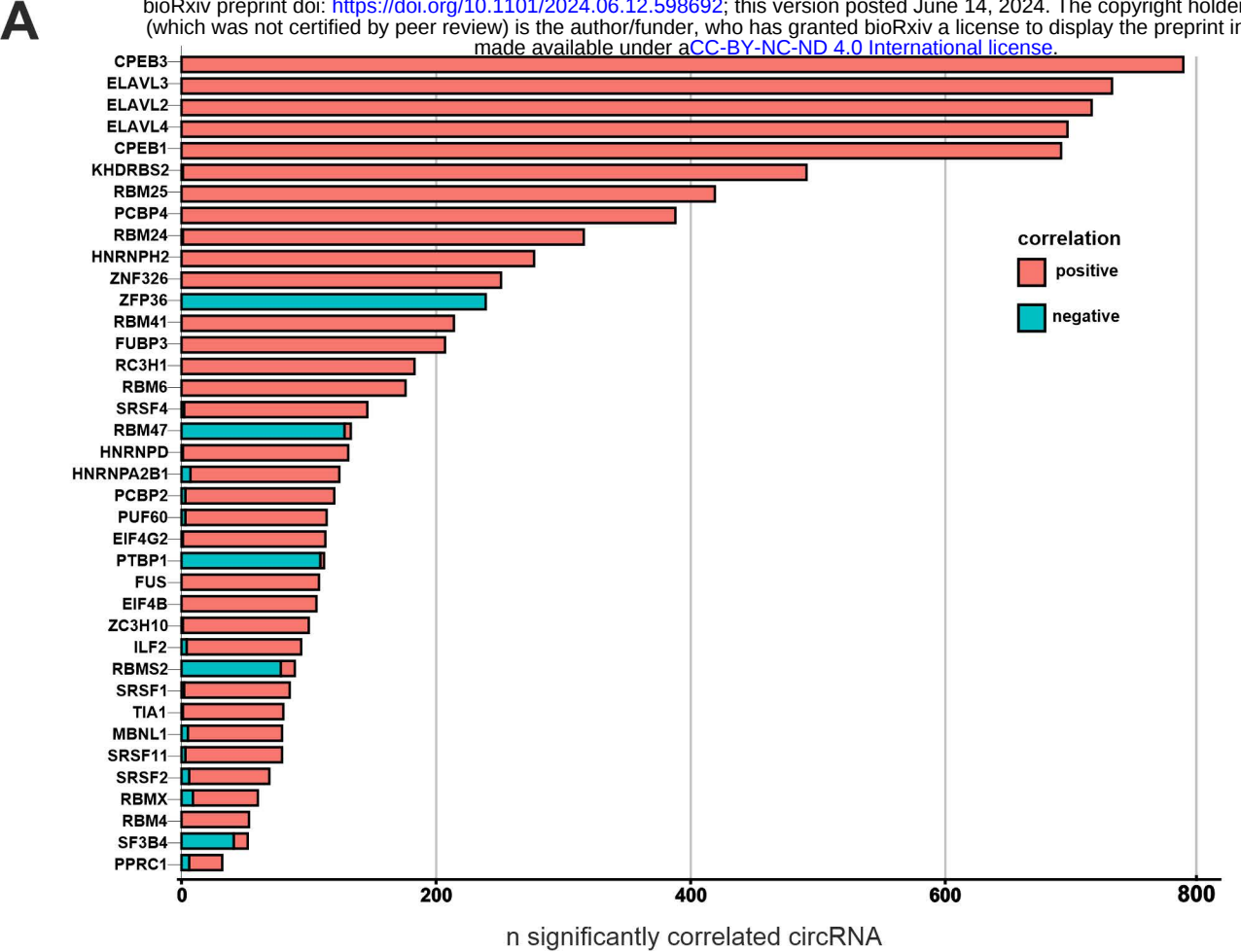


H

Gene ID	Pearson Correlation Coefficient (r)	p-value
CADPS2	0.1440	0.7336
EPB41L5	0.1440	0.5504
UNC13C	0.9970	<0.0001
USP45	-0.5331	0.1737
ARID1A	0.2221	0.2385
GUSBP1	0.4587	0.2529
PLOD2	0.4497	0.2636
VCAN	0.6957	0.05533

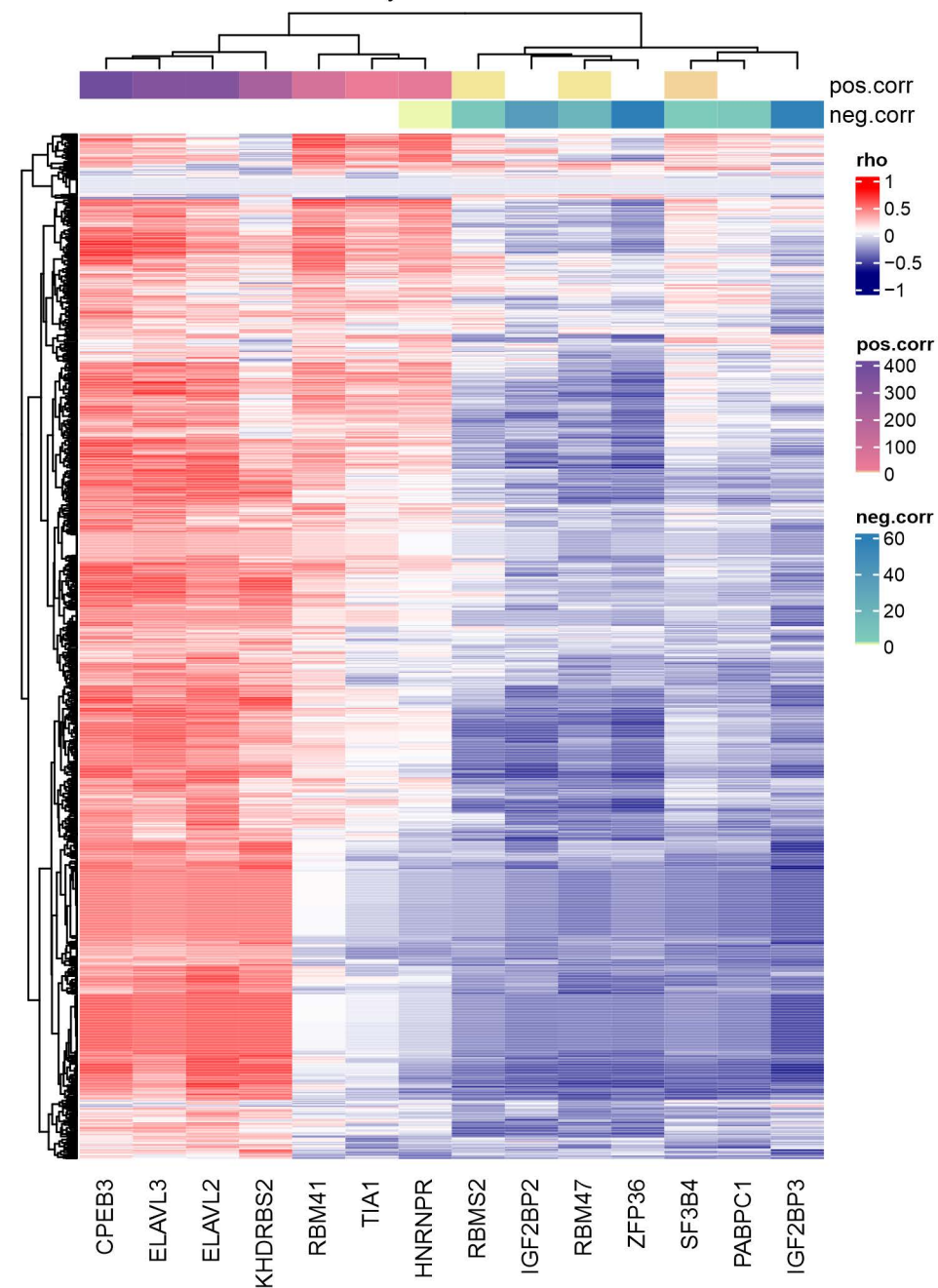
I

Gene ID	Pearson Correlation Coefficient (r)	p-value
EGFR	0.9175	0.003587
HLA-B	0.8896	0.007315
Intergenic 1	-	-



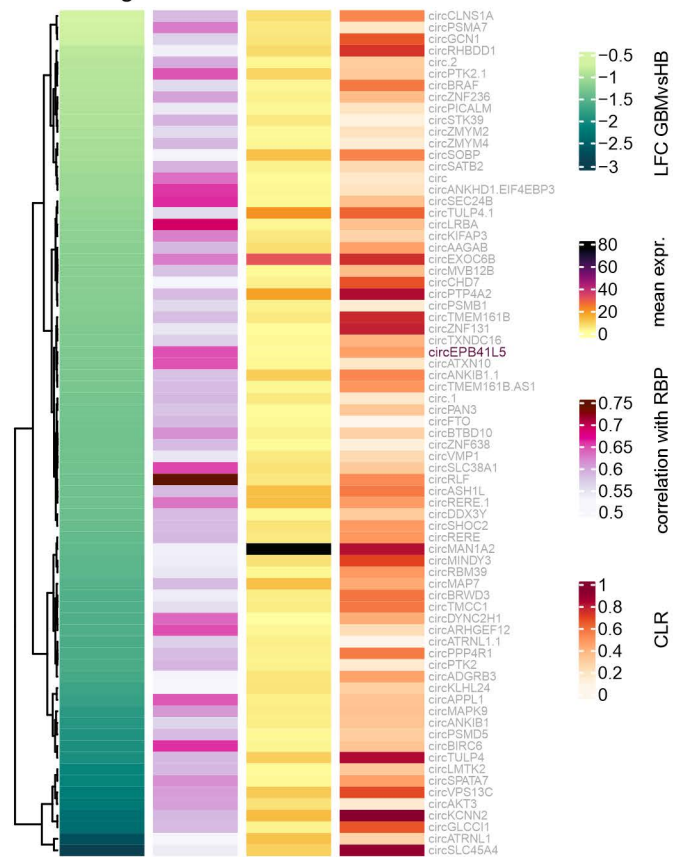
A

Correlation analysis of RBPs with circRNAs



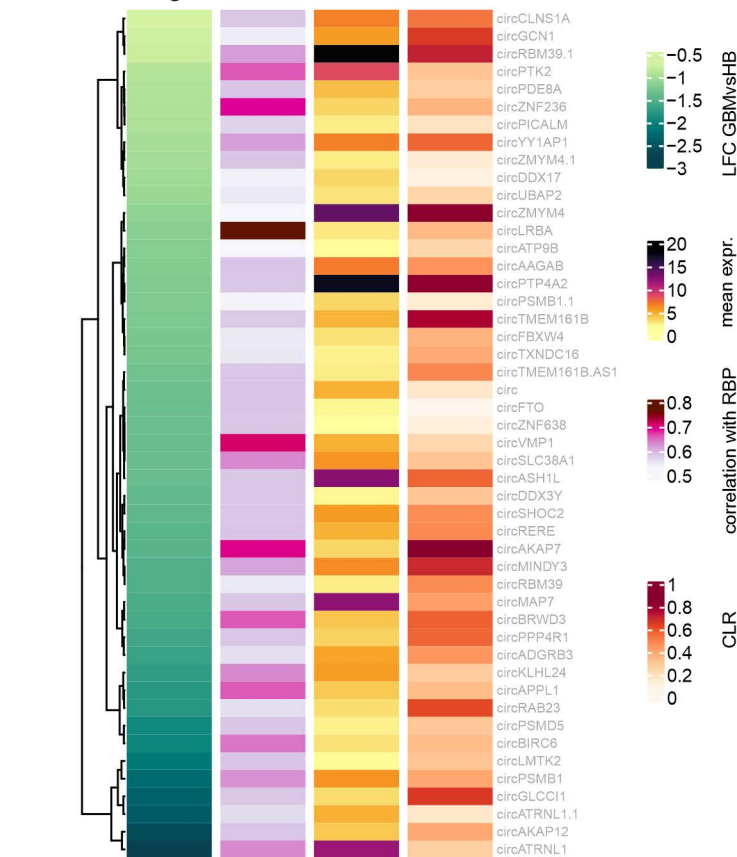
B

downregulated circRNAs correlated with CPEB3

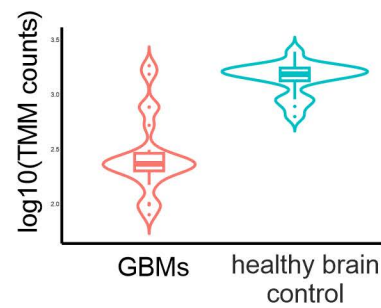


C

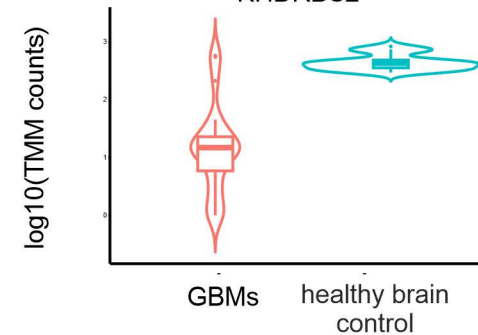
downregulated circRNAs correlated with KHDRBS2



