2020

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Long non-coding RNA profiling of pediatric Medulloblastoma

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Abstract

Background: Medulloblastoma (MB) is one of the most common malignant cancers in children. MB is primarily classified into four subgroups based on molecular and clinical characteristics as (1) WNT (2) Sonic-hedgehog (SHH) (3) Group 3 (4) Group 4. Molecular characteristics used for MB classification are based on genomic and mRNAs profiles. MB subgroups share genomic and mRNA profiles and require multiple molecular markers for differentiation from each other. Long non-coding RNAs (lncRNAs) are more than 200 nucleotide long RNAs and primarily involve in gene regulation at epigenetic and post-transcriptional levels. lncRNAs have been recognized as diagnostic and prognostic markers in several cancers. However, the IncRNA expression profile of MB is unknown.

Methods: We used the publicly available gene expression datasets for the profiling of IncRNA expression across MB subgroups. Functional analysis of differentially expressed IncRNAs was accomplished by Ingenuity pathway analysis (IPA).

Results: In the current study, we have identified and validated the IncRNA expression profile across pediatric MB subgroups and associated molecular pathways. We have also identified the prognostic significance of IncRNAs and unique IncRNAs associated with each MB subgroup.

Conclusions: Identified IncRNAs can be used as single biomarkers for molecular identification of MB subgroups that warrant further investigation and functional validation.

Keywords: Long non-coding RNA, Pediatric Medulloblastoma, Cancer biomarkers, Gene expression and pathways, Therapeutic targets

Background

Medulloblastoma (MB), the most common pediatric brain tumor, constitutes nearly 20% of newly diagnosed brain tumors in children [1, 2]. Treatment of MB involves radiation therapy, chemotherapy and surgical resection. These strategies have improved the survival by 70–80% but also lead to serious morbidities [3, 4]. MB are classified into four major molecular subgroups as WNT, Sonic hedgehog (SHH), Group 3 and Group 4.

The WNT subgroup is least common among all 4 subgroups and present in only 10% of cases. Genetic changes in genes: CTNNB1, DDX3X, SMARCA4 and DKK1 are frequently observed in the WNT subgroup. WNT has the best prognosis among all types of MB. SHH is second most common subgroup with abnormalities in SHH signaling pathway and accounts for ~30% of total MB cases. Genetic anomalies in genes: MYCN, GLI1, PTCH1, SLF4, MLL2, SMO, TPS3, BCR1, GAB1, GABRG1 and LDB1 are frequently seen in the SHH subgroup. The SHH subgroup has an intermediate prognosis among MB subgroups. Group 3 is the third most common subgroup with 25% of the total MB cases.
Table 1 Top 10 up-regulated IncRNAs in WNT subgroup of MB

| Gene Symbol | Fold Change | P-val     | FDR P-val |
|-------------|-------------|-----------|-----------|
| EMX2OS      | 38.18       | 9.07E-14  | 4.92E-10  |
| OTX2-AS1    | 37.84       | 1.14E-09  | 3.93E-07  |
| PGMS-AS1    | 30.26       | 9.54E-09  | 1.63E-06  |
| DSCR8       | 24.56       | 0.0001    | 0.0013    |
| LOXL1-AS1   | 21.06       | 1.03E-08  | 1.73E-06  |
| HAND2-AS1   | 18.51       | 9.37E-07  | 3.59E-05  |
| TMEM51-AS1  | 16.9        | 3.88E-09  | 8.82E-07  |
| RMST        | 13.92       | 1.14E-07  | 8.49E-06  |
| LINC01305   | 11.11       | 0.0001    | 0.001     |
| PART1       | 10.94       | 1.89E-05  | 0.0003    |

Group 3 is mainly MYC-driven and genetic aberrations are seen in genes: MYC, PVT1, OTX2, ML2, SMARCA4, and CHD7 in this subgroup. The prognosis of the Group 3 is very poor and 5 year overall survival is less than 50%. Group 4 is the most common subgroup of MB and accounts for 35% of total cases. The prognosis of the Group 4 is intermediate and genetic aberrations are commonly present in genes: OTX2, DDX31, CHD7, NCAIP, MYCN, CDK6, GF11/GF11B, ML2, KDM6A, ML3, and ZMYM3 [5–9]. Molecular markers used for WNT identification are CTNNB1 (nuclear), FLIA, YAP1 and DKK1; for SHH are SFRP1, GLI1, FLIA, YAP1 and GAB1; for Group 3, NPR3; and for Group 4, KCNA1. Identification of new molecular markers for drug targeting, diagnosis and prognosis are important due to need for improved molecular profiling of MB [10].

