Non-Coding RNAs Participate in the Pathogenesis of Neuroblastoma

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Neuroblastoma is one of the utmost frequent neoplasms during the first year of life. This pediatric cancer is believed to be originated during the embryonic life from the neural crest cells. Previous studies have detected several types of chromosomal aberrations in this tumor. More recent studies have emphasized on expression profiling of neuroblastoma samples to identify the dysregulated genes in this type of cancer. Non-coding RNAs are among the mostly dysregulated genes in this type of cancer. Such dysregulation has been associated with a number of chromosomal aberrations that are frequently detected in neuroblastoma. In this study, we explain the role of non-coding transcripts in the malignant transformation in neuroblastoma and their role as biomarkers for this pediatric cancer.

Keywords: miRNA, lncRNA, neuroblastoma, expression, polymorphism

INTRODUCTION

Neuroblastoma is a neoplasm originated from the neural crest of the sympathetic part of autonomic system (1) during the embryonic life (2). This malignancy is among the most common childhood cancers particularly during the first year of life (3). Neuroblastoma has a heterogeneous course in terms of both pathobiology and clinical manifestations. Several therapeutic options such as surgical removal of the tumor, chemotherapy, radiotherapy, and bone marrow transplantation are being applied for neuroblastoma (4). Spontaneous regression might also happen in the course of neuroblastoma (5). This tumor is associated with several genetic and chromosomal abnormalities that affect its clinical course and prognosis namely MYCN amplification, loss of distal portion of chromosome (chr) 1p and gain of 17q (6). Other chromosomal abnormalities detected in neuroblastoma are loss of 11q, 3p, 4p, 9p, 14q, and gain of 1q, 7q, 2p, and 11p (7–9). In addition to these chromosomal aberrations, dysregulation of several genes including non-coding RNAs (ncRNAs) are linked with this cancer (10). These kinds of transcripts have regulatory impact on other genes, hence constructing an epigenetic layer of gene regulation. They are classified based on
their sizes to long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) with the former having more than 200 nucleotides and the latter being about 22 nucleotides (11). Based on the speculation stated by the ENCODE consortium regarding the recognition of “biochemical functions for 80% of the genome” (12), ncRNAs have attained much attention during the recent decade particularly in the field of cancer research. In the current study, we explain the role of lncRNAs and miRNAs in the evolution of neuroblastoma and their role as biomarkers for this pediatric cancer.

**Dysregulated miRNAs in Neuroblastoma**

Chen and Stallings have measured expression of 157 miRNAs in neuroblastoma samples. They have displayed differential pattern of 32 miRNAs between tumor with favorable prognosis and those with poor prognosis. Notably, several of these miRNAs were down-regulated in neuroblastoma samples harboring MYCN amplification, which was associated with unfavorable outcome. Cell line studies have shown the role of retinoic acid in the modulation of expression of miRNAs in a MYCN-amplified cell line. Among the dysregulated miRNAs has been miR-184 which participates in the regulation of apoptosis. MYCN might exert its tumorigenic effects via modulating expression of miRNAs that participate in neural cell differentiation or apoptotic processes (13).

Among the firstly discovered tumor suppressor miRNAs in neuroblastoma was miR-34a (14), which is transcribed from a frequently deleted region in neuroblastoma i.e. 1p36.23. This miRNA was particularly down-regulated in neuroblastoma samples with 1p deletion (14). Since miR-34a inhibits expression of the E2F3 transcription factor, its down-regulation facilitates cell cycle progression (14). Subsequent studies have also verified the tumor suppressive impact of miR-34a in the neuroblastoma cells and its inhibitory effects on the expression of BCL2 and MYCN (15, 16). miR-34a also binds with the 3’ UTR of ATG5 and CD44 transcripts and decreases their expressions. Down-regulation of miR-34a in neuroblastoma cells results in the over-expression of ATG5 and CD44 (17, 18). CD44 is a cell surface receptor which can bind with hyaluronan and induce expression of genes that promote progression of cancer (19). ATG5 can dissociate V1V0-ATPase, increase pH in multivesicular bodies and enhance secretion of exosomes to facilitate cancer metastasis (20). Thus, miR-34a affects the progression of neuroblastoma through different mechanisms. **Figure 1** shows some aspects of participation of miR-34a in the pathogenesis of neuroblastoma.