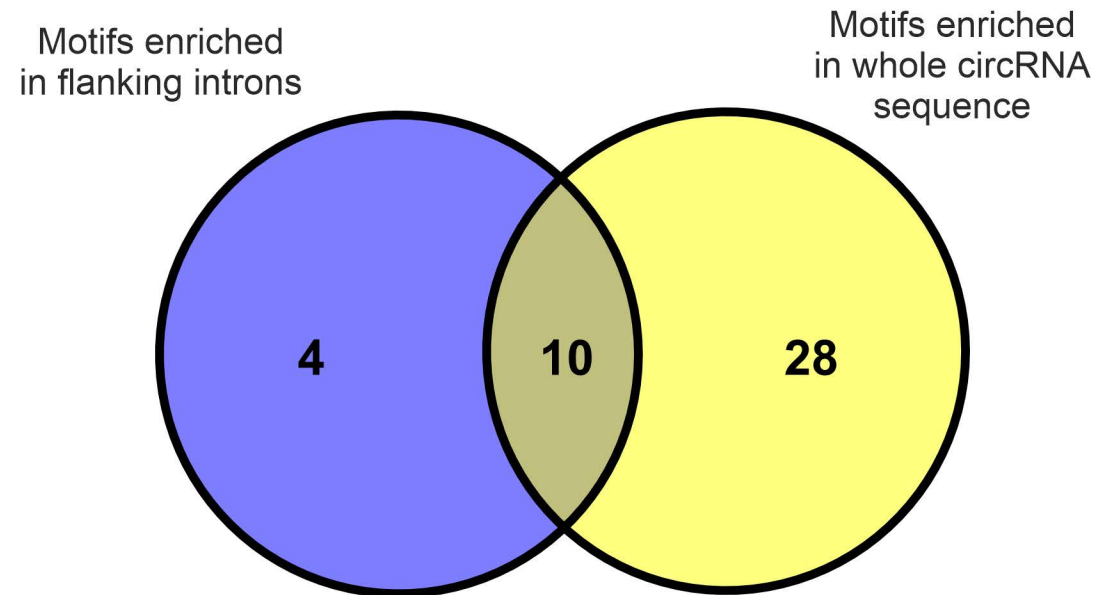
CPEB3



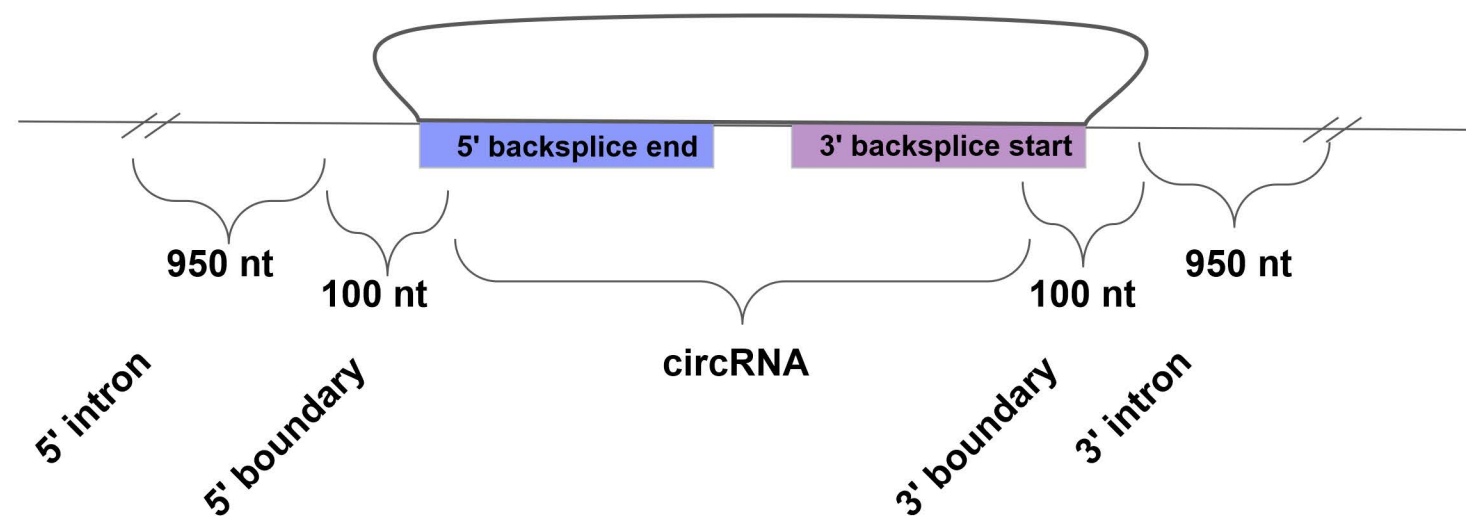
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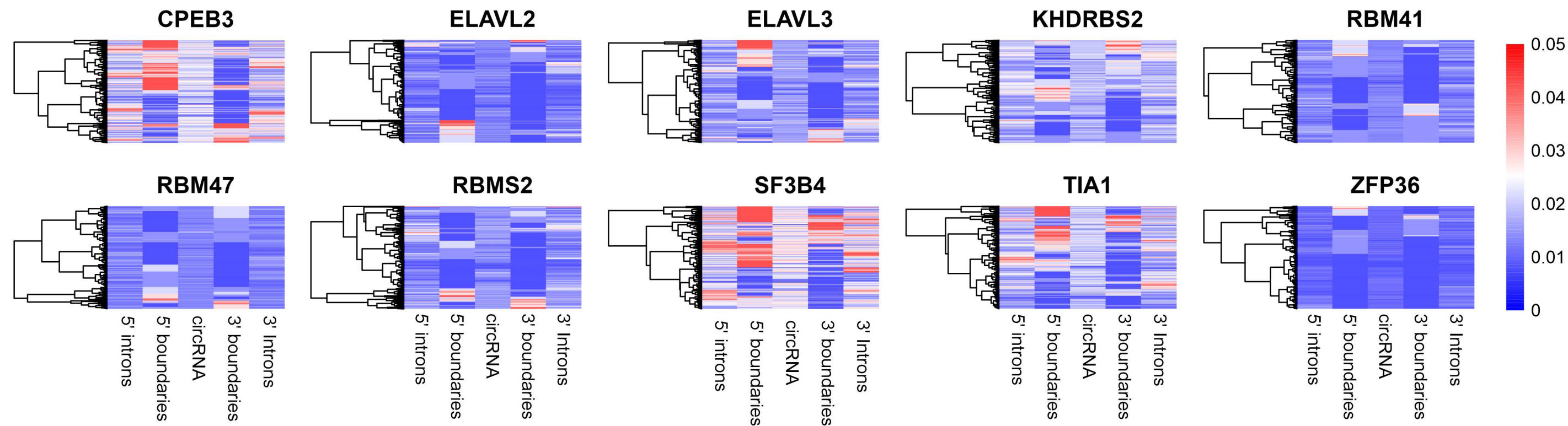
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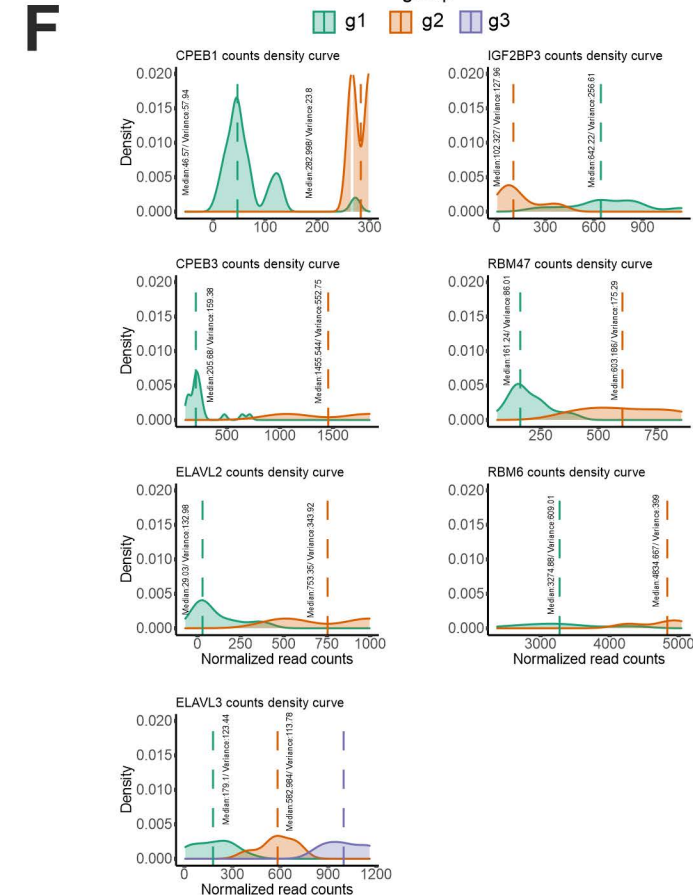
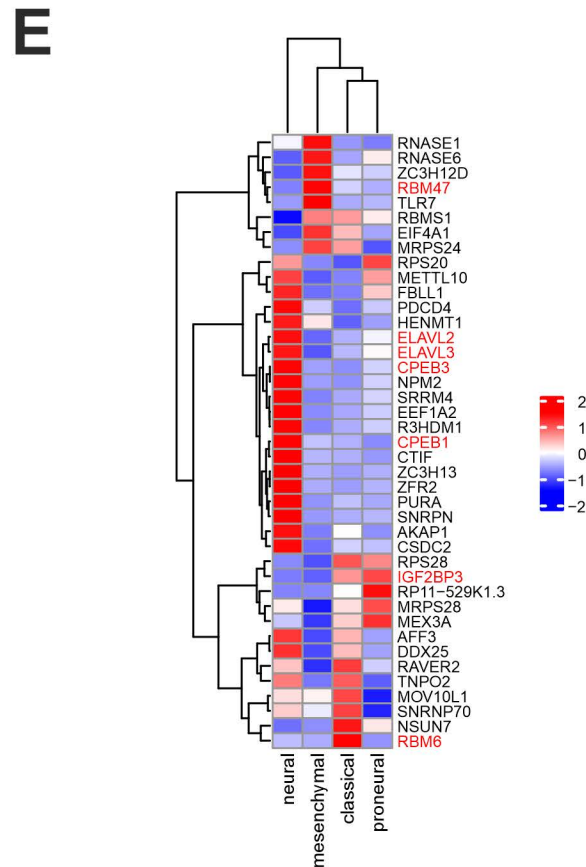
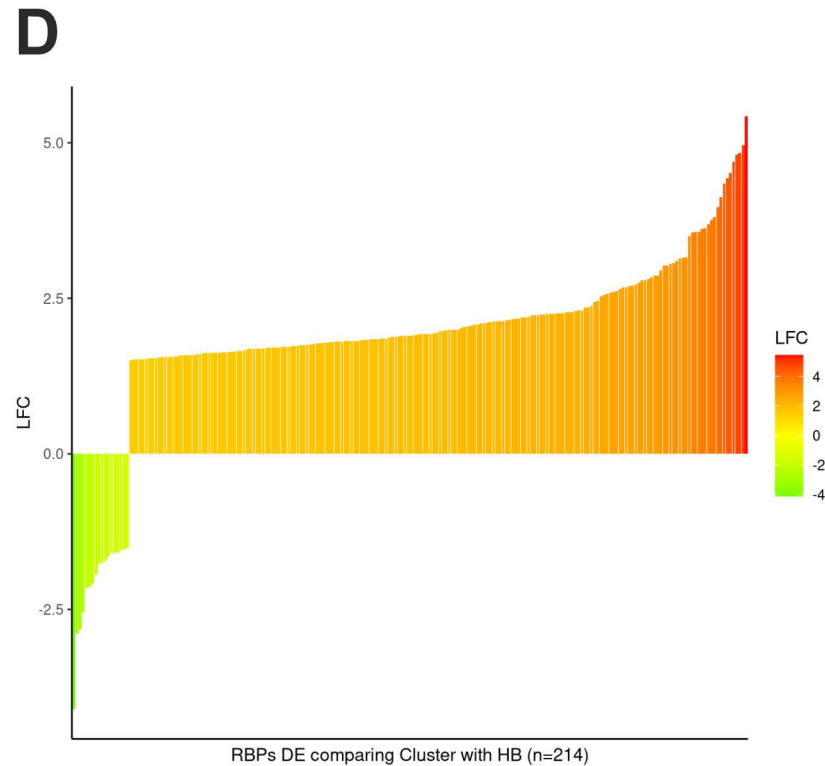
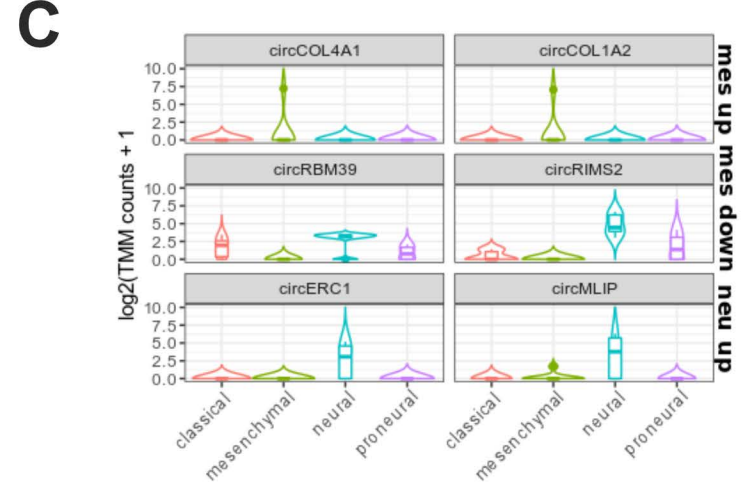
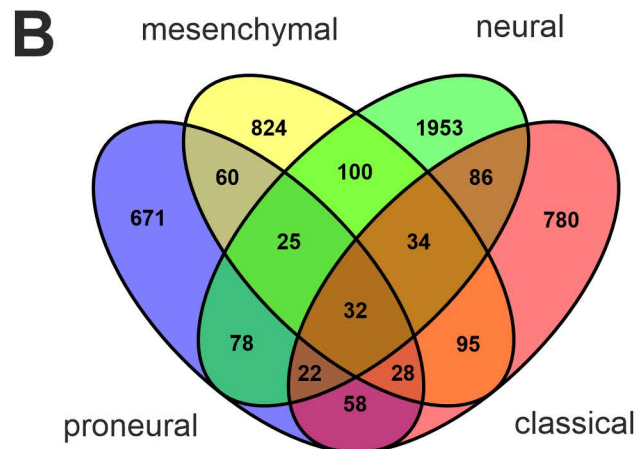
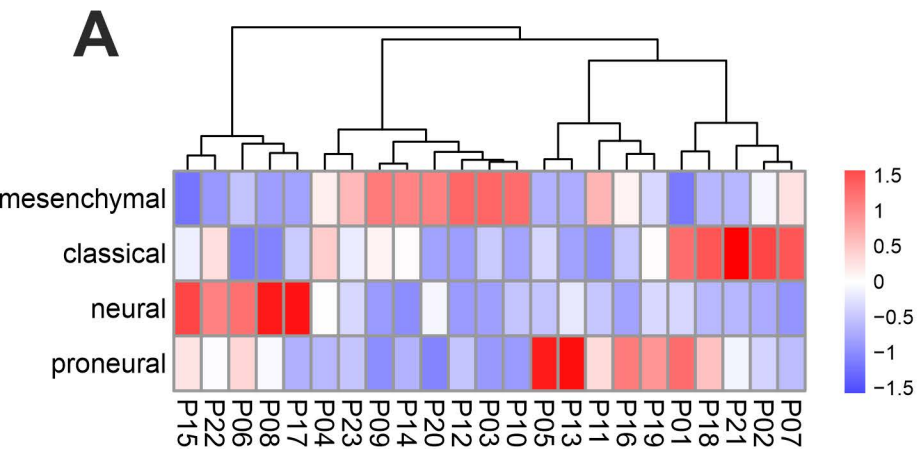


B



C





Supplementary Figure 1. Overview of the features of circRNAs identified in GBM-PRM and GBM-REC tissues compared to HB control. **A.** Barplot presents the genomic origin of identified circRNAs from which the vast majority are derived from exons. **B.** Histogram displays a spliced length distribution of identified circRNAs for analyzed tissues.

Supplementary Figure 2. Percentage of unique circRNA per chromosome in GBM-PRM and GBM-REC in comparison to the HB control.

Supplementary Figure 3. Cluster heatmap illustrating differential expression of circRNAs among GBM (GBM-PRM and GBM-REC) versus HB samples with the presence of different circRNAs in individual molecular GBM subtypes.

Supplementary Figure 4. A. GO ontologies. Enrichment was calculated using mean circRNA log2 fold change for the particular host genes. **B.** Bubble map of KEGG enriched terms using GO ontologies. Enrichment was calculated using mean circRNA log2 fold change for the particular host genes.

Supplementary Figure 5. Cluster heatmap illustrating differential expression of RBPs among GBM (GBM-PRM and GBM-REC) versus HB samples. Expression of 214 RBPs can be used to define novel patients' subgroups beyond known molecular subtypes.

Supplementary Figure 6. RNase R treatment of circRNAs and their linear counterparts. **A-C.** Bands represent PCR products on agarose gel of selected downregulated, upregulated and progression-related candidates, respectively. **1.** Band represent PCR product on agarose gel of circRNA without RNase R treatment; **2.** Band represent PCR product on agarose gel of mRNA without RNase R treatment; **3.** Band represent PCR product on agarose gel of circRNA with RNase R treatment; **4.** Band represent PCR product on agarose gel of mRNA with RNase R treatment; **5, 6.** Negative control of PCR product.

Supplementary Figure 7. Normalized expression distribution of RBP's transcripts in HB and GBM. **A.** Upregulated RBPs with motifs enriched in upregulated circRNAs. **B.** Downregulated RBPs with motifs enriched in upregulated circRNAs. **C.** Upregulated RBPs with motifs enriched in downregulated circRNAs. **D.** Downregulated RBPs with motifs enriched in downregulated circRNAs. Sequence logos represent motifs enriched in circRNAs.