Long non-coding RNAs (lncRNAs) are RNAs of more than 200 bp in length and can be transcribed from an intergenic region, genic regions or super enhancer regions in the genome. lncRNAs can modulate chromatin structure, gene regulation via interactions with epigenetic modifiers and transcriptional co-factors, and also have post-translation effects via affecting the stability of mRNA or proteins [11, 12]. Deregulated lncRNA expression is associated with many cancers [13]. LncRNA signatures have been used to classify different types of cancer as biomarkers for diagnosis, prognosis and therapy [14–18]. LncRNAs are secreted in serum, plasma, and CSF in a stable form protected from endogenous RNAase and can be used for non-invasive analysis from patient samples [19, 20]. The role of lncRNA in brain development is well studied [21–26]. However, there is not much known about role of lncRNAs in MB. LncRNA LOXL1-AS1 promotes the proliferation and metastasis of MB by activating the PI3K-AKT pathway [27]. LncRNA CCAT1 promotes cell proliferation and metastasis in human

Table 2 Top 10 down-regulated IncRNAs in WNT subgroup of MB

| Gene Symbol | Fold Change | P-val     | FDR P-val |
|-------------|-------------|-----------|-----------|
| LINC00461   | -62.39      | 1.16E-06  | 4.17E-05  |
| MEG3        | -58.9       | 9.41E-07  | 3.60E-05  |
| LINC00844   | -24.94      | 0.0003    | 0.0024    |
| LINC00643   | -13.3       | 6.95E-06  | 0.0001    |
| SOX2-OT     | -12.13      | 0.0003    | 0.0024    |
| PEG3-AS1    | -10.02      | 3.49E-07  | 1.84E-06  |
| TUNAR       | -7.72       | 2.04E-12  | 5.87E-09  |
| MALAT1      | -7.39       | 1.65E-07  | 1.10E-05  |
| LINC01105   | -7.39       | 3.77E-05  | 0.0005    |
| LINC01351   | -6.48       | 2.24E-05  | 0.0003    |
MB by regulating the MAPK pathway [28]. Silencing of ANRIL in MB cell lines significantly lowered cell viability and migration. ANRIL promoted the apoptosis of MB cell lines through miR-323-mediated regulation of BRI3, which activates p38 MAPK, ERK, and AKT as well as the WNT signaling pathway [29]. LINC-NeD125 expression is upregulated in Group 4 MB and after interacting to miRNA-induced silencing complex (MISC), it directly binds to miR-19a-3p, miR-19b-3p and miR-106a-5p. Functionally, LINC-NeD125 acts by sequestering the three miRNAs, which leads to the de-repression of major driver genes (CDK6, MYCN, SNAIP, and KDM6A) of Group 4 MB [30]. LncRNA CRNDE expression is elevated in MB and knockdown of CRNDE significantly reduced cell proliferation and inhibited colony formation in MB cell lines, Daoy and D341 [31].

In the current study, we have identified the IncRNAs expression profile of pediatric MB subgroups and associated molecular pathways. We have also identified the unique IncRNAs associated with each subgroup.

**Methods**

We searched the Gene Expression Omnibus (GEO) database for MB related microarray datasets and found two relevant studies, GSE37418 [for pediatric MB subgroups expression data] and GSM1094863, GSM1094864, GSM1094865, GSM1094866, GSM1094867 [for pediatric primary cerebellum expression data from GSE44971] for our analyses. We further used large GSE124814 datasets for the validation of IncRNAs expression profiles of MB subgroups obtained from our original analyses. We selected the age < 18 years as an inclusion criteria for selecting pediatric MB samples. We selected the datasets which

| Table 3 | Top 10 upstream regulators involved in DE IncRNAs in WNT subgroup |
|---------|------------------------------------------------------------------|
| MAX     | transcription regulator                                          |
| miR-150-5p (and other miRNAs w/seed CUCCCCA)                     | mature microRNA                                                 |
| miR-133a-3p (and other miRNAs w/seed UUGGUCC)                    | mature microRNA                                                 |
| miR-133 | microRNA                                                         |
| FOLR1   | transporter                                                      |
| EZF     | group                                                            |
| ATP5    | transcription regulator                                          |
| NCAM1   | other                                                            |
| miR-150 | microRNA                                                         |
| GAS2L3  | other                                                            |

| P-value of overlap | Target molecules in dataset |
|-------------------|-----------------------------|
| 5.53E-03          | DLEU1,DLEU2                 |
| 5.54E-03          | MIAT                        |
| 7.38E-03          | MALAT1                      |
| 9.22E-03          | MALAT1                      |
| 1.31E-02          | GASS,PVT1                   |
| 1.37E-02          | DLEU1,DLEU2                 |
| 1.47E-02          | GASS                        |
| 1.84E-02          | MALAT1                      |
| 2.56E-02          | MIAT                        |
| 2.92E-02          | PV11                        |
Table 4 Top 10 disease and function identified by IPA from DE IncRNAs in WNT subgroup