miR-542-5p is another tumor suppressor miRNA whose down-regulation in neuroblastoma has conferred poor clinical outcome. Notably, forced up-regulation of miR-542-5p has resulted in attenuation of neuroblastoma invasive properties and tumor growth both in vitro and in vivo (21). Moreover, expression of miR-490-5p has been diminished in neuroblastoma tissues and cells. Forced overexpression of miR-490-5p has diminished cell proliferation migration and invasiveness, prompted G0/G1 arrest in cells and induced cell apoptosis. MYEOV has been confirmed to be the target of miR-490-5p through which miR-490-5p blocks neuroblastoma progression (22).

**Table 1** recapitulates the results

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**FIGURE 1** | miR-34a binds with the 3’ UTR of ATG5 and CD44 transcripts to reduce their expressions. Decreased expression of miR-34a in neuroblastoma leads to over-expression of ATG5 and CD44 (17, 18). CD44 is a cell surface receptor which can bind with hyaluronan and induce expression of genes that promote progression of cancer (19). ATG5 can dissociate V1V0-ATPase, increase pH in multivesicular bodies and enhance secretion of exosomes to promote cancer metastasis (20).
| miRNA   | Specimens                  | Cell line       | Targets/ regulators | Signaling pathway | Function                                                                 | Effect of miRNA down-regulation on patient’s prognosis | Reference |
|---------|----------------------------|-----------------|--------------------|-------------------|--------------------------------------------------------------------------|--------------------------------------------------------|-----------|
| miR-490-5p | 72 tumor tissues and ANTs | SH-SYSY, SK-NSH, U343 | MYEOV              | –                 | Down-regulated miR-490-5p levels correlate with advanced INSS stage, lymph node involvement, and poor outcome. MR-490-5p overexpression thwarts cell proliferation, migratory capacities, invasive effects, and enhances the cell cycle arrest and apoptosis. | Poor survival                                         | (22)      |
| miR-144   | SH-SYSY, SK-N-SH, HUVEC    | MYCN            | –                  | –                 | miR-144 influences proliferation, apoptosis and cisplatin resistance.    | –                                                      | (23)      |
| miR-144-3p | 46 pairs of NB ANTs      | SK-N-SH, SH-SYSY, HUVEC | HOXA7             | –                 | miR-144-3p repression results in the advancement of cell proliferation, cell cycle progression, and cell migration. Down-regulation of miR-144-3p level correlates with advanced tumor stage, greater carcinoma size, and lymph node metastasis. | –                                                      | (24)      |
| miR-34a   | 35 pediatric NB patients, 15 normal adrenal tissue | SH-SYSY         | MMP-2, MMP-14, HNF4x | –                 | miR-34a down-regulation increases cell proliferation, migration, and invasion. | –                                                      | (24)      |
|           | 18 NB primary and their metastatic tissues | SH-SYSY, IMR-32 | CD44               | –                 | miR-34a repression results in enhanced metastasis, proliferation, and invasion rates in NB cells. | –                                                      | (17)      |
|           | 32 NB and ANTs            | SH-SYSY, SK-N-SH, HUVEC | ATG5              | –                 | miR-34a repression results in enhanced metastasis, proliferation, and invasion rates in NB cells. | –                                                      | (18)      |
| miR-183   | –                         | IMR-32, SH-SYSY, SK-N-MC, SK-N-SH, H2K93, KCLB, HEF, SK-N-DZ BE2(C), Kelly | -/MYCN, HDAC2     | –                 | MYCN inhibition increases the pro-apoptotic miR-183 levels. | –                                                      | (25)      |
| miR-323a-5p | 253 NB patients          | SK-N-AS, SH-SYSY, IMR-32, H2K93T141, OHLA-90, SK-N-BE(2), LA1-5 | CHAF1A, KIF11, INCENP, CD25A, COND1, FADD, E2F2, AKT2, COND1, MKNK2, BCLX, DELL1 | –                 | These miRNAs reduce cell proliferation, cell viability, cell cycle, and tumor growth, though they increase the apoptosis rate. | –                                                      | (27)      |