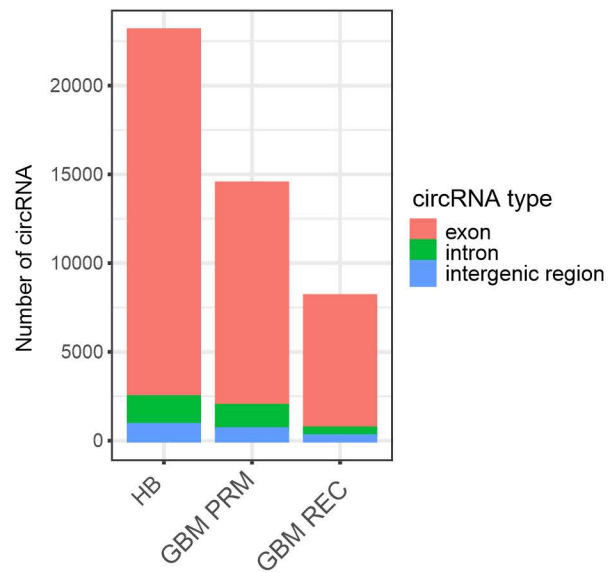
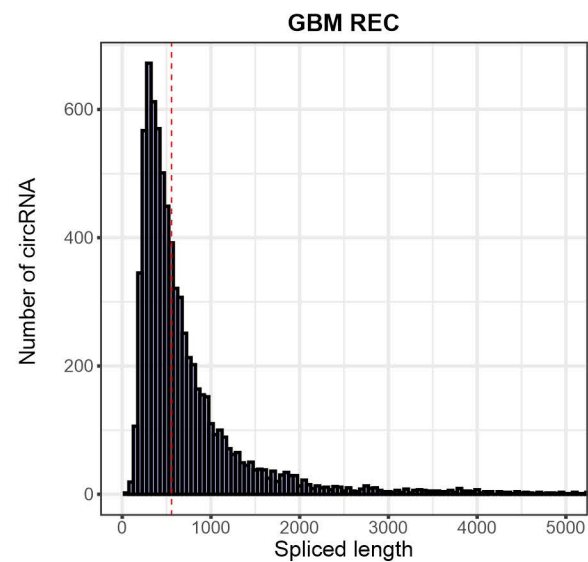
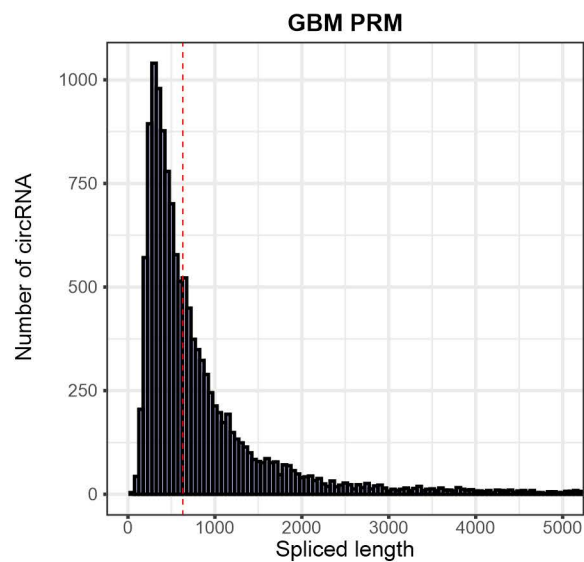
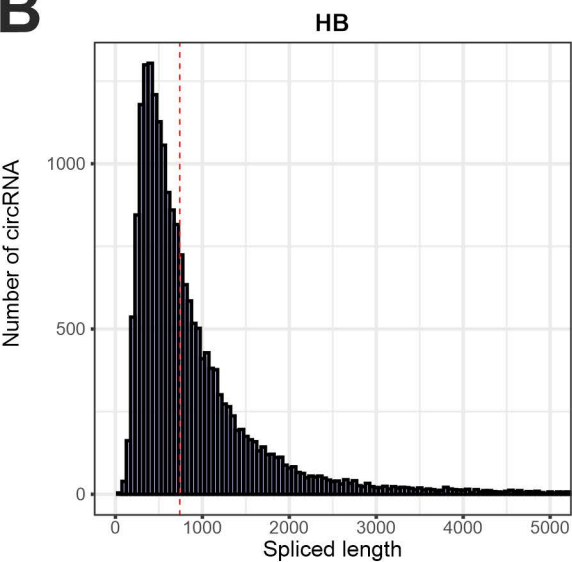
Supplementary Figure 8. Boxplots representing correlation coefficient between RBPs with motifs enriched in circRNAs and differentially expressed circRNAs.

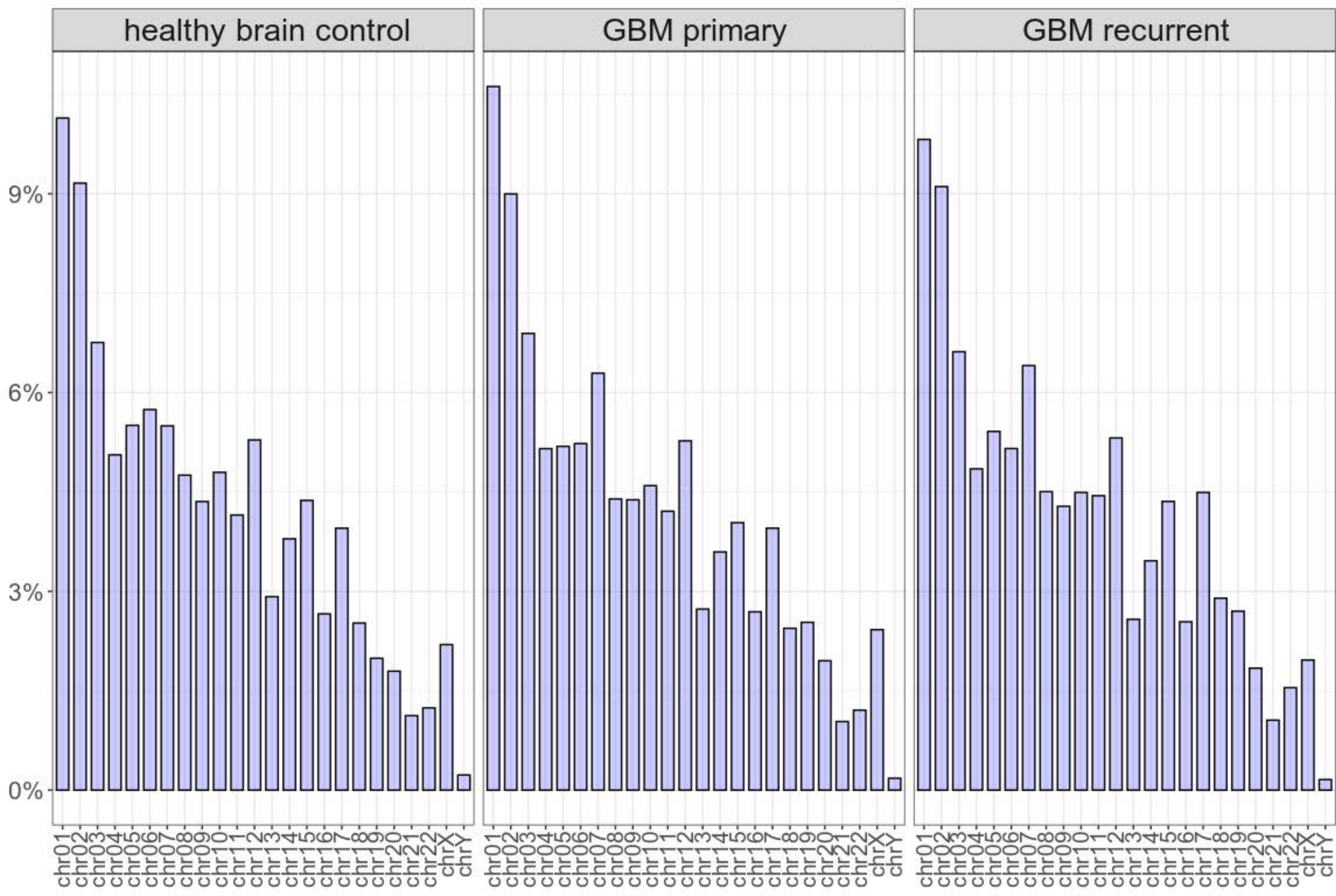
Supplementary Figure 9. Upset plot for RBPs with binding motifs in flanking introns vs RBPs with binding motifs in circRNAs.

Supplementary Figure 10. Survival analysis for differentially expressed RBPs based on TCGA glioblastoma dataset. **A.** Kaplan-Meier curves for RBPs upregulated in analyzed 23 GBM samples and significantly correlated with overall survival rate with TCGA GBM dataset. **B.** The same as A, for downregulated RBPs. RBPs highlighted red in both panels were previously shown to be brain tumor markers, correlated with disease outcome or response to treatment.

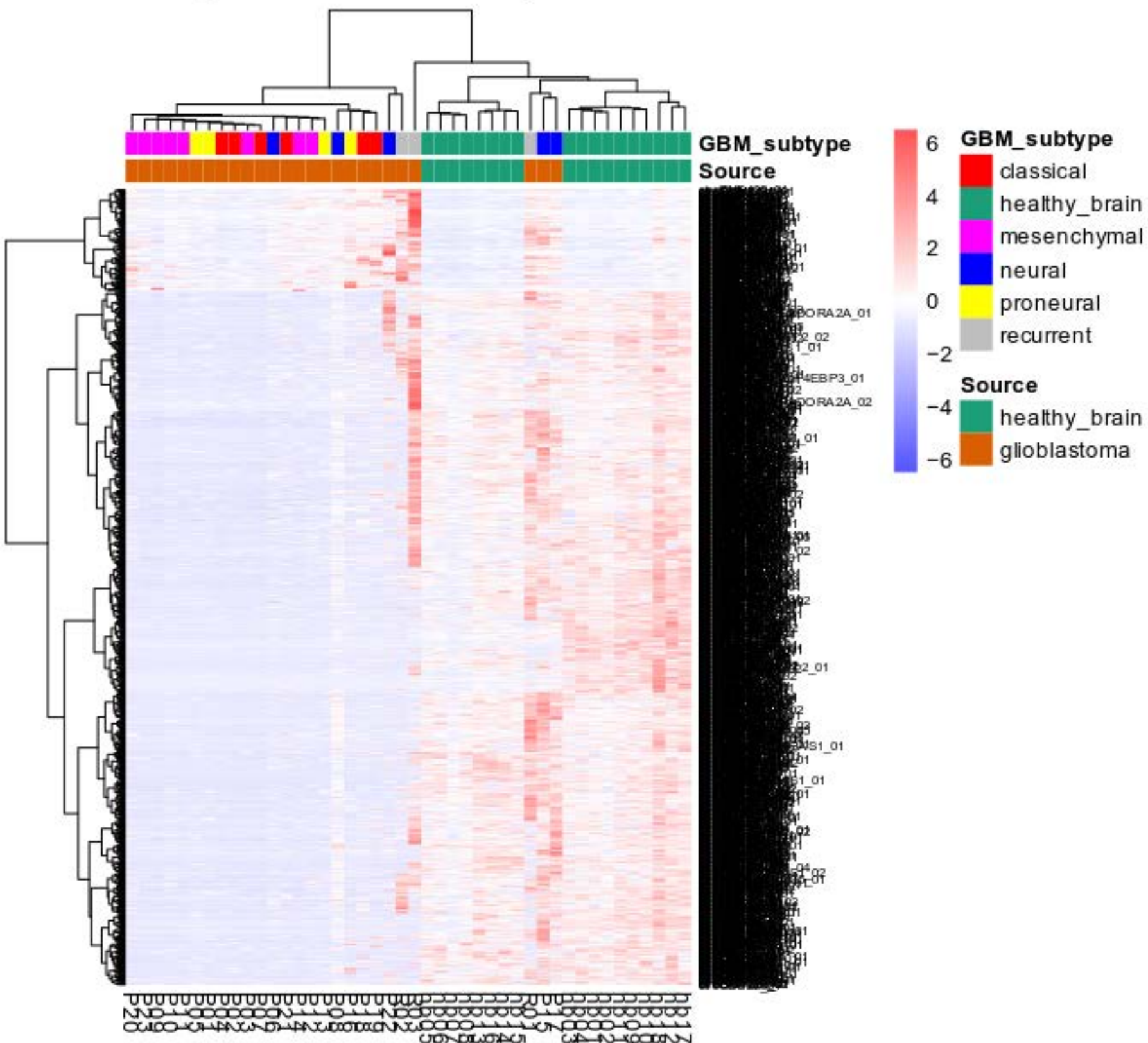
Supplementary Figure 11. Electrophoretic separation of total RNA isolated from HB samples. The electrophoretic separation was prepared using the Agilent 2100 Bioanalyzer system. Only samples with RIN (RNA Integrity Number) value above 8 were taken into further investigation.

Supplementary Figure 12. Electrophoretic separation of total RNA isolated from GBM-PRM and GBM-REC samples. Electrophoretic separation was prepared using the Agilent 2100 Bioanalyzer system. Only samples with RIN (RNA Integrity Number) value above 7 were taken into further investigation.