| Categories                                                                 | Diseases or Functions Annotation                  | Pval   | Activation z-score |
|---------------------------------------------------------------------------|---------------------------------------------------|--------|--------------------|
| Cellular Development, Cellular Growth and Proliferation, Nervous System Development and Function | Neurogenesis of nervous tissue cell lines          | 3.38E-06 |                    |
| Cellular Movement                                                          | Cell movement of tumor cell lines                 | 1.12E-05 | 1.324              |
| Cellular Movement                                                          | Migration of tumor cell lines                     | 1.14E-05 | 1.498              |
| Cellular Movement                                                          | Invasion of tumor cell lines                      | 1.55E-04 | 1.083              |
| Cell Cycle                                                                 | Arrest in G0 phase of tumor cell lines            | 3.83E-04 |                    |
| Cancer, Organisinal Injury and Abnormalities                                | Metastasis of tumor cell lines                    | 4.26E-04 | -0.277             |
| Cell Death and Survival                                                     | Cell death of eye cell lines                      | 5.07E-04 |                    |
| Cellular Movement                                                          | Migration of cells                                | 6.27E-04 | 0.573              |
| Cellular Movement                                                          | Cell movement                                     | 6.75E-04 | 0.453              |
| Cellular Movement                                                          | Migration of hepatoma cell lines                  | 1.34E-03 |                    |

used the Affymetrix U133 Plus2 array for probe level RNA expression studies. For data analyses, we first did background correction, normalization (RMA), quality control checks, intensity and batch effect corrections of each dataset. Following that, we did probe level differential analyses of datasets using the limma package (ANOVA with eBayes) with criteria of p < 0.001 and fold change greater than two folds. We then annotated the probe sets with the Affymetrix U133 Plus2 library and filtered out IncRNA genes. The IncRNA gene database used is verified and approved by HGNC. Functional analysis of differentially expressed IncRNAs was done by Ingenuity pathway analysis (IPA) software from BioRad, Inc. We used default parameters and checked all the node types, all species (except uncharted), and all tissue types for core analysis in IPA.

Results
Differentially expressed IncRNAs in the WNT subgroup and their functional roles

Comparative analyses of WNT MB (N = 8) and normal cerebellum tissue (N = 5) datasets with p < 0.05 and fold changes > 2 provided 199 differentially expressed IncRNAs with approved status. Tables 1 and 2 show the fold change in the top 10 upregulated and downregulated IncRNAs. Heatmap of top 10 upregulated and downregulated IncRNAs is shown in Fig. 1a. The complete list of IncRNAs can be seen in Additional file 1. We found 73% overlap with IncRNAs in validation datasets [WNT N = 31, Control = 5] (Additional file 2). We found all the top 10 upregulated and downregulated IncRNAs present in validation datasets. We mostly see non-overlap in IncRNAs at lower expression values.

We did functional analysis of differentially expressed (DE) IncRNAs of the WNT subgroup using IPA. We identified different functional parameters involved in this subgroup. MAX (a MYC interacting partner), miR-150, miR-133a, FOLR1, E2F NCAM1, GAS2L3 and ATF5 are the most significantly associated upstream regulators, while cancer, neurogenesis, metastasis and cellular development are the most important biological functions.

Table 5 Top 10 up-regulated IncRNAs in SHH subgroup of MB

| Gene Symbol | Fold Change | P-val  | FDR P-val |
|-------------|-------------|--------|-----------|
| NEAT1       | 23.48       | 0.0003 | 0.0022    |
| DLEU2       | 13.24       | 5.79E-11 | 2.41E-08 |
| PRRT4A-S1   | 8.07        | 1.58E-07 | 8.49E-06 |
| LINC01355   | 8.05        | 2.93E-09 | 5.15E-07 |
| MIRLET7BHG  | 7.49        | 1.79E-07 | 9.34E-06 |
| CKMT2-A51   | 6.23        | 1.86E-09 | 3.59E-07 |
| SLC16A1-A51 | 5.65        | 8.13E-08 | 5.36E-06 |
| TPT1-A51    | 5.28        | 4.44E-08 | 3.50E-06 |
| LINC01000   | 4.96        | 1.10E-08 | 1.32E-06 |
| ANP32A-H1   | 4.94        | 9.36E-07 | 3.07E-05 |