| miR-342-5p | –                         | SH-SYSY, IMR-32, KELLY | Notch-Delta       | –                 | miR-34b markedly down-regulates the DLL1 mRNA expression levels, arrests cell proliferation, induces neuronal differentiation in malignant NB cells. | Poor OS                                                | (28)      |
| miR-34b   | –                         | SH-SYSY, IMR-32, KELLY | Notch-Delta       | –                 | miRNA-34b markedly down-regulates the DLL1 mRNA expression levels, arrests cell proliferation, induces neuronal differentiation in malignant NB cells. | Poor OS                                                | (28)      |
| miR-145   | –                         | SH-SYSY         | Bnip3             | –                 | miR-145 inhibition promotes mitophagy activity and subsequently increases SH-SYSY cell survival. miR-2110 overexpression induces cell differentiation and inhibits cell survival. | Poor OS and EFS                                        | (29)      |
| miR-2110  | –                         | BE2(C), SKNDZ, OHLA-90, SKNFI | TSKU              | –                 | miR-145 inhibition promotes mitophagy activity and subsequently increases SH-SYSY cell survival. miR-2110 overexpression induces cell differentiation and inhibits cell survival. | Poor OS and EFS                                        | (30)      |
| miR-186   | GSE62564 dataset: 498 NB patients | OHLA-136, LAN-5, OHLA-255, HEK293T | MYCN, ALPRA, TGFB1, TGFB2, TGFB3, TGF-β, TLR, LMO1, MYCN | –                 | miR-186 lower expression levels relate to a poor prognosis in NB patients that directly correlates with NK activation markers. | Poor EFS and OS                                       | (31)      |
| let-7     | –                         | KELLY, BE2C, SH-SYSY | –                 | –                 | let-7 decreases the expression levels of TGF-β, LMO1, and MYCN. | –                                                      | (32)      |
| miRNA          | Specimens                          | Cell line                  | Targets/ regulators | Signaling pathway | Function                                                                 | Effect of miRNA down-regulation on patient’s prognosis | Reference |
|---------------|-----------------------------------|----------------------------|---------------------|-------------------|--------------------------------------------------------------------------|--------------------------------------------------------|------------|
| miR-15a/miR-16-1 | GSE81500 dataset: 172 NB patients | BE(2)C, PA-1, IMR90, SK-N-AS, SH-SYSY, HCT116, SK-N-DZ, Kelly HTLA-230, HTLA-ER, HOT116 T5P2--/-- | BMI-1, p16/p53 | MAPK               | miR-15a/16-1 down-regulation enhances BMI-1 oncoprotein up-regulation, which decreases p16 tumor suppressor and increases etoposide resistance. | Lower OS                                             | (34)       |
| miR-129       | 88 NB and 23 ANTs                  | NB69, SK-N-SH, SK-SY-SY, SK-N-AS, IMR32, Neuro-2a, BEM17, NB1, Kelly, NB-1643, HEK293T | MYO10              |                    | miR-129 down-regulates MYO10 levels and then represses cell proliferation and increased chemosensitivity. |                                             | (36)       |
| miR-1247      | 10 primary NB and the corresponding ANTs | SH-SYSY, SK-N-SH            | ZNF346              |                    | miR-1247 markedly decreases cell proliferation and induces cell cycle arrest and cell death. |                                             | (40)       |
| miR-204       | 200 NB tumors                      | BE(2)C, SH-SYSY, SHEP, Kelly, SK-N-AS, SK-N-FI, IMR32 | MYC                |                    | MYCN binds to the miR-204 promoter and represses miR-204 transcription. miR-204 directly binds MYCN mRNA and diminishes MYCN expression. |                                             | (41)       |