A**B**

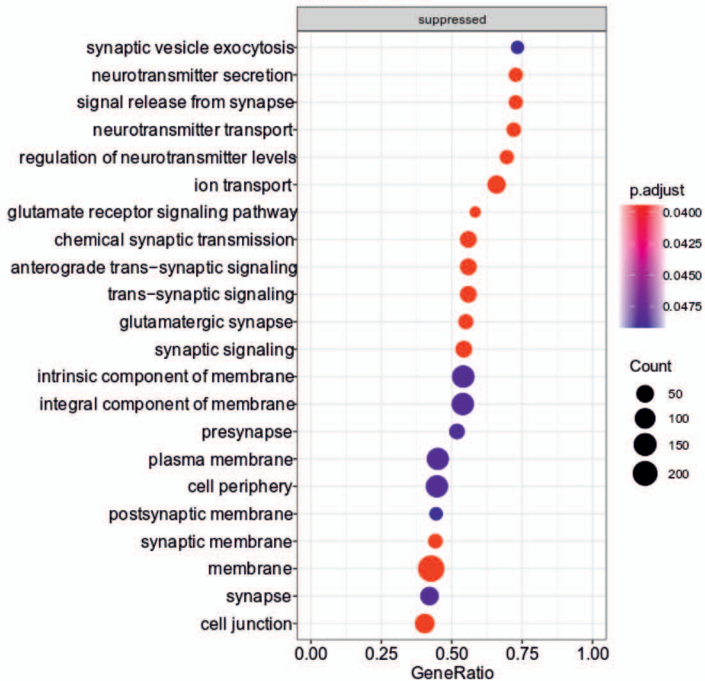


Differential circRNA expression glioblastoma vs healthy brain



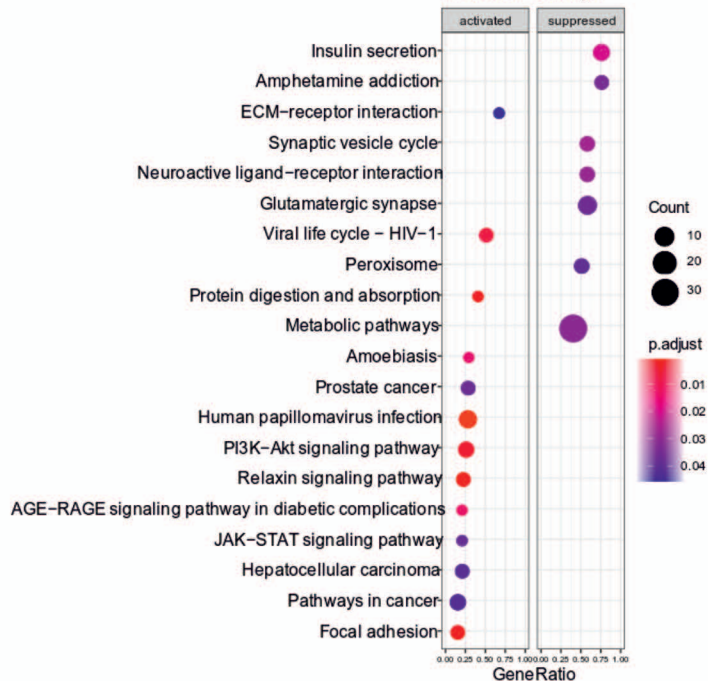
A

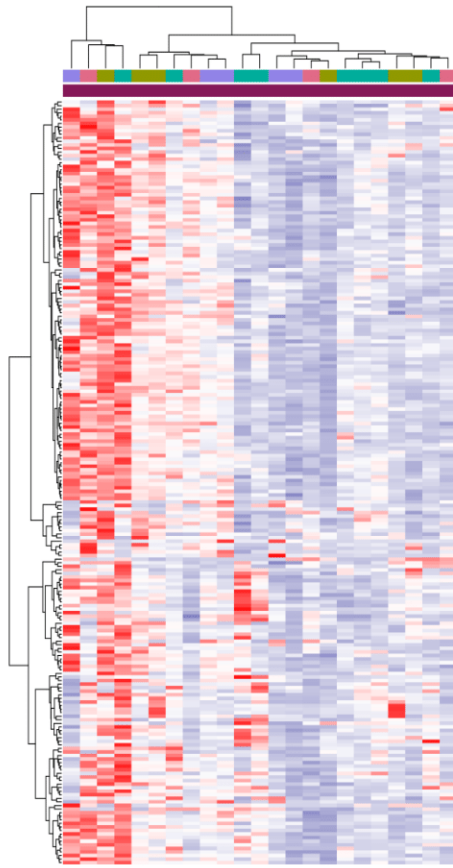
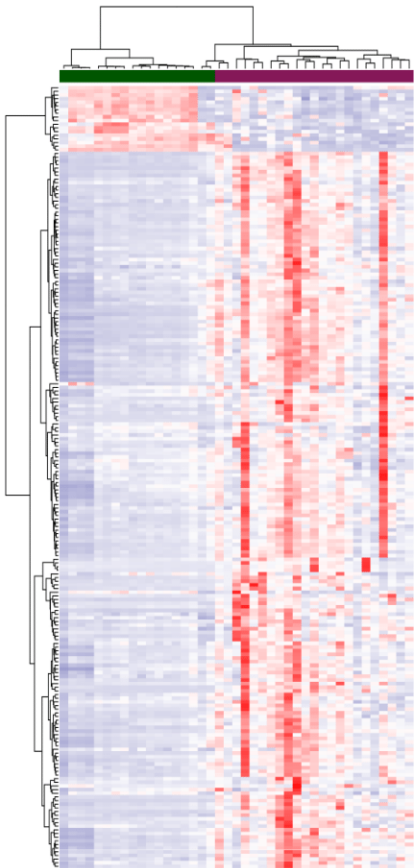
Enriched Terms



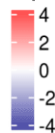
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Enriched Pathways



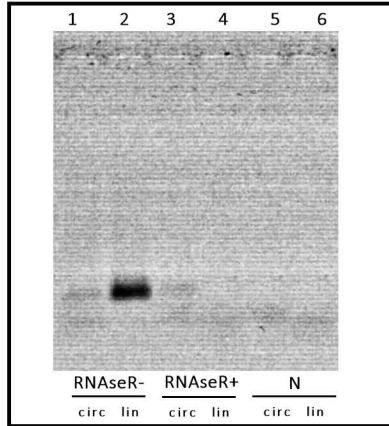
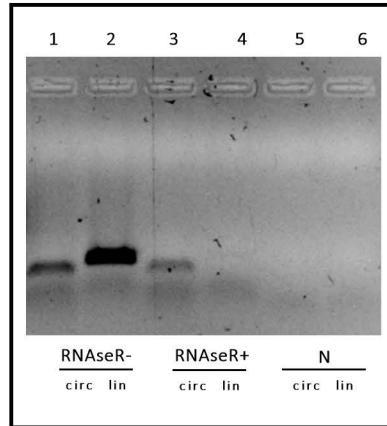
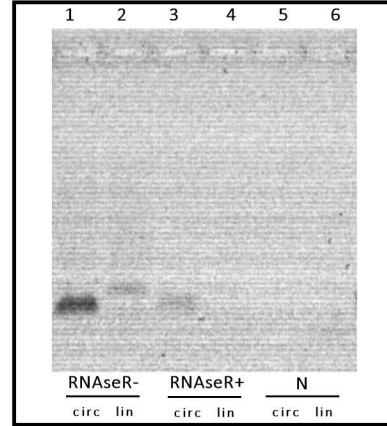
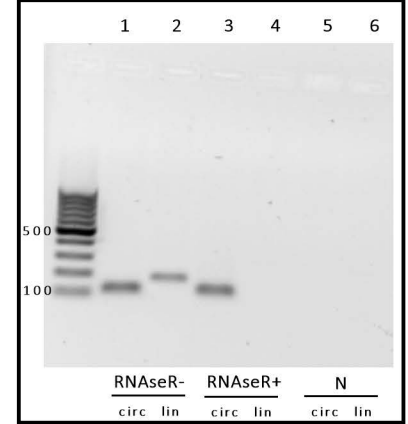
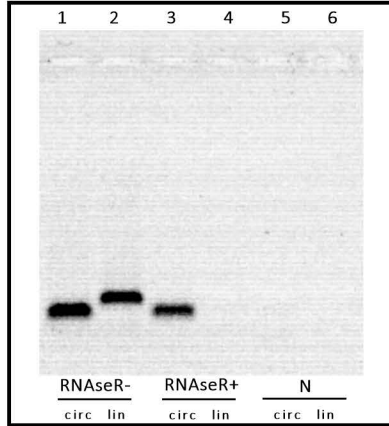
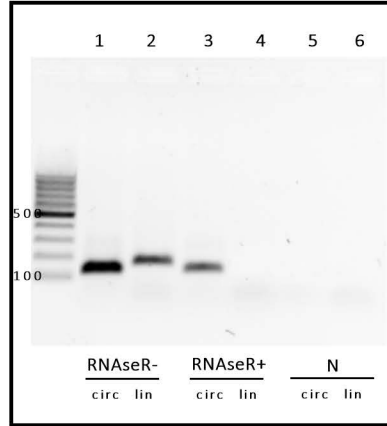
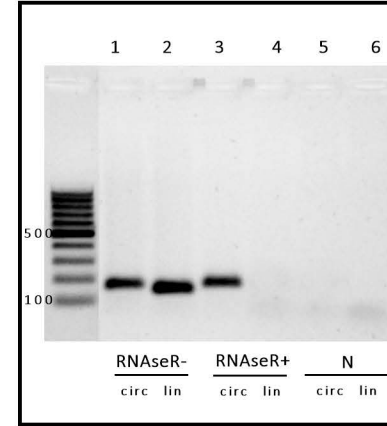
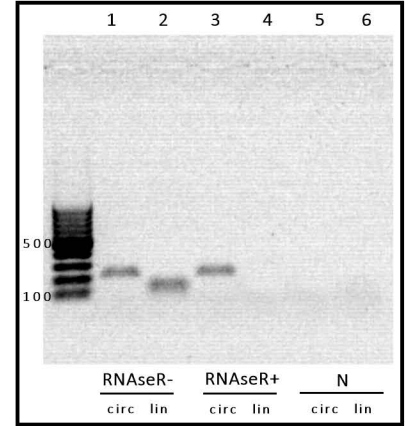
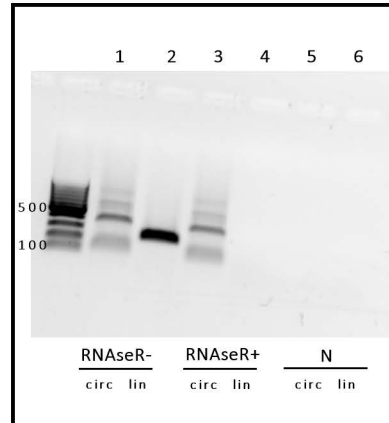
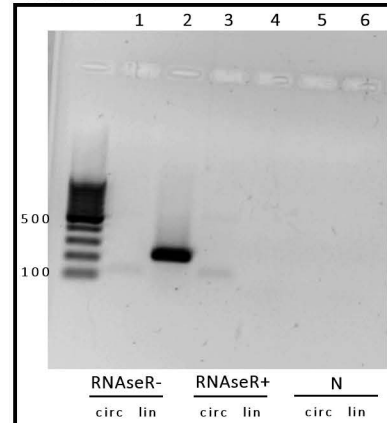
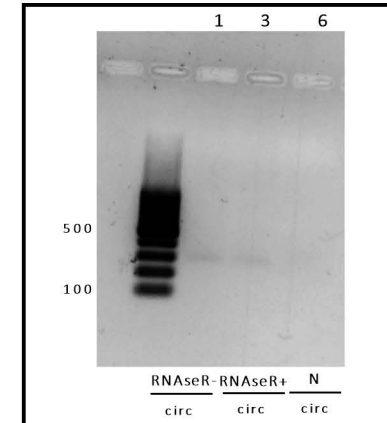


RBP expression



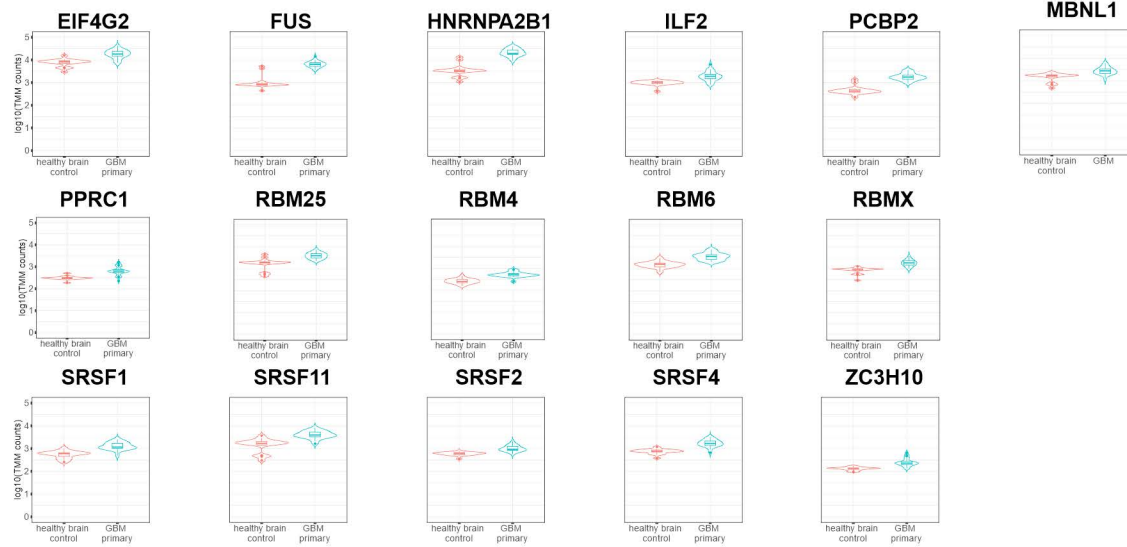
GBM
HB

classical
mesenchymal
neural
proneural

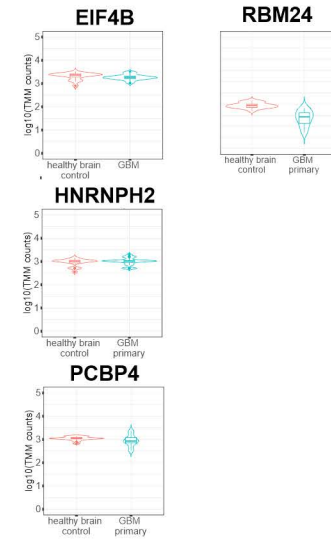
a**CADPS2****EPB41L5****UNC13C****USP45****b****ARID1A****GUSBP1****PLOD2****VCAN****c****EGFR****HLA-B****Intergenic circRNA**

upregulated circRNA

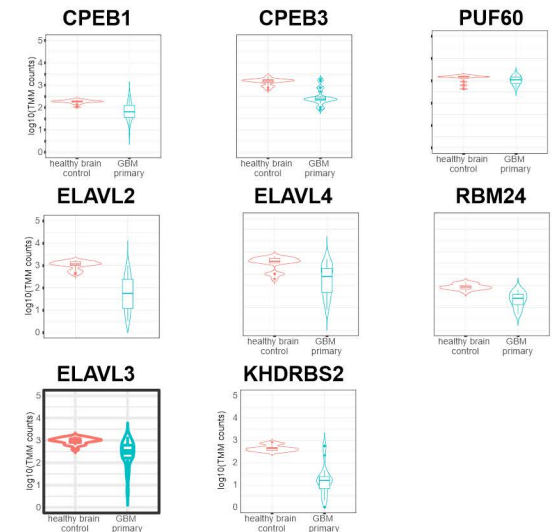
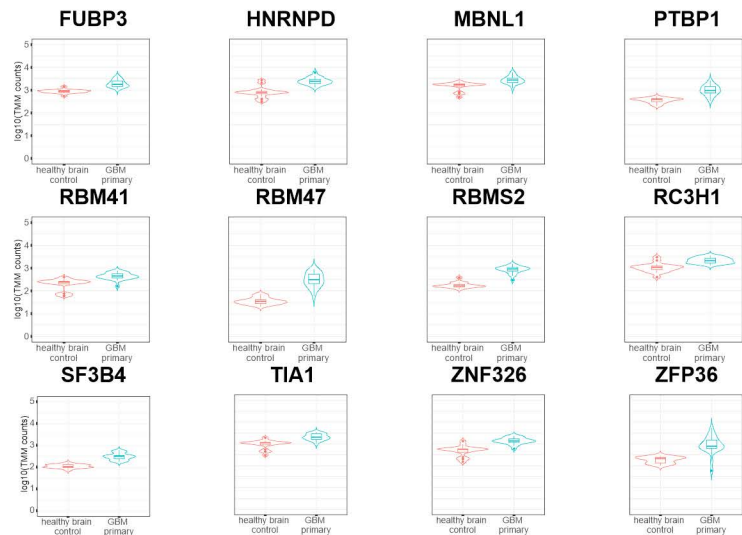
upregulated RBPs