Table 6 Top 10 down-regulated IncRNAs in SHH subgroup of MB

| Gene Symbol | Fold Change | P-val  | FDR P-val |
|-------------|-------------|--------|-----------|
| LINC00844   | -33.36      | 1.08E-08 | 1.32E-06 |
| MIR124-2HG  | -28.13      | 0.0005 | 0.0032    |
| SOX2-OT     | -13.83      | 2.39E-07 | 1.15E-05 |
| PEG3A51     | -12.94      | 5.12E-08 | 3.88E-06 |
| LINC00643   | -11.76      | 3.97E-06 | 8.83E-05 |
| HCG11       | -11.26      | 0.0012 | 0.0065    |
| RMST        | -9.43       | 0.0036 | 0.0155    |
| CCEPR       | -8.93       | 1.49E-06 | 4.27E-05 |
| MEG3        | -8.53       | 0.0002 | 0.0018    |
| MALAT1      | -8.25       | 2.82E-06 | 6.86E-05 |
affected in this subgroup (Tables 3 and 4). Heatmap of 5 upstream regulators is shown in supplementary Fig. 1 (Additional file 3). The two most important non-canonical networks enriched with DE IncRNAs are shown in Fig. 1b and c. In networks 1; CCND1, AKT1, SOX2, POU5F1, DNMT3B, and CTNNB1, in network 2; TP53, MYC, EZH2, and MDM2 are the central regulators linked with DE IncRNAs.

**Differentially expressed IncRNAs in the SHH subgroup and their functional roles**

Comparative analyses of the SHH subgroup (N = 10) and normal cerebellum tissue (N = 5) datasets with p < 0.05 and fold change > 2 provided 145 differentially expressed IncRNAs with approved status. Tables 5 and 6 show the fold change in the top 10 upregulated and downregulated IncRNAs. Heatmap of top 10 upregulated and downregulated IncRNAs is shown in Fig. 2a. The complete list of IncRNAs can be seen in Additional file 1. We found 50% overlap with IncRNAs in validation datasets [SHH N = 65, Control = 5] (Additional file 2). We found all the top 10, upregulated and downregulated IncRNAs, present in validation datasets except DLEU2 and PRR34-AS1.

Functional analysis of DE IncRNAs of SHH MB subgroup using IPA predicts, MAX (a MYC interacting partner), miR-133a, FOLR1, E2F, ATF5, AM1, E2F3, GAS2L3 and ACSL5 as most significantly associated upstream regulators, while cancer, neurogenesis, cell proliferation, metastasis and cellular development are the most important biological functions affected in this subgroup (Tables 7 and 8). Heatmap of 5 upstream regulators is shown in supplementary Fig. 1 (Additional file 3). The two most important non-canonical networks enriched with DE IncRNAs are shown in Fig. 2b and c. In network 1; CCND1, TP53, MYC, MALAT1,

### Table 7: Top upstream regulators involved in DE IncRNAs in SHH subgroup

| Upstream Regulator | Molecule Type         | P-val of overlap | Target molecules in dataset |
|--------------------|-----------------------|------------------|-----------------------------|
| MAX                | transcription regulator| 2.74E-03         | DLEU1, DLEU2                |
| miR-133a-3p (and other miRNAs w/seed UUGGUCC) | mature microRNA       | 5.17E-03         | MALAT1                      |
| miR-133            | microRNA              | 6.46E-03         | MALAT1                      |
| FOLR1              | transporter           | 6.58E-03         | GASS, PVT1                  |
| E2F                | group                 | 6.85E-03         | DLEU1, DLEU2                |
| ATF5               | transcription regulator| 1.03E-02         | GASS                        |
| NCAM1              | other                 | 1.29E-02         | MALAT1                      |
| E2F3               | transcription regulator| 1.49E-02         | MALAT1, NEAT1               |
| GAS2L3             | other                 | 2.05E-02         | PVT1                        |
| ACSL5              | enzyme                | 2.18E-02         | ST7-AS1                     |
CTNNB1, and SP1, in network 2; Histone H3, MDM2, CCNA2, SOX2, POU2F1, SP1, and ESR1 are the central regulators linked with DE lncRNAs.