| miR-664a-5p   |                                    | SH-SYSY, M17                | -                   |                    | miR-664a-5p enhances neuronal differentiation.                             |                                             | (42)       |
| miR-124       |                                    | M17                        | β-Tubulin III, MAP2, SYN, NF-M, Nestin |                    | miR-124 up-regulation increases differentiation in neuronal lineages.     |                                             | (43)       |
| miR-505-3p    |                                    | N2a, U251                  | SRSF1               |                    | miR-505-3p impedes neural tumor proliferation driven by SRSF1, solely in serum-reduced condition. |                                             | (44)       |
| miR-513       | 10 primary NB and matched ANTs     | SK-N-SH, SK-N-BE2, SH-SYSY, SK-N-AS, SK-N-DZ | GLS                |                    | miR-513c inhibits migration, invasion, and proliferation.                |                                             | (45)       |
| miR-205       | 28 tumor and adjacent normal tissues of NB patients | SH-SYSY, SK-N-SH, IMR32, BE(2)-C, HUVEC | CREB1, BCL-2, MMP9 |                    | Expression of miR-205 is down-regulated in poorly differentiated NB tissues and those of advanced stage. |                                             | (46)       |
| miRNA     | Specimens                          | Cell line                                    | Targets/regulators                          | Signaling pathway | Function                                                                 | Effect of miRNA down-regulation on patient’s prognosis | Reference |
|-----------|------------------------------------|----------------------------------------------|---------------------------------------------|-------------------|--------------------------------------------------------------------------|--------------------------------------------------------|-----------|
| miR-628-3p | 22 primary NB and 21 normal tissues | KCNR, HEK293T, LAN5, SH-SYSY, SK-N-SH         | MYCN                                        | –                 | miR-628-3p has a tumor-suppressor characteristic and down-regulates MYCN. | –                                                      | (47)      |
| miR-17    | –                                  | SK-N-BE(1)n, LA1-55n, KON-83n, BE(2)-M17V, SK-N-LD, SK-N-HM, BE (2)-C, LA1-5s, SH-SYSY, SMS-LH, CB-JMN, SH-EP1, SMS-KCNs | N-myc/ELAVL4 | –                 | miR-17 down-regulates N-myc mRNA and protein levels, while ELAVL4 up-regulates N-myc and is a competitive factor for miR-17. | –                                                      | (48)      |
| miR-149   | 117 NB patients                    | SH-SYSY, CHP-212, IMR-32, SK-N-SH, SK-N-AS, NB1691, LAN1, LAN5, LAN6 | Rap1                                        | –                 | Down-regulation of miR-149 expression is associated with advanced stages of primary NB tumors and poor OS. | Poor OS                                                | (49)      |
| miR-137   | –                                  | SH-SYSY, SK-N-SH, SH-SY5Y, CHP-212, LA1-5s, SH-SY5Y, SMS-LHN, CB-JMN, SH-EP1, SMS-KCNs | N-myc/ELAVL4 | –                 | miR-17 down-regulates N-myc mRNA and protein levels, while ELAVL4 up-regulates N-myc and is a competitive factor for miR-17. | –                                                      | (50)      |
| miR-149   | 88 NB patients                     | N-2a, SH-SYSY                                 | EZH2, GLI, NGR                              | –                 | Resveratrol induces miR-137 up-regulation and reduces EZH2 repression. EZH2 reduction results in increased GLI and NGR tumor suppressors. RBM3 abolishes the induction of miR-137 and sensitivity to doxorubicin. | Lower OS                                                | (51)      |