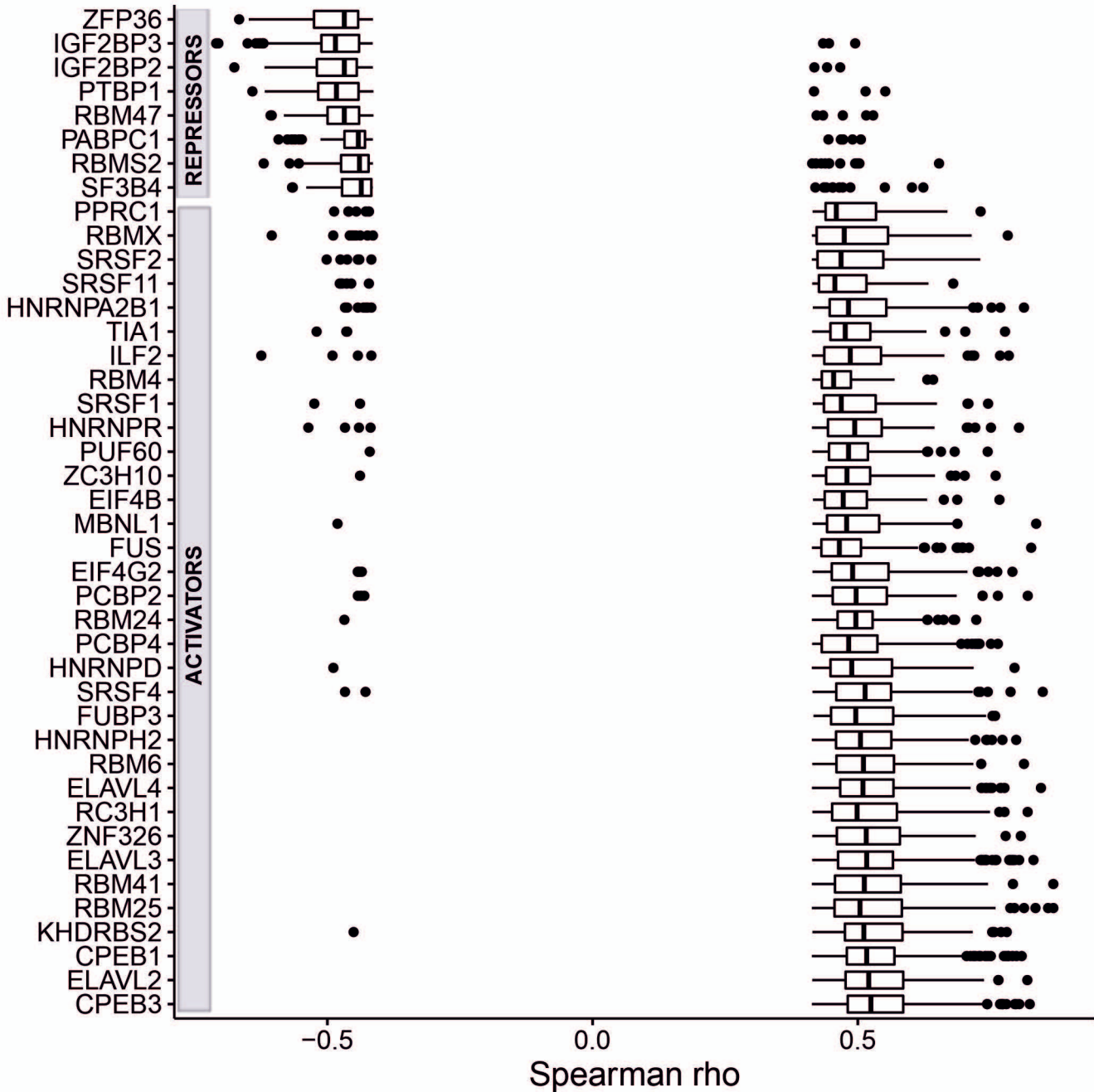


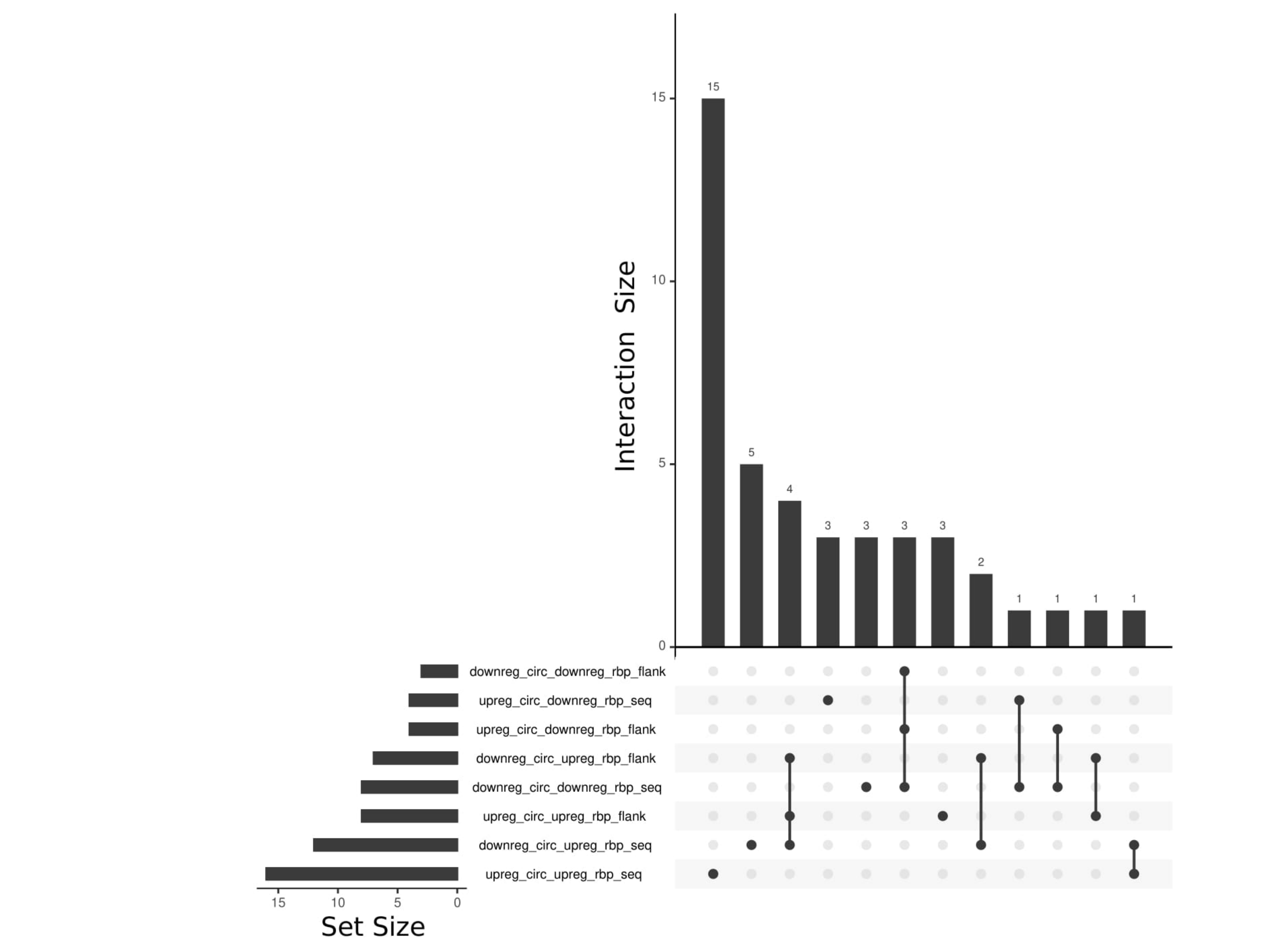
downregulated RBPs



downregulated circRNA







RBP											
dC_uR_s*				dC_dR_s*				dC_uR_s*	dC_dR_s*	dC_dR_s*	uC_uR_f*
uC_uR_s*	dC_uR_s*	uC_uR_f*	uC_dR_s*	dC_dR_s*	uC_dR_f*	uC_uR_f*	dC_uR_s*	dC_dR_s*	dC_dR_s*	uC_uR_f*	uC_uR_s*
dC_uR_f*				dC_dR_f*				dC_uR_f*	uC_dR_s*	uC_dR_f*	dC_uR_f*
EIF4G2	FUBP3	RBMS2	EIF4B	CPEB1	CPEB3	HNRNPR	RBM41	RBM24	ELAVL3	PABPC1	MBNL1
FUS	HNRNPD	SF3B4	HNRNPH2	ELAVL4	ELAVL2	IGF2BP2	RBM47				
HNRNPA2	PTBP1	TIA1	PCBP4	PUF60	KHDRBS2	IGF2BP3					
B1	PCBP2	PCBP3	ZNF326								
ILF2	ZNF326										
PCBP2											
PPRC1											
RBM25											
RBM4											
RBM6											
RBMX											
SRSF1											
SRSF11											
SRSF2											
SRSF4											
ZC3H10											

*dC_dR_s – downregulated circRNA, downregulated RBP with motifs enriched in circRNA sequences

*dC_uR_s – downregulated circRNA, upregulated RBP with motifs enriched in circRNA sequences

*uC_dR_s – upregulated circRNA, downregulated RBP with motifs enriched in circRNA sequences

*uC_uR_s – upregulated circRNA, upregulated RBP with motifs enriched in circRNA sequences

*dC_dR_f – downregulated circRNA, downregulated RBP with motifs enriched in circRNA flanking introns

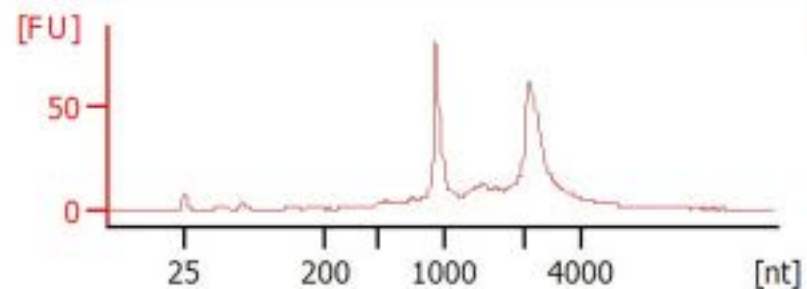
*dC_uR_f – downregulated circRNA, upregulated RBP with motifs enriched in circRNA flanking introns

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*uC_uR_f – upregulated circRNA, upregulated RBP with motifs enriched in circRNA flanking introns

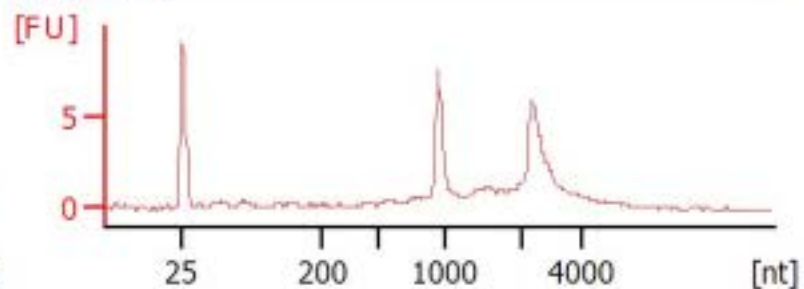
Takara

RIN: 9



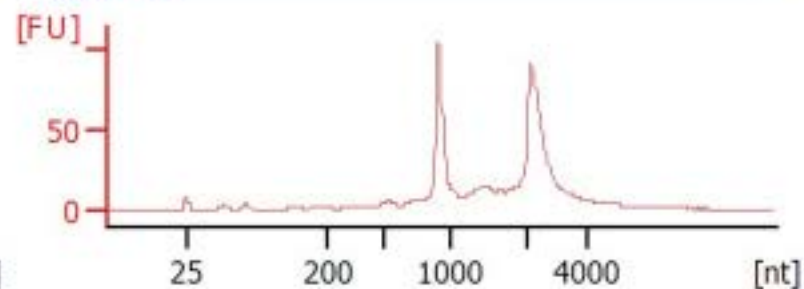
Ambion 6051

RIN: 8.80



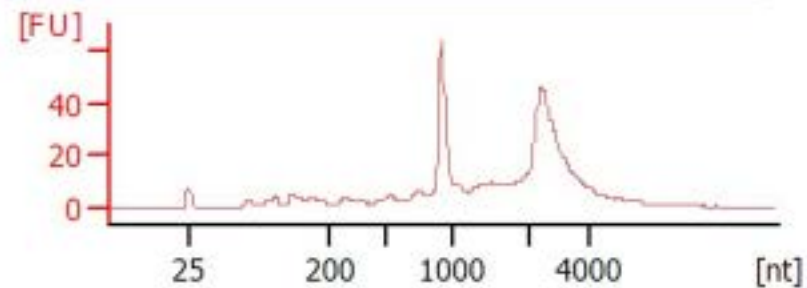
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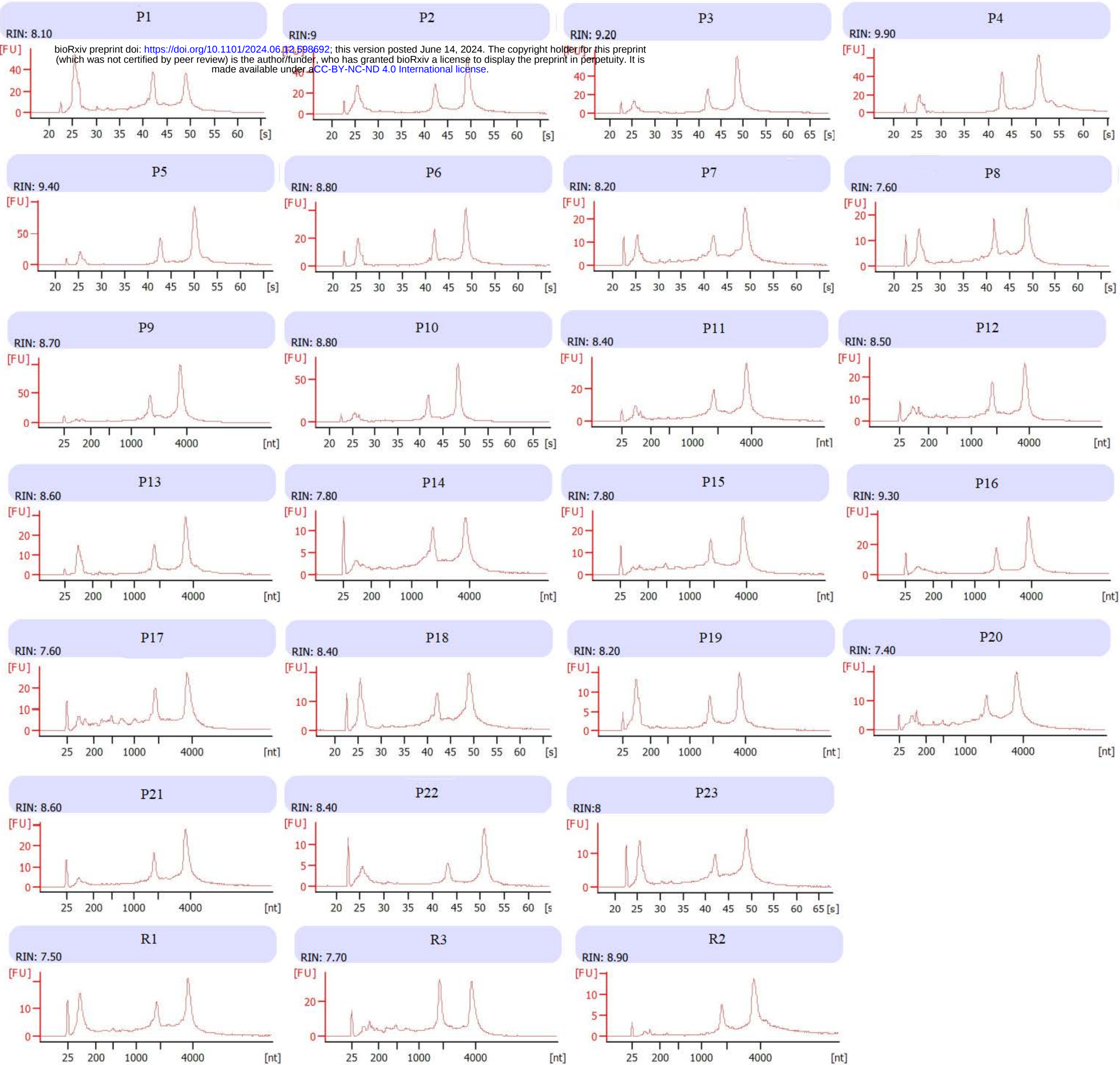
RIN: 9.10



Clontech

RIN: 8.20





Patient ID	Sex	Age	Symptoms				Tumor location (hemisphere)			TNM classifica	Extent of resection		RNA RIN value
			Headache	Dizziness	Aphasia	Other	Right	Left	Both		Total	Subtotal	
P01	Male	59	-	-	-	x	-	x	-	T3	-	x	8.1
P02	Female	58	-	-	x	-	-	x	-	T2	x	-	9
P03	Female	56	x	x	-	-	x	-	-	T3	x	-	9.2
P04	Female	65	x	x	-	-	x	-	-	-	-	x	9.9
P05	Male	-	-	-	x	x	-	x	-	-	-	x	9.4
P06	Male	-	-	-	-	x	x	-	-	-	x	-	8.8
P07	Female	58	-	-	-	x	x	-	-	-	x	-	8.2
P08	Male	61	-	-	-	x	-	x	-	T2	x	-	7.6
P09	Female	63	-	-	-	x	x	-	-	T1	x	-	8.7
P10	Male	52	x	-	-	x	x	-	-	T2	x	-	8.8
P11	Male	62	-	-	-	x	x	-	-	T2	x	-	8.4
P12	Male	67	No data available										8.5
P13	Male	49	-	-	x	-	-	x	-	T1	x	-	8.6
P14	Male	60	x	x	-	-	x	-	-	T1	x	-	7.8
P15	Female	70	x	x	-	x	-	-	x	T4	-	x	7.8
P16	Male	83	x	x	-	-	x	-	-	T3	x	-	9.3
P17	Male	64	-	-	x	-	-	-	x	T4	x	-	7.6
P18	Female	74	-	-	-	x	x	-	-	-	-	x	8.4
P19	Male	68	-	-	-	x	x	-	-	-	-	x	8.2
P20	Male	65	x	-	x	x	-	x	-	-	x	-	7.4
P21	Female	68	-	-	-	x	x	-	-	-	x	-	8.6
P22	Female		No data available										8.4
P23	Female	58	No data available										8
R1	Female	52	-	-	-	-	-	-	-	-	-	x	7.5
R2	Male	49	-	-	x	x	-	x	-	T3	x	-	8.9
R3	Male	47	-	-	-	x	x	-	-	-	x	-	7.7