Differentially expressed lncRNAs in the Group 3 subgroup and their functional roles
Comparative analyses of the Group 3 MB (N = 16) and normal cerebellum tissue (N = 5) datasets with p < 0.05 and fold change >2 provided 149 differentially expressed lncRNAs with approved status. Tables 9 and 10 show the fold change in the top 10 upregulated and downregulated lncRNAs. Heatmap of top 10 upregulated and downregulated lncRNAs is shown in Fig. 3a. The complete list of lncRNAs can be seen in Additional file 1. We found 86% overlap with lncRNAs in validation datasets [Group 3 N = 46, Control N = 5] (Additional file 2). We found all the top 10 upregulated and downregulated lncRNAs in the validation dataset, except NEAT1.

| Categories                                                                 | Diseases or Functions Annotation                                      | P-val   | Activation z-score |
|----------------------------------------------------------------------------|------------------------------------------------------------------------|---------|--------------------|
| Cellular Development, Cellular Growth and Proliferation, Nervous System Development and Function | Neurogenesis of nervous tissue cell lines                              | 1.79E-06|                    |
| Cellular Development, Cellular Growth and Proliferation                   | Proliferation of kidney cancer cell lines                              | 3.01E-06| -0.095             |
| Cellular Development, Cellular Growth and Proliferation                   | Cell proliferation of tumor cell lines                                 | 3.90E-04| 0.933              |
| Cellular Movement                                                         | Migration of carcinoma cell lines                                     | 5.25E-04| 0.762              |
| Cellular Movement                                                         | Migration of kidney cancer cell lines                                  | 6.69E-04|                    |
| Cellular Movement                                                         | Cell movement of tumor cell lines                                     | 6.69E-04| 0.751              |
| Cellular Movement                                                         | Migration of tumor cell lines                                         | 1.14E-03| 1.033              |
| Cellular Development, Cellular Growth and Proliferation                   | Cell proliferation of carcinoma cell lines                            | 1.30E-03| 0.277              |
| Cellular Development, Connective Tissue Development and Function, Tissue Development | Osteogenic differentiation of nucleus pulposus cells                  | 1.36E-03|                    |
| Cancer, Gastrointestinal Disease, Organismal Injury and Abnormalities     | Stage I colorectal adenocarcinoma                                      | 1.36E-03|                    |

Functional analysis of DE lncRNAs of Group 3 MB using IPA predicted C17orf98, ZNF426, RNFL65, FBXO8, CTCF, LAYN, PYGO1, Firre, TSIX and miR-150-5pa as most significantly associated upstream regulators, while activation/inactivation of X-chromosome, cell movement, and metastasis are the most important biological functions affected in this subgroup (Tables 11 and 12). Heatmap of 5 upstream regulators is shown in supplementary Fig. 2 (Additional file 3). The two most important non-canonical networks enriched with DE lncRNAs are shown in Fig. 3b and c. In network 1; CCND1, EP300, CREBBP, ESR1, CTNNB1, and PRKCD, in network 2; Histone H3, TP53, MYC, XIST, and EZH2 are the central regulators linked with DE lncRNAs.

Differentially expressed lncRNAs in the Group 4 MB and their functional roles
Comparative analyses of Group 4 MB (N = 39) and normal cerebellum tissue (N = 5) datasets with p < 0.05 and
fold change > 2 provided 150 differentially expressed lncRNAs with approved status. Tables 13 and 14 show the fold change in the top 10 upregulated and downregulated lncRNAs. Heatmap of top 10 upregulated and downregulated lncRNAs is shown in Fig. 4a. The complete list of lncRNAs can be seen in Supplementary file 1. We found 82% overlap with lncRNAs in validation datasets [Group 4 N = 95, Control = 5] (Additional file 2). We found all the top 10 upregulated and downregulated lncRNAs in validation datasets.

Functional analysis of DE lncRNAs of Group 4 MB using IPA predicted C17orf98, ZNF426, RNF165, FBX08, CTCF, LAYN, PYGO1, Firre, TSIX and mir-150-5p as most significantly associated upstream regulators, while activation/inactivation of X-chromosomes, cell movement, methylation of DNA and metastasis are the most important biological functions affected in this subgroup (Tables 15 and 16). Heatmap of 5 upstream regulators is shown in supplementary Fig. 2 (Additional file 3). The two important non-canonical networks enriched with DE lncRNAs are shown in Fig. 4b and c. In network 1; AR, MYC, XIST, SP1, CCND1, and EZH2, in network 2; Histone H3, SP1, ESR1, MYC, SOX2, POUSF1, CDH1, and CEBPB are the central regulators linked with DE lncRNAs.