| miR-143   | –                                  | SH-SYSY, CHP-212, IMR-32, SK-N-SH, SH-SY5Y, CHP-212, LA1-5s, SH-SY5Y, SMS-LHN, CB-JMN, SH-EP1, SMS-KCNs | MDR1/HDAC8                                    | –                 | miR-137 overexpression reduces the proliferation of multiple chemoresistant NB cell lines and induced apoptosis in MYCN-amplified cell lines. Moreover, miR-137 in NB xenografts diminishes tumor growth and inhibits vascular permeabilization. | Lower progression-free survival                       | (52)      |
| miR-410   | 61 cases of NB and normal tissues  | SK-N-BE(2), NB1691                           | VEGFA/SPARC                                  | –                 | miR-137 up-regulation reduces proliferation and radiation restricts tumor growth and angiogenesis by down-regulating VEGF-A via miR-410. | –                                                      | (53)      |
| miR-93-5p | –                                  | SK-N-AS                                      | VEGF, IL-8                                   | –                 | miR-93-5p is down-regulated in NB cells, which promotes VEGF and IL-8 and tumorogenesis. miR-141 up-regulation inhibits cancer proliferation, cell cycle progression, tumor growth, migration, and rises cisplatin sensitivity. | –                                                      | (54)      |
| miR-141   | –                                  | IMR-32, SH-SYSY, S-K-NAS, NB1691, LAN-5, LAN-6, HEK293T | FUS                                          | –                 | miR-141 up-regulation inhibits cancer proliferation, cell cycle progression, tumor growth, migration, and rises cisplatin sensitivity. | –                                                      | (55)      |
| miR-497   | 365 NB samples                     | CHL-A-90, SK-N-BE(2), LA1-5s, SK-N-AS, HEK293T | WEE1, CHEK1, AKT3, BCL2, VEGFA                | –                 | miR-497 overexpression reduces the proliferation of multiple chemoresistant NB cell lines and induced apoptosis in MYCN-amplified cell lines. Moreover, miR-497 in NB xenografts diminishes tumor growth and inhibits vascular permeabilization. | Lower progression-free survival                       | (56)      |
| miR-451   | 37 NB and ANTs                     | SK-N-SH, GI–LA-N                             | MIF                                          | –                 | miR-451 reduces cell proliferation, invasion, and migration. Reduction in miR-451 increases tumor size, dedifferentiation, lymph node metastasis, TNM stage, and remote metastases. | –                                                      | (57)      |
| miR-203   | 16 NB and ANTs                     | SK-N-SH, SH-SYSY                             | Sam68                                        | –                 | Up-regulation of miR-203 inhibits the proliferation, migration, and invasion rates. | –                                                      | (58)      |
| miR-26a-5p | 200 patients with primary NB, GSE32664 dataset; 75 primary tumors | SK-N-SH, SKN-AS, SH-SYSY, SK-N-BE(2), HepG2, PC-3, HeLa, 786-O, HUVEC | MMP14, AGO2                                    | –                 | miR-26a-5p overexpression reduces miR-26a-5p (not in the transcription stage), and miR-26b-5p results in LIN28B up-regulation. | Lower OS rate                                       | (59)      |
| miR-337-3p | 30 primary NB cases and 21 normal dorsal ganglia | SK-N-SH, SKN-AS, SH-SYSY, SK-N-BE(2), HepG2, PC-3, HeLa, 786-O, HUVEC | PIK3-AK02                                      | –                 | miR-337-3p inhibits the activity of MMP-14 promoter and, its nascent transcription. | Lower OS rate                                       | (60)      |
| miR-362-5p | 12 metastatic and 12 primary NB tissues | SH-SYSY, IMR-32, HEK293 | PIK3-AK02                                    | –                 | miR-362-5p inhibits cell proliferation, tumor growth, migration, and invasion of NB cells. | –                                                      | (61)      |
| miR-659-3p | 22 bone marrow                    | HTLA-230, SH-SYSY                            | CNOT1, AKT3                                   | –                 | Inhibiting miR-659-3p results in over-expressed CNOT1 and down-regulated AKT3, BCL2, CYR61, | Lower OS rate                                       | (62)      |