Manufacturer	Product name	Catalog number	Lot number	Number of patients	Number of females	Number of males	RNA RIN value
Ambion	First Choice Human Brain Reference RNA	AM6050	1204014	23	10	13	9.1
Ambion	FirstChoice® Human Brain Reference Total RNA	6051	105P055201A	23	10	13	9
Clontech	Human Brain Total RNA	636530	1812054	3	0	3	8.2
Takara	Human Brain Total RNA	636530	1602002	3	0	3	8.8

Manufacturer	Product name	Catalog number	Lot number	Number of patients	Number of females	Number of males	RNA RIN value
Ambion	First Choice Human Brain Reference RNA	AM6050	1204014	23	10	13	9.1
Ambion	FirstChoice® Human Brain Reference Total RNA	6051	105P055201A	23	10	13	9
Clontech	Human Brain Total RNA	636530	1812054	3	0	3	8.2
Takara	Human Brain Total RNA	636530	1602002	3	0	3	8.8

Gene ID	Circular RNA					Linear RNA		
	hsa name	Chromosomal coordinates	Fold change RNA-seq	Fold change qPCR	RefSeq ID	Chromosomal coordinates	Fold change RNA-seq	Fold change qPCR
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EPB41L5	hsa_circ_0008278	chr2:120885263-120932580	-3,88636	-4,49000	NM_020909.4	chr2:120770653-120936695	-1,47374	2,27899
UNC13C	hsa_circ_0103896	chr15:54304844-54308083	-4,09834	-5,07000	NM_001080534.3	chr15:54270638-54920803	-4,42962	-3,08617
USP45	hsa_circ_0077426	chr6:99912479-99958106	-4,99468	-0,03000	NM_001080481.3	chr6:99880201-99963299	-1,38392	-0,43514
ARID1A	hsa_circ_0008494	chr1:27056141-27059283	2,63866	0,35705	NM_006015.6	chr1:26693236-26782104	1,02467	2,28585
GUSBP1	hsa_circ_0128780	chr5:21491429-21497305	4,47198	2,90187	NR_027028.3	chr5:21459622-21497305	ns	2,15453
PLOD2	hsa_circ_0141963	chr3:145838898-145842016	2,78193	2,37705	NM_182943.3	chr3:146069440-146163653	2,34880	4,43969
VCAN	hsa_circ_0073237	chr5:82832825-82838087	3,87227	4,54000	NM_004385.5	chr5: 83471618-83582303	2,42000	4,44258
EGFR	hsa_circ_0080229	chr7:55231426-55233130	11,38770	12,83759	NM_005228.5	chr7:55019017-55211628	4,17302	1,50212
HLA-B	No record available	chr6:31237743-31322442	6,92219	-0,39654	NM_005514	chr6:31237743-3132242	2,35819	-0,61401
Intergenic circRNA	No record available	chr6:29913011-29976954	7,17446	0,31399	-	-	-	-

ns – no statistical significance for $p \geq 0.05$

neuVSothersGBMres

seqnames	start	end	width	strand	CLR	lfc	pval	fdr	ENSEMBL	geneName
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chr6	170846322	170858201	11880	-	0,045	3,955494779	9,7373E-09	2,76113E-06	ENSG00000008018	PSMB1
chr3	183368084	183390272	22189	+	0,103	4,605576186	1,0647E-08	2,76113E-06	ENSG00000114796	KLHL24
chr2	120885264	120932580	47317	+	0,222	4,617070935	2,9503E-08	5,04834E-06	ENSG00000115109	EPB41L5
chr3	183361268	183390272	29005	+	0,136	3,83319274	3,62364E-08	5,04834E-06	ENSG00000114796	KLHL24
chr3	27420740	27465643	44904	-	0,105	4,709664508	3,89332E-08	5,04834E-06	ENSG00000033867	SLC4A7
chr8	142264088	142264728	641	-	1	3,063474475	1,64285E-07	1,82591E-05	ENSG00000022567	SLC45A4
chr6	62362160	62407158	44999	-	0,909	4,928230881	1,99074E-07	1,936E-05	n/a	
chr6	54013854	54067031	53178	+	0,4	5,166361442	3,26084E-07	2,81882E-05	ENSG00000146147	MLIP
chr12	1399018	1481143	82126	+	0,091	3,43193012	3,84713E-07	2,99307E-05	ENSG00000082805	ERC1
chr9	88190230	88248289	58060	-	0,171	4,063879351	8,13574E-07	5,71873E-05	ENSG00000135049	AGTPBP1
chr11	58317259	58318705	1447	-	0,357	4,602237706	8,82066E-07	5,71873E-05	ENSG00000110031	LPXN
chr5	113740135	113740553	419	+	0,769	3,681516973	1,30918E-06	7,83495E-05	ENSG00000080709	KCNN2
chr2	2840691	2842060	1370	-	0,316	5,689434335	1,6356E-06	8,49899E-05	ENSG00000237720	
chr12	1399018	1516199	120602	+	0,177	5,421173295	1,63862E-06	8,49899E-05	ENSG00000082805	ERC1
chr10	116879949	116931050	51102	+	0,32	3,148113792	2,04735E-06	9,95524E-05	ENSG00000107518	ATRNL1
chr7	82763566	82764972	1407	-	0,364	3,746826896	2,55915E-06	0,000117119	ENSG00000186472	PCLO
chr6	54013854	54095715	81862	+	0,571	5,321185378	3,04547E-06	0,000131632	ENSG00000146147	MLIP
chr3	183361268	183369064	7797	+	0,07	2,854247068	8,39473E-06	0,000343742	ENSG00000114796	KLHL24
chr7	22330794	22357656	26863	-	0,571	4,251590287	9,81878E-06	0,000381951	ENSG00000136237	RAPGEF5
chr1	32381496	32385259	3764	-	0,667	2,023764581	1,1983E-05	0,000443942	ENSG00000184007	PTP4A2
chr5	79745410	79770649	25240	+	0,274	4,032438375	1,34184E-05	0,000474525	ENSG00000039319	ZFYVE16
chr15	67524152	67529158	5007	-	0,125	2,341385628	1,70285E-05	0,000567904	ENSG00000103591	AAGAB
chr6	136709531	136710655	1125	-	0,138	3,303743339	1,75189E-05	0,000567904	ENSG00000135525	MAP7
chr1	243708812	243859018	150207	-	0,135	2,687572131	2,04721E-05	0,000619259	ENSG00000117020	AKT3
chr10	52193236	52350007	156772	-	0,545	4,81732562	2,0695E-05	0,000619259	ENSG00000198964	SGMS1
chr9	26424107	26569673	145567	-	0,312	5,289695405	2,24047E-05	0,000645589	n/a	
chr15	33149216	33194241	45026	-	0,4	3,905815301	3,20048E-05	0,000860736	ENSG00000248905	FMN1
chr7	22347958	22357656	9699	-	0,5	3,911370045	3,2084E-05	0,000860736	ENSG00000136237	RAPGEF5
chr6	73016961	73043538	26578	+	0,526	3,258524438	3,99216E-05	0,0010353	ENSG00000079841	RIMS1
chr8	105080740	105161076	80337	+	1	3,597941612	4,23829E-05	0,001046778	ENSG00000176406	RIMS2
chr5	10415600	10417516	1917	+	0,052	2,115779451	4,30551E-05	0,001046778	ENSG00000145495	MARCHF6
chr13	84376512	84389879	13368	-	0,889	4,292221494	5,15011E-05	0,001214178	n/a	
chr18	8718422	8720494	2073	+	0,4	3,002830577	5,94144E-05	0,001359541	ENSG00000168502	MTCL1
chr18	19345733	19359646	13914	+	0,298	1,950692771	7,0778E-05	0,001573294	ENSG00000101752	MIB1
chr11	46098305	46113774	15470	-	0,169	1,776897459	7,61272E-05	0,001645193	ENSG00000135365	PHF21A
chr6	107824861	107827631	2771	+	0,197	2,079324083	8,75885E-05	0,001841726	ENSG00000112320	SOBP
chr10	15875629	15889642	14314	-	0,148	2,420495441	0,000106484	0,002180128	ENSG00000148481	MINDY3
chr14	99924616	99932150	7535	-	0,146	1,684126126	0,0001148	0,002290111	ENSG00000183576	SETD3
chr7	22306583	22357656	51074	-	0,273	3,824113557	0,00014436	0,002807806	ENSG00000136237	RAPGEF5
chr3	18419662	18462483	42822	-	0,144	3,951722322	0,000175025	0,003321201	ENSG00000182568	SATB1
chr14	32559708	32586493	26786	+	0,273	1,680381595	0,000181317	0,003358681	ENSG00000100852	ARHGAP5
chr14	93760204	93762503	2300	-	0,231	2,975823129	0,000248786	0,004501288	ENSG00000011114	BTBD7
chr9	103261047	103312442	51396	+	0,2	3,480834438	0,00030921	0,005372671	ENSG00000241697	TMEFF1
chrX	139865340	139866824	1485	+	0,911	2,228808943	0,000310759	0,005372671	ENSG00000203930	LINC00632
chr2	40366541	40405633	39093	-	0,279	4,187347741	0,000340041	0,005751134	ENSG00000183023	SLC8A1
chr6	170852689	170858201	5513	-	0,06	3,120004332	0,00035769	0,005920912	ENSG00000008018	PSMB1
chr6	136704809	136710655	5847	-	0,142	4,177726512	0,000408704	0,006624414	ENSG00000135525	MAP7
chr15	54304845	54308083	3239	+	0,571	3,891185257	0,000538629	0,008552107	ENSG00000137766	UNC13C
chr4	52729603	52758017	28415	+	0,08	2,237421408	0,000568347	0,008641482	ENSG00000109184	DCUN1D4
chr8	141749117	141762415	13299	-	0,07	2,575411686	0,000569392	0,008641482	ENSG00000169398	PTK2
chr1	8601273	8617582	16310	-	0,152	1,806280991	0,00057758	0,008641482	ENSG00000142599	RERE
chr14	104245082	104263855	18774	-	0,381	3,418653985	0,000750489	0,010957512	ENSG00000088808	PPP1R13B
chr9	103261047	103279053	18007	+	0,217	1,873800556	0,000760547	0,010957512	ENSG00000241697	TMEFF1
chr7	14613837	14712655	98816	-	0,364	2,636741417	0,000916648	0,012966407	ENSG00000136267	DGKB
chr2	72945232	72960247	15016	-	0,547	1,438495517	0,001148258	0,01595258	ENSG00000144036	EXOC6B
chr14	97299804	97327072	27269	+	0,2	2,31095923	0,001213125	0,016558098	ENSG00000100749	VRK1
chr12	100166700	100175875	9176	-	0,6	2,940845415	0,001283174	0,017212233	ENSG00000185046	ANKS1B
chr2	168920010	168986268	66259	-	0,429	1,555020917	0,00144853	0,01910096	ENSG00000198648	STK39
chr2	207144264	207162097	17834	+	0,125	3,208150864	0,001678295	0,021464066	ENSG00000204186	ZDBF2
chr7	38050523	38053183	2661	+	0,933	3,575119826	0,00171814	0,021464066	ENSG00000106483	SFRP4
chr9	37126309	37127260	952	+	0,3	2,391414649	0,001747904	0,021464066	ENSG00000147905	ZCCHC7
chrX	110385324	110416309	30986	+	0,211	2,600384509	0,001782976	0,021464066	ENSG00000077264	PAK3
chr14	66028055	66028484	430	+	0,27	2,412641838	0,001789829	0,021464066	ENSG00000033170	FUT8
chr6	158703295	158735300	32006	+	0,364	1,473241057	0,00179327	0,021464066	ENSG00000130338	TULP4
chr10	86198268	86237420	39153	+	0,3	1,870019922	0,001918997	0,022620906	ENSG00000107771	CCSER2
chr16	53288350	53308214	19865	+	0,04	2,925267877	0,00237183	0,027541547	ENSG00000177200	CHD9
chr7	86223627	86226365	2739	-	1	2,915965361	0,002483987	0,02821497	n/a	
chr12	12397196	12397589	394	-	0,198	1,736377083	0,002502356	0,02821497	ENSG00000070018	LRP6
chr1	243776973	243859018	82046	-	0,065	2,261623707	0,002660108	0,029565199	ENSG00000117020	AKT3
chr14	32559708	32563592	3885	+	0,146	1,788528495	0,002809101	0,0303872	ENSG00000100852	ARHGAP5
chr2	136432902	136437894	4993	+	0,207	1,621839528	0,002813168	0,0303872	ENSG00000048991	R3HDM1
chr3	157839892	157841780	1889	+	0,129	1,674350904	0,002878342	0,0303872	ENSG00000174891	RSRC1
chr10	112723883	112745523	21641	+	0,235	1,915700248	0,002890299	0,0303872	ENSG00000108061	SHOC2
chr22	28692186	28693840	1655	-	0,162	1,859169432	0,002952538	0,030627666	ENSG00000100154	TTC28
chr11	128993341	129034322	40982	-	0,312	2,975180961	0,003084831	0,031419117	ENSG00000134909	ARHGAP32
chr15	63988323	64008622	20350	-	0,255	1,560946522	0,003109604	0,031419117	ENSG00000103657	HERC1
chr3	66286968	66313803	26836	+	0,417	2,25423707	0,003203301	0,031950878	ENSG00000144741	SLC25A26
chr10	116879949	117001514	121566	+	0,089	3,350245595	0,003356802	0,03305813	ENSG00000107518	ATRNL1
chr13	78293667	78324793	33827	+	0,152	1,734048851	0,00353967	0,034285692	ENSG00000139737	SLAIN1
chr18	54426096	54448887	22792	+	0,143	2,494371401	0,00356959	0,034285692	ENSG00000091157	WDR7
chr3	129546646	129551669	5024	-	0,267	1,970306773	0,003665235	0,034758765	ENSG00000172765	TMCC1
chr2	72958136	72960247	2112	-	0,174	1,82741032	0,003708197	0,034758765	ENSG00000144036	EXOC6B
chr18	29691717	29704808	13092	+	0,581	2,717263365	0,004221218	0,038598644	ENSG00000134758	RNF138
chr18	45391430	45423180	31751	-	0,052	2,790593859	0,004230583	0,038598644	ENSG00000175387	SMAD2
chr8	62593527	62596747	3221	-	0,129	1,686486894	0,004266688	0,038598644	ENSG00000198363	ASPH
chr10	116879949	116975638	95690	+	0,323	2,504294172	0,004320213	0,038633631	ENSG00000107518	ATRNL1
chr5	36953720	36976504	22785	+	0,097	1,431578198	0,005318323	0,047018814	ENSG00000164190	NIPBL

neuVSothersGBMres									
chr6	76344423	76388643	44221 +	0,08	2,057179159	0,005407217	0,047267582	ENSG00000112701	SENP6
chr8	141745350	141762415	17066 -	0,043	2,75439305	0,005526409	0,047772734	ENSG00000169398	PTK2