Prognostic significance of lncRNAs in different subgroups of MB

We used a publicly available dataset GSE85217 (Cavalli dataset) to understand the prognostic significance of DE lncRNAs of different MB subgroups. As shown in Fig. 5, high expression of HAND2-AS1 is associated with poor prognosis in WNT MB. Similarly, low expression of MEG3 in SHH, high expression of DLEU2 and DSCR8

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**Table 11** Top 10 upstream regulators involved in DE lncRNAs in Group 3 MB

| Upstream Regulator | Molecule Type                | P-val of overlap | Target molecules in dataset |
|--------------------|------------------------------|------------------|-----------------------------|
| C17orf98           | other                        | 1.11E-03         | XIST                        |
| ZNF426             | transcription regulator      | 1.11E-03         | XIST                        |
| RNF165             | enzyme                       | 1.11E-03         | XIST                        |
| FBX08              | other                        | 1.11E-03         | XIST                        |
| CTCF               | transcription regulator      | 2.08E-03         | TSIX,XIST                   |
| LAYN               | other                        | 2.22E-03         | XIST                        |
| PYGO1              | other                        | 2.22E-03         | XIST                        |
| Firre              | other                        | 3.33E-03         | XIST                        |
| TSIX               | other                        | 3.33E-03         | XIST                        |
| mir-150-5p (and other miRNAs w/seed CUCCCAA) | mature microRNA  | 3.33E-03         | MIAT                        |
in Group 3 and high expression of DLEU2 and low expression of XIST in Group 4 are associated with poor prognosis in MB ($p < 0.05$).

**Discussion**

lncRNAs are known regulators of gene expression. Disruptions in gene regulatory pathways in cancers dictate the aberrant lncRNAs expression [11–13]. Notably, almost 40% of lncRNAs are aberrantly expressed in the brain-related disorders including brain tumors. However, lncRNA expression profile in MB is largely unexplored.

In this study, we have identified the lncRNA expression profile of pediatric MB subgroups and associated molecular pathways. The identified key lncRNAs require further functional validation in vitro and in vivo to explore their potential role in MB subgroup-specific manner. Here, we discuss the known cancer-relevant function of the key lncRNAs identified in MB subgroups.

EMX2OS is the most differentially expressed lncRNA in the WNT subgroup. This lncRNA is known to regulate EMX gene expression in the brain development [32, 33]. OTX2-AS1 (antisense strand of the OTX2 gene) is predominantly involved in eye development [34]. High PGM5-AS1 (antisense strand of the PGM5 gene) expression is associated with development and poor prognosis of colorectal cancer (CRC) [35]. Increased expression of DSC8R is associated with malignant pathology and poor survival in hepatocellular carcinoma (HCC) patients [36]. LOXL1-AS1 (antisense strand of the LOXL1 gene) is involved in the progression and metastasis of MB by regulating the PI3K-AKT signaling [27]. In addition, it is also known to play roles in the proliferation and survival of prostate cancer (PC) cells via miR-541-3p and cell cycle gene CCND1 [37] as well as aggressive nature of glioblastoma by activating NF-kB pathway [38]. HAND2-AS1 (antisense strand of the HAND2 gene) is overexpressed in esophageal squamous cell carcinoma (ESCC) [39] while it is downregulated in non-small cell

| Gene Symbol | Fold Change | P-Val  | FDR P-Val |
|-------------|-------------|--------|-----------|
| LINC01419   | 139.78      | 0.0047 | 0.0175    |
| OTX2-AS1    | 60.12       | 9.95E-16| 2.03E-13  |
| BLACAT1     | 27.67       | 1.13E-18| 4.59E-16  |
| DLEU2       | 11.58       | 2.25E-15| 4.16E-13  |
| LINC01355   | 7.09        | 2.23E-07| 3.85E-06  |
| MIRLE178HG  | 7.01        | 2.03E-06| 2.55E-05  |
| PRR34-AS1   | 6.82        | 8.84E-12| 6.11E-10  |
| LINC01000   | 6.29        | 4.10E-12| 3.13E-10  |
| CKMT2-AS1   | 6.19        | 5.04E-11| 2.82E-09  |
| MIR99AHG    | 5.27        | 9.82E-07| 1.38E-05  |
Table 14: Top 10 down-regulated IncRNAs in Group 4 of MB

| Gene Symbol | Fold Change | P-val  | FDR P-val |
|-------------|-------------|--------|-----------|
| XET         | -343.06     | 0.0287 | 0.0745    |
| SOX2-OT     | -31.6       | 1.90E-13 | 2.06E-11  |
| MALAT1      | -13.08      | 5.80E-10 | 2.34E-08  |
| LINC00643   | -11.64      | 4.39E-13 | 4.32E-11  |
| LINC00844   | -9.89       | 1.26E-05 | 0.0001    |
| LRR75A-AS1  | -9.53       | 1.52E-08 | 3.87E-07  |
| MIAT        | -7.87       | 2.15E-10 | 9.90E-09  |
| PRKAG2-AS1  | -7.8        | 4.29E-07 | 6.75E-06  |
| NR2F1-AS1   | -5.98       | 8.89E-11 | 4.63E-09  |
| PEG3-AS1    | -5.74       | 1.92E-08 | 4.73E-07  |