(Continued)
miR-182-5p
miR-432-5p
miR-449a
miR-520f
miR-542-3p

Table 2 lists up-regulated miRNAs in neuroblastoma. Aberrant expression of miRNAs in neuroblastoma samples can be used as biomarkers for prediction of the course of malignancy. For instance, down-regulation of miR-490-5p has been correlated with INSS stage, lymph node involvement, and poor clinical outcome of patients with neuroblastoma (22). Similarly, decreased expression of miR-186, let-7, miR-497 and miR-432-5p predicts lower survival rates (31, 34, 56, 63). Table 3 reviews the results of studies which evaluated this aspect of miRNAs.

Dysregulated IncRNAs in Neuroblastoma

LncRNAs can regulate expression of genes via different mechanisms including alterations in chromatin configuration, modulation of transcription, splicing, mRNA stability and bioavailability as well as post-translational modifications (83). Therefore, they contribute in the pathogenesis of human cancers. Prajapati et al. have analyzed RNA-seq data of a number of neuroblastoma samples to recognize their differential expression in among primary neuroblastoma, relapsed ones and metastasized tumors. They reported up-regulation of RFPL1S,
miR-19b – miR-181a/miR-640, miR-196-3p, miR-21 CHL1 miR-21 promotes the proliferation and invasion of NB

CASC15, PPP1R26-AS1, and USP3-AS1 lncRNAs as putative regulators along with ZRANB2-AS2 and LINC00511 compared with the corresponding MNCs. They suggested that miR-25 Versteeg dataset: 88 samples, Kocak dataset: 649 samples, SEQC dataset: 498 samples.

miR-19b – miR-3613-3p

CHRM3-AS2 and RP6-99M1.2 in tumor cells compared with corresponding non-tumor mononuclear cells isolated from bone marrow (MNCs). Moreover, expression of these up-regulated lncRNAs along with ZRANB2-AS2 and LINC00511 were increased in the disseminated tumor cells (DTCs) compared with the corresponding MNCs. They suggested that miR-21 promotes the proliferation and invasion of NB cells.

TABLE 2 | Up-regulated miRNAs in neuroblastoma (NB, neuroblastoma; OS, overall survival).