mesVSothersGBMres

seqnames	start	end	width	strand	CLR	lfc	pval	fdr	ENSEMBL	geneName	
chr13	110827687	110829071	1385	-	0,053		8,00650727	1,3333E-06	0,000651962	ENSG00000187498	COL4A1
chr7	94047043	94049596	2554	-	0,021		7,840550664	1,67599E-06	0,000651962	ENSG00000164692	COL1A2
chr11	120916383	120930794	####	+	0,167		-2,618296874	5,22973E-05	0,013069658	ENSG00000154114	TBCEL
chr8	105080740	105161076	####	+		1	-5,921963777	6,71962E-05	0,013069658	ENSG00000176406	RIMS2
chr3	171965323	171969331	4009	+	0,429		1,321684286	0,000254304	0,039569779	ENSG00000075420	FNDC3B
chr20	34309662	34313077	3416	-	0,125		-4,57441018	0,000377026	0,044854413	ENSG00000131051	RBM39
chr5	72370569	72373320	2752	+	0,435		1,295700561	0,000403574	0,044854413	ENSG00000157107	FCHO2
chr12	69644909	69656342	####	+	0,055		3,243730437	0,000564496	0,049634316	ENSG00000111605	CPSF6
chr3	56694759	56707753	####	-	0,19		-2,482971844	0,000636479	0,049634316	ENSG00000163946	TASOR
chr17	28011581	28030080	####	-	0,19		2,138788477	0,000637973	0,049634316	ENSG00000141298	SSH2

ass_rbp

RBP	pvalue.ass	SYMBOL	n_group
ENSG00000004534	0,020578807	RBM6	2
ENSG00000005189	0,197567493	AC004381.6	2
ENSG00000005436	0,164102912	GCFC2	2
ENSG00000011243	0,057761447	AKAP8L	2
ENSG00000011304	0,731756685	PTBP1	2
ENSG00000012048	0,488484745	BRCA1	2
ENSG00000020577	0,108423932	SAMD4A	2
ENSG00000021776	0,957366961	AQR	2
ENSG00000023191	0,250124641	RNH1	2
ENSG00000037241	0,469403619	RPL26L1	2
ENSG00000041802	0,829079549	LSG1	2
ENSG00000047315	0,49759389	POLR2B	2
ENSG00000048828	0,469403619	FAM120A	2
ENSG00000048991	0,006074548	R3HDM1	2
ENSG00000051596	0,592786454	THOC3	2
ENSG00000055332	0,154473554	EIF2AK2	2
ENSG00000055917	0,418279569	PUM2	2
ENSG00000056586	0,435100901	RC3H2	2
ENSG00000058729	0,592786454	RIOK2	2
ENSG00000059378	0,686168216	PARP12	2
ENSG00000059588	0,312226848	TARBP1	2
ENSG00000061794	0,404506065	MRPS35	2
ENSG00000062582	0,049296155	MRPS24	2
ENSG00000063046	0,342592939	EIF4B	2
ENSG00000063177	0,250124641	RPL18	2
ENSG00000063244	0,146834519	U2AF2	2
ENSG00000065457	0,575120851	ADAT1	2
ENSG00000067248	0,606269411	DHX29	2
ENSG00000067334	0,58538203	DNTTIP2	2
ENSG00000067533	0,957366961	RRP15	2
ENSG00000071626	0,801810074	DAZAP1	2
ENSG00000072364	0,723040907	AFF4	2
ENSG00000074071	0,223191711	MRPS34	2
ENSG00000075151	0,606269411	EIF4G3	2
ENSG00000075975	0,966141153	MKRN2	2
ENSG00000076108	0,492064899	BAZ2A	2
ENSG00000076924	0,694288351	XAB2	2
ENSG00000077348	0,488484745	EXOSC5	2
ENSG00000078687	0,323707606	TNRC6C	2
ENSG00000079785	0,288144259	DDX1	2
ENSG00000080007	0,090903107	DDX43	2
ENSG00000080608	0,723040907	PUM3	2
ENSG00000082515	0,956169331	MRPL22	2
ENSG00000083223	0,469403619	ZCCHC6	2
ENSG00000083520	0,654957627	DIS3	2
ENSG00000083845	0,592786454	RPS5	2
ENSG00000084092	0,956169331	NOA1	2
ENSG00000084623	0,829079549	EIF3I	2
ENSG00000087365	0,528439641	SF3B2	2
ENSG00000087995	0,38283849	METTL2A	2

ass_rbp

ENSG00000088247	0,480555433 KHSRP	2
ENSG00000089009	0,673441635 RPL6	2
ENSG00000089127	0,101991278 OAS1	2
ENSG00000089157	0,373026335 RPLP0	2
ENSG00000090097	0,402468069 PCBP4	2
ENSG00000090263	0,316909836 MRPS33	2
ENSG00000090861	0,213632162 AARS	2
ENSG00000091127	0,492064899 PUS7	2
ENSG00000092199	0,829079549 HNRNPC	2
ENSG00000092208	0,488484745 GEMIN2	2
ENSG00000092847	0,961230483 AGO1	2
ENSG00000095627	0,621398465 TDRD1	2
ENSG00000096080	0,38283849 MRPS18A	2
ENSG00000099381	0,723040907 SETD1A	2
ENSG00000099899	0,090903107 TRMT2A	2
ENSG00000100028	0,070252278 SNRPD3	2
ENSG00000100056	0,76292291 DGCR14	2
ENSG00000100142	0,654957627 POLR2F	2
ENSG00000100226	0,823170425 GTPBP1	2
ENSG00000100227	0,418279569 POLDIP3	2
ENSG00000100354	0,536196196 TNRC6B	2
ENSG00000100410	0,606269411 PHF5A	2
ENSG00000100416	0,592786454 TRMU	2
ENSG00000100461	0,24155334 RBM23	2
ENSG00000100601	0,829079549 ALKBH1	2
ENSG00000100722	0,067867657 ZC3H14	2
ENSG00000100813	0,106170094 ACIN1	2
ENSG00000100823	0,488484745 APEX1	2
ENSG00000101210	0,04843365 EEF1A2	2
ENSG00000101343	0,492064899 CRNKL1	2
ENSG00000101347	0,219920247 SAMHD1	2
ENSG00000101361	0,449849983 NOP56	2
ENSG00000101452	0,26868431 DHX35	2
ENSG00000101665	0,755319488 SMAD7	2
ENSG00000101782	0,829079549 RIOK3	2
ENSG00000101811	0,829079549 CSTF2	2
ENSG00000101888	0,323707606 NXT2	2
ENSG00000101916	0,192782278 TLR8	2
ENSG00000102053	0,052947117 ZC3H12B	2
ENSG00000102081	0,111078139 FMR1	2
ENSG00000102241	0,488484745 HTATSF1	2
ENSG00000102786	0,967305004 INTS6	2
ENSG00000102898	0,24652005 NUTF2	2
ENSG00000103342	0,183749599 GSPT1	2
ENSG00000104356	0,956169331 POP1	2
ENSG00000104408	0,592786454 EIF3E	2
ENSG00000104613	0,606269411 INTS10	2
ENSG00000104835	0,24155334 SARS2	2
ENSG00000104897	0,480555433 SF3A2	2
ENSG00000104967	0,112993652 NOVA2	2
ENSG00000105171	0,559962154 POP4	2

ass_rbp

ENSG00000105193	0,592786454 RPS16	2
ENSG00000105258	0,488484745 POLR2I	2
ENSG00000105278	0,035800723 ZFR2	2
ENSG00000105323	0,227198262 HNRNPUL1	2
ENSG00000105364	0,480555433 MRPL4	2
ENSG00000105447	0,348735756 GRWD1	2
ENSG00000105576	0,029330017 TNPO2	2
ENSG00000105618	0,350354656 PRPF31	2
ENSG00000105640	0,250124641 RPL18A	2
ENSG00000106462	0,575120851 EZH2	2
ENSG00000106591	0,606269411 MRPL32	2
ENSG00000107105	0,04843365 ELAVL2	2
ENSG00000107164	0,449849983 FUBP3	2
ENSG00000107290	0,469403619 SETX	2
ENSG00000107581	0,654957627 EIF3A	2
ENSG00000107614	0,101991278 TRDMT1	2
ENSG00000107833	0,773267653 NPM3	2
ENSG00000107864	0,04843365 CPEB3	2
ENSG00000107937	0,823170425 GTPBP4	2
ENSG00000107951	0,575120851 MTPAP	2
ENSG00000108064	0,49759389 TFAM	2
ENSG00000108298	0,267967643 RPL19	2
ENSG00000108312	0,575120851 UBTF	2
ENSG00000108424	0,529650851 KPNB1	2
ENSG00000108561	0,488484745 C1QBP	2
ENSG00000108883	0,956169331 EFTUD2	2
ENSG00000109606	0,469403619 DHX15	2
ENSG00000109832	0,01630266 DDX25	2
ENSG00000110060	0,323707606 PUS3	2
ENSG00000110104	0,686168216 CCDC86	2
ENSG00000110107	0,092382616 PRPF19	2
ENSG00000110619	0,200818792 CARS	2
ENSG00000110958	0,981577129 PTGES3	2
ENSG00000111331	0,101991278 OAS3	2
ENSG00000111335	0,316909836 OAS2	2
ENSG00000111405	0,116301347 ENDOU	2
ENSG00000111639	0,829079549 MRPL51	2
ENSG00000111640	0,686168216 GAPDH	2
ENSG00000111880	0,288144259 RNGTT	2
ENSG00000112031	0,205008486 MTRF1L	2
ENSG00000112183	0,682932969 RBM24	2
ENSG00000112855	0,686168216 HARS2	2
ENSG00000112941	0,592786454 PAPD7	2
ENSG00000113272	0,536196196 THG1L	2
ENSG00000113360	0,418279569 DROSHA	2
ENSG00000113407	0,686168216 TARS	2
ENSG00000113460	0,592786454 BRX1	2
ENSG00000113649	0,312226848 TCERG1	2
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ENSG00000114686	0,350354656 MRPL3	2
ENSG00000114784	0,116301347 EIF1B	2

ass_rbp

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ENSG00000115053	0,883090109	NCL	2
ENSG00000115128	0,723040907	SF3B6	2
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ENSG00000115524	0,956169331	SF3B1	2
ENSG00000115816	0,823170425	CEBPZ	2
ENSG00000115866	0,350645042	DARS	2
ENSG00000115875	0,829079549	SRSF7	2
ENSG00000116221	0,592786454	MRPL37	2
ENSG00000116350	0,956169331	SRSF4	2
ENSG00000116560	0,418279569	SFPQ	2
ENSG00000116668	0,697644867	SWT1	2
ENSG00000116747	0,76292291	TROVE2	2
ENSG00000116898	0,592786454	MRPS15	2
ENSG00000117133	0,492064899	RPF1	2
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ENSG00000118197	0,606269411	DDX59	2
ENSG00000119203	0,49759389	CPSF3	2
ENSG00000119314	0,654957627	PTBP3	2
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ENSG00000119446	0,469403619	RBM18	2
ENSG00000119707	0,213632162	RBM25	2
ENSG00000119917	0,316909836	IFIT3	2
ENSG00000120688	0,258576264	WBP4	2
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ENSG00000125743	0,559962154	SNRPD2	2
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ENSG00000125844	0,245861244	RRBP1	2
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ENSG00000126814	0,127303204	TRMT5	2
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ENSG00000129084	0,956169331	PSMA1	2
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ENSG00000130255	0,090903107	RPL36	2
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ENSG00000130713	0,49759389	EXOSC2	2
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ENSG00000130810	0,090903107	PPAN	2
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ENSG00000131773	0,600252591	KHDRBS3	2
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ENSG00000134030	0,04843365	CTIF	2
ENSG00000134597	0,823170425	RBMX2	2
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ENSG00000134684	0,649438117	YARS	2
ENSG00000134697	0,829079549	GNL2	2
ENSG00000134744	0,164102912	ZCCHC11	2
ENSG00000134874	0,166544911	DZIP1	2
ENSG00000135097	0,402468069	MSI1	2
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ENSG00000135482	0,166544911	ZC3H10	2
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ENSG00000135972	0,304717938	MRPS9	2
ENSG00000136231	0,004650069	IGF2BP3	2
ENSG00000136270	0,350645042	TBRG4	2
ENSG00000136522	0,821778914	MRPL47	2
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ENSG00000136628	0,606269411	EPRS	2
ENSG00000136718	0,966141153	IMP4	2
ENSG00000136807	0,966141153	CDK9	2
ENSG00000136942	0,250124641	RPL35	2
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ENSG00000139343	0,575120851	SNRPF	2
ENSG00000139546	0,318597342	TARBP2	2
ENSG00000139675	0,144707639	HNRNPA1L2	2
ENSG00000139746	0,304717938	RBM26	2
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ENSG00000140319	0,492064899	SRP14	2
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ENSG00000141499	0,24155334	WRAP53	2
ENSG00000141543	0,956169331	EIF4A3	2
ENSG00000141646	0,760627951	SMAD4	2
ENSG00000142207	0,101991278	URB1	2
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ENSG00000143303	0,966141153	RRNAD1	2
ENSG00000143368	0,981577129	SF3B4	2
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ENSG00000145907	0,686168216	G3BP1	2
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ENSG00000147140	0,956169331	NONO	2
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ENSG00000151576	0,829079549	QTRT2	2
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ENSG00000152147	0,823170425	GEMIN6	2
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ENSG00000152601	0,469403619	MBNL1	2

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ENSG00000153048	0,200818792 CARHSP1	2
ENSG00000153187	0,529650851 HNRNPU	2
ENSG00000155636	0,449849983 RBM45	2
ENSG00000156304	0,984239369 SCAF4	2
ENSG00000156414	0,208740861 TDRD9	2
ENSG00000156508	0,367243066 EEF1A1	2
ENSG00000157110	0,245861244 RBPMS	2
ENSG00000158042	0,755319488 MRPL17	2
ENSG00000158526	0,203803223 TSR2	2
ENSG00000158545	0,829079549 ZC3H18	2
ENSG00000158806	0,04843365 NPM2	2
ENSG00000159409	0,121360745 CELF3	2
ENSG00000160193	0,755319488 WDR4	2
ENSG00000160633	0,339474019 SAFB	2
ENSG00000160818	0,606269411 GPATCH4	2
ENSG00000160862	0,469403619 AZGP1	2
ENSG00000161265	0,105080145 U2AF1L4	2
ENSG00000161960	0,043558937 EIF4A1	2
ENSG00000161970	0,592786454 RPL26	2
ENSG00000162244	0,090903107 RPL29	2
ENSG00000162385	0,829079549 MAGOH	2
ENSG00000162639	0,035800723 HENMT1	2
ENSG00000162851	0,829079549 TFB2M	2
ENSG00000163239	0,592786454 TDRD10	2
ENSG00000163319	0,723040907 MRPS18C	2
ENSG00000163659	0,488484745 TIPARP	2
ENSG00000163694	0,005385051 RBM47	2
ENSG00000163714	0,592786454 U2SURP	2
ENSG00000163811	0,829079549 WDR43	2
ENSG00000163874	0,250124641 ZC3H12A	2
ENSG00000163877	0,723040907 SNIP1	2
ENSG00000163950	0,592786454 SLBP	2
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ENSG00000164896	0,350645042 FASTK	2
ENSG00000165630	0,203803223 PRPF18	2
ENSG00000165733	0,852942148 BMS1	2
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ENSG00000166166	0,592786454 TRMT61A	2
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ENSG00000167112	0,956169331 TRUB2	2
ENSG00000167721	0,956169331 TSR1	2
ENSG00000167862	0,75810532 MRPL58	2
ENSG00000167978	0,75810532 SRRM2	2
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ENSG00000168517	0,492064899 HEXIM2	2
ENSG00000168724	0,430716066 DNAJC21	2
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ENSG00000169217	0,680108282	CD2BP2	2
ENSG00000169714	0,829079549	CNBP	2
ENSG00000169813	0,956169331	HNRNPF	2
ENSG00000169871	0,350645042	TRIM56	2
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ENSG00000171858	0,760627951	RPS21	2
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ENSG00000172183	0,077309037	ISG20	2
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ENSG00000182774	0,316909836	RPS17	2
ENSG00000182872	0,721703421	RBM10	2
ENSG00000182934	0,981577129	SRPRA	2
ENSG00000183207	0,649438117	RUVBL2	2
ENSG00000183258	0,686168216	DDX41	2
ENSG00000183684	0,956169331	ALYREF	2
ENSG00000184220	0,829079549	CMSS1	2
ENSG00000184575	0,981577129	XPOT	2
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ENSG00000185246	0,829079549 PRPF39	2
ENSG00000185608	0,966141153 MRPL40	2
ENSG00000185736	0,121360745 ADARB2	2
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ENSG00000186416	0,117546991 NKRF	2
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ENSG00000188846	0,852942148 RPL14	2
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ENSG00000196141	0,316909836 SPATS2L	2
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ENSG00000196504	0,823170425 PRPF40A	2
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ENSG00000213741	0,529650851 RPS29	2
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ENSG00000229117	0,823170425 RPL41	2
ENSG00000241962	0,575120851 RP11-111H13.1	2
ENSG00000242265	0,294104116 PEG10	2
ENSG00000243927	0,469403619 MRPS6	2
ENSG00000254726	0,025086182 MEX3A	2