lung cancer (NSCLC) cells [40]. TMEM51-AS1 (antisense strand of the TMEM51 gene) is associated with renal cell carcinoma (RCC) [41]. RMST1 acts as a tumor suppressor in triple-negative breast cancer (TNBC) by inducing apoptosis and inhibiting proliferation/invasion and migration [42]. PART1 promotes gefitinib-resistance in ESCC by regulating the miR-129/Bcl-2 pathway [43] and also associated with PC tumorigenesis [44]. LINC00461 is involved in glioma tumorigenesis via MAPK/ERK and PI3K/AKT signaling pathways [45]. Downregulation of MEG3 is involved in the proliferation and apoptosis of PC cells by regulating miR-9-5p and its target gene QKI-5 [46]. Downregulation of LINC00844 is associated with poor clinical outcomes and suppressed tumor progression/metastasis in PC [47]. SOX2-OT is overexpressed and promotes tumorigenesis by upregulating SOX2 gene and activating PI3K/AKT signaling pathway in cholangiocarcinoma (CCA) [48]. SOX2-OT is also a prognostic biomarker for osteosarcoma (OS) and involved in cell survival and cancer stem cells [49]. TUNAR plays a tumor suppressive role in glioma cells by upregulating miR-200a and inhibiting Rac1 [50]. MALAT1 promotes the chemo-resistance of cervical cancer via BRWD1-PI3K/AKT pathway [51]. MALAT1 is a well-studied IncRNA in several solid and hematological cancers [52].

NEAT1 is overexpressed in most cancer types, except leukemia and myeloma, where it is down-regulated [53–55]. DLEU2 exhibits role in the proliferation and survival of laryngeal cancer cells via miR-16-1 [56]. DLEU2 is also significantly overexpressed in gastric cancer and contributes to cell proliferation [57]. TPT1-AS1 (antisense strand of the TPT1 gene) expression is upregulated in cervical cancer and has influence on proliferation and migration.

**Fig. 4** a) Heatmap of top 10 upregulated and downregulated IncRNAs in Group 4 MB. Expression value of different IncRNAs was clustered using correlation distance method. b) Differentially expressed IncRNAs in a non-canonical biological network in Group 4 MB. The important nodes in this biological network are AR, MYC, XIST, SP1, CCND1, and EZH2. c) Differentially expressed IncRNAs in another non-canonical biological network in Group 4 MB. The important nodes in this biological network are Histone H3, SP1, ESR1, MYC, SOX2, POU5F1, CDH1, and CEBPB. Green indicates downregulated and red indicates upregulated IncRNAs.
Table 15 Top 10 upstream regulators involved in DE IncRNAs in Group 4 MB

| Upstream Regulator | Molecule Type       | P-val of overlap | Target molecules in dataset |
|--------------------|---------------------|------------------|-----------------------------|
| C1orf98            | other               | 1.34E-03         | XIST                        |
| ZNF426             | transcription regulator | 1.34E-03     | XIST                        |
| RNF165             | enzyme              | 1.34E-03         | XIST                        |
| FBXO8              | other               | 1.34E-03         | XIST                        |
| LAYN               | other               | 2.68E-03         | XIST                        |
| PYGO1              | other               | 2.68E-03         | XIST                        |
| CTCF               | transcription regulator | 3.03E-03     | TSKXIST                     |
| Fire               | other               | 4.02E-03         | XIST                        |
| TSIX               | other               | 4.02E-03         | XIST                        |
| miR-150-5p (and other miRNAs w/seed CUCCCAA) | mature microRNA | 4.02E-03 | MIAT |

[58]. HCG11 is significantly overexpressed in hepatocellular carcinoma (HCC) and genetic-silencing of HCG11 in HCC cells leads to decreased proliferation [59]. HCG11 expression is downregulated in PC and associated with poor prognosis of patients [60]. CCPEPR contributes significantly in promoting cell proliferation and inhibiting apoptosis in bladder cancer [61].

BLACAT1 is overexpressed in chemo-resistant NSCLC and induces autophagy by regulating miR-17 and ATG7 pathway [62]. It also triggers proliferation/survival by regulating WNT signaling in cervical cancer [63].

XIST is elevated in bladder cancer and inhibits p53 function via binding to TET1 [64]. XIST also binds to miR-34a and elicits proliferation and tumor development in thyroid cancer [65]. XIST is an important regulator of progression and oxaliplatin-resistance in malignant melanoma [66]. MIR100HG is known to be involved in cetuximab-resistance in CRC via the β-catenin cellular pathway [67]. In addition, elevated expression of MIR100HG is correlated with poor prognosis of osteosarcoma [68]. MIAT is overexpressed in clear cell renal cell carcinoma (CCRCC) and associated with poor prognosis [69]. MIAT associates with miR-133 and contributes a role in the progression pancreatic cancer development [70]. MIAT also plays a key role in CRC tumorigenesis via miR-132/Derlin-1 axis [71]. NR2F1-AS1 (antisense strand of the NR2F1 gene) promotes chemotherapy-resistance in HCC by regulating miR-363-ABCC1 drug-transporter pathway [72].