| miRNA   | Number of clinical samples | Assessed cell line | Targets/ regulators | Signaling pathway | Function | Effect of miRNA up-regulation on patients’ prognosis | Ref |
|---------|----------------------------|--------------------|---------------------|-------------------|----------|-----------------------------------------------|-----|
| miR-25  | Versteeg dataset: 88 samples, Kocak dataset: 649 samples, SEQC dataset: 498 samples | SH-SY5Y | Gsk3β/SLC34A2 | Wnt | SLC34A2 inhibits the stemness of NB cells via the miR-25–Gsk3β axis. | – | (71) |
| miR-640, miR-543, miR-624-3p, miR-196-3p | 50 NB tissues | SH-SY5Y, SK-N-AS, NGP, SK-N-BE2 | ING5 | – | Suberoylanilide hydroxamic acid downregulates these miRNAs to induce ING5 overexpression. | – | (69) |
| miR-181a/b | 32 primary NB tissues and 6 gangliocytoma tissues as controls | SK-SY5Y, SK-N-SH, BE(2) C, IMR-32, HUVEC, HEK293T | ABL1 | – | The up-regulation of miR-3613-3p increases viability but reduces the apoptosis of NB cells. | – | (72) |
| miR-181a | – | SH-SY5Y, A172, U251 | p38MAPK/tripolide | NF-kB | High miR-181a/b expression markedly enhances the proliferation, tumorigenesis, progression, migration, and invasion of NB cells, though it reduces the apoptosis rate. MYCN amplification and miR-181a expression are correlated. | – | (73) |
| miR-221 | 31 NB tissues | SK-N-AS, SK-N-DZ, IMR-32, HEK293T, SH-SY5Y | LEF1, NLK, p21, p27, p57 | Wnt | Through down-regulating miR-181a/b level, Triptolide inhibits cell viability, proliferation, and migration, but induces cell apoptosis. | – | (74) |
| miR-558 | 30 primary NB and 10 ganglioneuroblastoma samples, GSE62564 database: 498 NB cases | NB-1643, SK-N-BE (2), NB-1691, IMR32, BE(2)-C, SK-N-AS, SH-SY5Y, SK-N-SH, HUVEC | AQO2, HIF-2α | – | miR-558 enhances the proliferation, invasion, metastatic capacities, and angiogenic potential. Poor OS | Poor survival rate | (77) |
| miR-1303 | 8 NB and adjacent normal nerve tissues | U343, SK-N-SH, SH-SY5Y, LAN5, IMR-32, SH-EP | HPSE, VEGF, AQO1, GSK3β, SFRP1, p21, p27, MYC, CyclinD1 | – | Knock-down of endogenous miR-558 reduced the proliferation, invasion, metastasis, and angiogenic potential. Poor survival rate | – | (78) |
| miR-19b | – | SH-SY5Y, BE(2)-M17 | p-AKT, PTEN | mTOR | A2D8055 significantly reduces miR-19b and p-AKT expression and enhances the cytotoxic activity of mTOR inhibitors and PTEN levels. miR-19b overexpression reverses mTOR inhibitors toxicity and cell viability. miR-21 promotes the proliferation and invasion of NB cells. | – | (79) |
| miR-21 | – | CHL1 | – | – | – | – | (80) |

PPP1R26-AS1, RP11-439E19.3, CASC15, AC004540.5, and CTD-2881E23.2 while down-regulation of USP3-AS1, CHRM3-AS2 and RP6-99M1.2 in tumor cells compared with the corresponding non-tumor mononuclear cells isolated from bone marrow (MNCs). Moreover, expression of these up-regulated lncRNAs along with ZRANB2-AS2 and LINC00511 were increased in the disseminated tumor cells (DTCs) compared with the corresponding MNCs. They suggested that miR-21 promotes the proliferation and invasion of NB cells.
TABLE 3 | Diagnostic importance of miRNAs in neuroblastoma (NB, neuroblastoma; OS, overall survival; EFS, event-free survival).