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ENSG00000100697	0,684381218 DICER1	>2
ENSG00000100883	0,871449683 SRP54	>2

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ENSG00000101654	0,950139524	RNMT	>2
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ENSG00000254093	0,30083148	PINX1	>2
ENSG00000259494	0,393104945	MRPL46	>2

RBPs from survival analysis

RBP	Functions connected with circRNA biogenesis and or regulation/functions in GBM
APOBEC3F	Prognostic factor in glioma [1].
BICC1	Can be used to predict prognosis and TMZ treatment response in GBM [2].
CALR	Can be used as immunotherapy response predictor in GBM [3].
CAVIN1	Transcriptional regulator [4] and putative glioma biomarker. Positive correlation was observed between CAVIN1 expression and glioma grade [5].
DDX25	Potential prognostic marker in GBM [6].
FASTK	High expression correlates with poor prognosis in astrocytoma [7].
IFIT1	High expression predicts improved clinical outcome in GBM [8]. IFIT1 expression can be regulated by circRNA [9].
IFIT5	Protective gene in GBM [10]
ISG20	Prognostic factor in glioma [1], risk factor in GBM [10], correlates with poor survival in glioma [11].
LSM5	Prognostic marker in glioma [12]. Involved in splicing [13].
MRPL41	Involved in apoptosis regulation in GBM [14].
NSUN5	According to [15] – tumor suppressor in glioma that change the translational program. According to [16,17] – risk factor, its expression negatively correlates with overall survival in low grade glioma.
NSUN7	Risk factor, its expression negatively correlates with overall survival in low grade glioma [16,17].
PARP12	Can play a role in TMZ resistance [18].
PTRH2	Prognostic biomarker in GBM [19] implicated in disease progression and overall survival [20].
RAN	Important for GBM cells survival [21]. Essential for the translocation of RNA through the nuclear pore complex [22].
RNH1	Prognostic biomarker in GBM [14].
RPP25	Prognostic risk factor for GBM with predictive value for the 1-year, 2-year, and 3-year survival [23].
REXO2	Its methylation status can be prognostic factor in lower grade gliomas [24].
SNRPF	Its downregulation inhibits human glioma cell migration and invasion [25]. Involved in spliceosome assembly [26].
SPATS2L	Prognostic factor in glioma [1] with expression negatively correlated with prognosis [27].
THOC7	Associated with longer survival in GBM [28]. Negatively correlates with SOX2, which promotes GBM malignancy [29]. Component of nuclear export complex which can be involved in circRNA export [30].
ZC3H12A	Its silencing suppress proliferation of GBM cell lines [31].

RBPs with binding motifs enriched in circRNA and/or flanking introns

RBP	Functions connected with circRNA biogenesis and or regulation/functions in GBM
CPEB1	Modulates differentiation of glioma stem cells via downregulation of HES1 and SIRT1 expression [32]. Regulates the expression of MTDH/AEG-1 and GBM cell migration [33]. Is potential tumor suppressor that restrains GBM proliferation through the regulation of p27Kip1 mRNA translation [34].
CPEB3	Loss of CPEB3 activity in high-grade gliomas is caused by expression of alternatively spliced variants lacking the B-region that overlaps with the kinase recognition site [35].
EIF4B	It is involved in translation of circRNA derived peptides [36].

EIF4G2	Upregulated in GBM [37]. LINC01579 modulates cell proliferation and cell apoptosis in GBM by competitively binding with miR-139-5p to regulate EIF4G2 expression [38]. EIF4G2 enhances circRNA translation [39].
ELAVL2	Downregulated in GBM [40], which can influence NF1 splicing [41].
ELAVL3	Downregulated in GBM [40], which can influence NF1 splicing [41].
ELAVL4	Downregulated in GBM [40], which can influence NF1 splicing [41]. Binds to <i>circHomer1a</i> and can influence its synaptic expression in the frontal cortex [42,43]. Binds to and regulates circRNAs derived from neuronal development and synaptic plasticity associated genes [43]. Regulates mRNA-circRNA-miRNA networks associated with neuronal development in mice [44].
FUBP3	It is associated with immune surveillance in GBM, indicating an impact on GBM development and progression [45].
FUS	Interaction between BACH2 and FUS promotes glioma progression via transcriptional inhibition of TSLNC8 [46]. FUS affects circular RNA expression in murine embryonic stem cell-derived motor neurons by regulating backsplicing [47]. FUS aggregates can affect circRNA function [48].
HNRNPA2B1	Oncogenic driver correlated with poor prognosis in GBM [49]. Regulates AKT and STAT3 pathways in glioma U251 cells [50].
HNRNPD	Interacts with ZHX2 regulating the vasculogenic mimicry formation of glioma cells via linc00707/miR-651-3p/SP2 axis [51]. SUMOylated FUS interact with HNRNPD, stabilizing its expression and glioma cells mitophagy [52].
HNRNPH2	Stabilizes m6A-modified transcripts, which may be important for GBM stem cells maintenance [53]. Regulates splicing of TRF2 [54], which depletion in GBM stem cells reduced cell proliferation [55].
HNRNPR	Prognostic factor associated with TMZ resistance [56].
IGF2BP2	By inhibiting PID1 expression through the DANCER/FOXO1 axis, induce drug resistance in GBM U-251 cells, and promotes progression [57]. Promotes the aerobic glycolysis of GBM by increasing HK2 stability [58]. Preserves GBM stem cells by preventing let-7 target gene silencing [59].
IGF2BP3	Can bind to and maintain the stability of circGNB1, thus promoting the malignant phenotype on GBM stem cells [60]. Proproliferative and proinvasive marker acting through IGF-2 resulting in the activation of oncogenic PI3K and MAPK pathways in GBM [61, 62]
ILF2	CircPOK interacts with interleukin enhancer binding factor 2/3 (ILF2/3) complex and supports the stabilization of IL-6 and VEGF mRNA by ILF2/3. It also potentiates the occupancy of ILF2/3 on the IL-6 promoter [63]. By interacting with circRNA ILF2 affect inflammatory response via STAT3/JNK signal pathway [64]. Expression of ILF2 correlates with malignant grade in gliomas and plays a role in tumor growth [65].
KHDRBS2	Together with BICC1 and GNL3l were considered as prognosis-associated hub RBPs effective in the prediction of GBM prognosis and treatment response [2]. Also considered as prognostic factor in another study [66].
MBNL1	Inhibits GBM tumor initiation and progression by reducing hypoxia-induced stemness [67]. Regulates vasculogenic mimicry and aerobic glycolysis in GBM cells [68,69]. Promotes the expression of circNTRK2 [69].
PABPC1	Induces stabilization of BDNF-AS and inhibits malignant progression of GBM cells through STAU1-mediated decay [70]. May contribute as potential predictor of proneural GBM subtype [71].
PCBP2	High expression of PCBP2 is associated with progression and poor prognosis in patients with GBM [72]. PCBP2 modulates glioma growth by regulating FHL3 [73], reduced

	oxidative stress-induced apoptosis in glioma through cGAS/STING pathway by METTL3-mediated m6A modification [74].
PCBP4	Molecular predictor of GBM resistance to anti-MDK treatment [75].
PPRC1	COL5A1 promotes the malignancy of glioblastoma through PPRC1-ESM1 axis activation and extracellular matrix remodeling, activates transcriptional activity of PPRC1 [76].
PTBP1	Upregulation of PTBP1 in GBM facilitates exon skipping events at PTBP1 target RNAs, resulting in the generation of oncogenic isoforms that promote cell proliferation and angiogenesis [77]. SON is overexpressed in GBM patients and SON knockdown causes failure in intron removal from the PTBP1 transcript, resulting in PTBP1 downregulation and inhibition of its downstream oncogenic splicing [78].
PUF60	Promotes glioblastoma progression through regulation of EGFR stability [79].
RBM24	According to TCGA data downregulated in GBM.
RBM4	Promotes backsplicing in reporter system [80].
RBM47	Suggested to be tumour suppressor [40].
RBM6	Promotes homologous recombination repair of double-strand breaks and modulates sensitivity to chemotherapeutic drugs in various cancer types [81].
RBMS2	One of the genes targeted by GBM-associated miRNA [82].
RBMX	Prognostic value in GBM [83]. In scRNA-seq from GBM RBMX expressed higher in malignant cells and monocytes/macrophages, which revealed the potential role of RBMX expression subgroup cells in the immune microenvironment [84].
RC3H1	One of the genes targeted by GBM-associated miRNA [82].
SF3B4	Its binding motifs appear in upstream or downstream of thousands of circRNAs [85].
SRSF1	Promotes backsplicing in reporter system [80]. Promotes gliomagenesis via oncogenic splice-switching of MYO1B [86]. CircSMARCA5 is a tumor suppressor in GBM and acts as a decoy for SRSF1 [87]. SRSF1 could bind to and promote circATP5B expression and regulate the proliferation of GSCs, while HOXB5 also transcriptionally regulated SRSF1 expression [88]. SRSF1 binding motifs appear in upstream or downstream of thousands of circRNAs [85].
SRSF11	It is regulated by miR-10b - a promising candidate for the development of targeted therapies against all GBM subtypes [89]. Overall survival rates are shorter for patients with high expression of SRSF11 [90]. It is a putative circRNA repressor [91].
SRSF2	Found to be overexpressed in GBM [92]
SRSF4	It regulates RPL22L1 isoform switch in GBM, which allows cells to survive acidosis, increases stemness and correlates with worse patient outcome [93]. Many of the splicing alterations induced by cisplatin are caused by SRSF4 and they contribute to apoptosis in a process requires class I PI3K [94].
TIA1	It is involved in splicing regulation, which cause differences in splicing profiles between GBM subtypes [95].
ZC3H10	It is a putative target gene repressed by the HOTAIR regulatory element in GBM that function in regulating glioma cell sensitivity to temozolomide [96].
ZFP36	It impairs GBM viability and invasiveness by targeting multiple pathways [97,98].
ZNF326	It promotes malignant phenotype of glioma by up-regulating HDAC7 expression and activating Wnt pathway [99,100].

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3604.159681	ENS0000007284	ENS0000007285	ENS0000007292	ENS0000007392	ENS0000007407	ENS0000007426	ENS0000007436	ENS0000007585	ENS00000075914	ENS0000007595	ENS0000007603	ENS0000007603	ENS0000007607	ENS0000007610	ENS0000007670	ENS00000076924
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2426.4074	549.745114	1173.321474	1173.321474	100.401852	1821.841	402.023865	699.013375	174.720284	17.95900219	8.97590193	1311.7077	1429.017605	121.430804	314.935625
4530.24344	1079.00398	5905.00191	3336.225785	1360.545727	2794.846266	355.96575	14699.7485	2190.92043	346.692833	3.983523208	1587.1982	1702.92842	1160.42032	217.336302
2534.27078	145.81393	2554.81393	2554.81393	2554.81393	2554.81393	2554.81393	2554.81393	2554.81393	2554.81393	2554.81393	2554.81393	2554.81393	2554.81393	2554.81393
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2627.77662	645.674985	2035.17578	1584.3035	907.490711	171.169125	505.627721	957.863305	2100.87014	81.1265633	13.320326	2286.94431	731.1641471	1406.01539	1406.01539
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2758.41939	1486.912761	5325.72325	3135.162098	816.742197	1257.55197	952.497387	1248.55584	2500.09627	53.1974653	13.0813493	2861.616207	10897.16769	1396.214539	1604.64859
2758.41939	1486.912761	5325.72325	3135.162098	816.742197	1257.55197	952.497387	1248.55584	2500.09627	53.1974653	13.0813493	2861.616207	10897.16769	1396.214539	1604.64859
2758.41939	1486.912761	5325.72325	3135.162098	816.742197	1257.55197	952.497387	1248.55584	2500.09627	53.1974653	13.0813493	2861.616207	10897.16769	1396.214539	1604.64859
2758.41939	1486.912761	5325.72325	3135.162098	816.742197	1257.55197	952.497387	1248.55584	2500.09627	53.1974653	13.0813493	2861.616207	10897.16769	1396.214539	1604.64859
2758.41939	1486.912761	5325.72325	3135.162098	816.742197	1257.55197	952.497387	1248.55584	2500.09627	53.1974653	13.0813493	2861.616207	10897.16769	1396.214539	1604.64859
2758.41939	1486.912761	5325.72325	3135.162098	816.742197	1257.55197	952.497387	1248.55584	2500.09627	53.1974653	13.0813493	2861.616207	10897.16769	1396.214539	1604.64859
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Gene ID	Circular RNA		Linear RNA	
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EPB41L5	GGGCCTGTAGCTGGAATACG	TCCATAGTGTGAGATGCCCA	CATGCTTTCTCCGCCTTCG	CATGCTTTCTCCGCCTTCG
UNC13	AAGCAAATGGCAGAGTTGGAAG	CAAACCAGAAGCAAAGCTCCA	GAGATGTGGCCATGACCCTG	CACCTCATGCCTTGCCTTGC
USP45	AAATATTCATCAACCTAGAGCTGCC	GGCCTTTTACTTCTTTTGGCTTTCT	GACTTTTCTGGAAGCGTCGTG	GACTTTTCTGGAAGCGTCGTG
ARID1A	CCAGTAAGGGAGGGCAAGAAG	CTGTTGCTGCGAGTATGGGT	AGCCGAATCTCATGCCTTCC	GCCGCTTGTAATTCTGCTGTT
GUSBP1	CGTGTATGGAGTGGAACGC	GCCTGGTTGTCCACGACTTT	AAAACACTGGGGCTGGTGAAT	TGTTCTGTCATCAGGTACGG
PLD2	AGTATTGGAGGGGGCCAGAA	GGAATCCATCACTTTCTTTTGTTC	CATGGACACAGGATAATGGCTG	AGGGGTTGGTTGCTCAATAAAAA
VCAN	AGAAGCTGCAGAAGCTAGG	AACATCAGGCTCACACCTG	AGGTGGTCTACTTGGGGTGA	CGATGGTTGTAGCCTCTTTAGGTTT
EGFR	AAACAACACCTGGTCTGGA	GGGTGGCACTGTATGCACTC	GACAGGCCACCTCGTCG	TCGTGCCTTGGCAAACCTTC
HLA-B	TGGCTGTCCTGGTTGCTCTAGC	CACCCCAACCACTTACACGCA	ATGGCGAGGACCAAACCTCAG	CACAACCTGCTAGGACAGCCA
Intergenic circRNA	GCCTCTCACAGGACGTTTTTC	GCCCAACACCCAACACACAT	-	-