Conclusions
We propose that the majority of DE IncRNAs in MB might have oncogenic properties as seen in other cancers (Supplementary Table S1 in Additional file 3) [73–82]. We found approximately 25% of these DE IncRNAs in MB are tumor suppressive. Also, each MB subgroup has unique and common IncRNAs in their expression.

Table 16 Top 10 disease and function identified by IPA from DE IncRNAs in Group 4 MB

| Categories                          | Diseases or Functions Annotation                  | P-val   | Activation z-score |
|-------------------------------------|---------------------------------------------------|---------|--------------------|
| Cellular Movement                   | Cell movement of tumor cell lines                 | 4.56E-06| -0.938             |
| Gene Expression                     | Inactivation of mouse X chromosome                | 6.13E-06|                    |
| Gene Expression                     | Activation of mouse X chromosome                  | 6.13E-06|                    |
| Cellular Movement                   | Migration of tumor cell lines                     | 6.36E-06| -0.877             |
| Gene Expression                     | Imprinting                                        | 2.27E-05|                    |
| Cell Death and Survival             | Apoptosis of kidney cancer cell lines             | 3.30E-05|                    |
| Cancer, Organism Injury and Abnormalities | Metastasis of tumor cell lines                  | 1.28E-04| 0.555              |
| Cellular Movement                   | Invasion of tumor cell lines                      | 1.36E-04| 0.031              |
| Cellular Development, Cellular Growth and Proliferation | Proliferation of kidney cancer cell lines         | 1.68E-04|                    |
| DNA Replication, Recombination, and Repair, Gene Expression | Methylation of DNA                               | 1.82E-04|                    |
| Cell Death and Survival             | Cell death of eye cell lines                      | 3.08E-04|                    |
Fig. 5 Kaplan Meier survival curves of different lncRNAs expressed in different subgroups of MB (Cavalli dataset) obtained using scan cut-off method on hsgserver (https://hsgserver1.amc.nl). a. High expression of HAND2-A51 is associated with poor prognosis in WNT MB. b. Low expression of MEG3 is associated with poor prognosis in SHH MB. c. High expression of DLEU2 and DSCR8 are associated with poor prognosis in Group 3 MB. d. High expression of DLEU2 and low expression of XIST in Group 4 MB are associated with poor prognosis (p < 0.05).
profile (Fig. 6). We performed a unique IncRNAs analysis in both original datasets and validation datasets (Additional files 1 and 2). Unique IncRNAs can be validated for differential diagnosis and prognosis of MB subgroups. Common IncRNAs and associated molecules in pathways can be important therapeutic targets. We identified important IncRNAs DELU2, CASC15, LINCO1355 and GASS are present in each subgroup and can be further explored for functional analyses in different MB subgroups. We also found SOX2, Protein kinase C delta (PRKCD), and EZH2 associated with functional networks of each subgroup and could be important drug targets. We also identified the prognostic significance of IncRNAs in different subgroups of MB.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12920-020-00744-7

Authors’ contributions
VK and NKC conceived and designed the study. VK, MJS and NKC analyzed and interpreted the data. D.T., JGS and SJ critically interpreted the data. VK and NKC wrote the manuscript. All authors read and approved the final version of the manuscript.

Funding
This work was supported by the State of Nebraska through the Pediatric Cancer Research Grant Funds (LI8905) awarded to D. W. Coulter, MD. This funding had no role in the study design, data collection and analysis, interpretation of the data, decision to publish, or writing the manuscript.

Availability of data and materials
We used publicly available GEO datasets ([https://www.ncbi.nlm.nih.gov/geo/](https://www.ncbi.nlm.nih.gov/geo/)) GSE57741, GSE1094863, GSE1094864, GSE1094865, GSE1094866, GSE1094867, GSE124814, and GSE124827 for our analyses. The gene expression data GSE124827 (Cavall dataset) was used for survival analyses in the R2-Genomics Analysis and Visualization Platform ([https://hgserver1.ancc.malignantcancer.org/gtia/bin/web/main.cgl](https://hgserver1.ancc.malignantcancer.org/gtia/bin/web/main.cgl)).

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interest.

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Received: 26 March 2020 Accepted: 19 June 2020
Published online: 26 June 2020

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