| Sample number | Kaplan-Meier analysis | Reference |
|---------------|----------------------|-----------|
| miR-490-5p expression in NB patients: 21 high and 51 low | Higher miR-490-5p expression levels markedly correlate with higher survival rate. | (22) |
| miR-323a-5p expression: high in 228 and low in 25 NB patients | Higher expression levels of miR-323a-5p expression correlates with higher OS rate. | (27) |
| miR-2110 expression in NB patients, derived from SEQC dataset: high=406, low=92 | Higher expression levels of miR-2110 correlate with lower OS. | (30) |
| miR-186 expression in NB patients: 235 high and 263 for EFS, 298 high and 200 low for OS | Low levels of miR-186 correlate with poor OS and EFS. | (31) |
| miR-149 expression in NB patients: low=59, high=58 | Higher miR-149 expression level significantly correlates with higher OS rate. | (49) |
| miR-221 expression in NB patients: low=17, high=14 | Higher miR-221 expression level negatively correlates with survival rate. | (76) |
| miR-181c expression: high=326, low=172 | Higher expression of miR-181c significantly correlates with higher OS in NB patients. | (81) |
| miR-558 expression in two sets of samples: 13 low and 17 high, 170 low and 328 high Let-7 expression in NB patients: normal levels=90, loss of Let-7 = 112 | Higher expression negatively correlates with the OS rate. | (77) |
| 70 patients with NB, divided into 3 groups based on their expression level of miR-21 and risk: low=22, moderate=23, high=25 | Loss of Let-7 expression correlates with lower OS rate. | (34) |
| miR-497 expression in NB patients from NRC dataset: high=100, low=228 | In patients with NB, higher miR-21 expression correlated with lower rates of OS. | (82) |
| miR-26a-5p expression in NB patients: high=44, low=48 | Lower miR-497 expression correlates with lower progression-free survival rates. | (56) |
| miR-337-3p expression in 30 NB patients: 17 high and 13 low | Lower miR-26a-5p and miR-26b-5p expression correlate with lower OS rate. | (59) |
| miR-432-5p expression in 100 NB patients | Lower miR-337-3p levels correlate with lower OS rate. | (60) |
| miR-137 expression in NB patients: 17 high and 71 low | Lower miR-432-5p expression levels relates to lower cumulative survival. | (63) |
| miR-542-3p expression level in NB patients: 34 high and 34 low | miR-137 expression negatively correlates with OS rate. | (51) |
| miR-34a expression in NB patients: 15 high and 15 low | miR-542-3p over-expression significantly correlates with better survival rate. | (66) |
| miR-497 expression in NB patients from NRC dataset: high=100, low=228 | Higher miR-34a level significantly correlates with better survival rate. | (18) |

and invasion of neuroblastoma cells through suppression of expression of target genes as well as induction of expression of neuronal-specific transcription factor NR5F/REST (85). Liu et al. have reported co-amplification of the IncUSMycN with MYCN in a portion of human neuroblastoma samples. This IncRNA has been shown to bind with the RNA-binding protein NONO, resulting in dysregulation of this type of ncRNAs in cancers. For instance, high levels of DLX6-AS1, IncNB1, LINC01296, SNHG16 and RMRP expression have been linked with poor prognosis and lower survival (90, 92, 94, 95, 104). Table 6 summarizes the results of studies which assessed correlation between expression levels of IncRNAs and survival of patients with neuroblastoma.

Expression and Function of circRNAs in Neuroblastoma
Circular RNAs (circRNAs) constitute a group of ncRNAs which are produced from exons or introns through construction of covalently-closed circles (134). Recent studies have shown dysregulation of this type of ncRNAs in cancers. For instance, circDGKB has been shown to be over-expressed in neuroblastoma tissues versus normal dorsal root ganglia. Notably, over-expression of this circRNA has been an indicator of poor survival of these patients. Mechanistically, circDGKB enhances cell proliferation, migration and invasion of neuroblastoma cells while inhibiting cell apoptosis. Moreover, up-regulation of circDGKB reduced expression level of miR-873 and increased GLI1 expression (135). Table 7 recapitulates the results of studies which assessed function of circRNAs in neuroblastoma.

Polymorphisms Within ncRNAs and Risk of Neuroblastoma
Single nucleotide polymorphisms (SNPs) within IncRNAs or miRNAs can modulate expression or activity of these transcripts, thus being implicated in the development of neuroblastoma. The
| IncRNA   | Specimens | Cell lines | Targets/regulators | Signaling pathway | Function                                                                 | Effect of IncRNA up-regulation on patient’s prognosis | Ref |
|----------|-----------|------------|-------------------|-------------------|--------------------------------------------------------------------------|------------------------------------------------------|-----|
| DLX6AS1  | 70 pairs of primary NB and ANTs | SK-N-SH, SH-SY5Y, SK-N-AS, SK-N-BE, HEK293T | miR-497-5p, YAP1  | –                  | DLX6-AS1 knock-down results in diminished proliferation rate, tumor proliferation, migration, EMT, and invasion. | Poor prognosis and OS (90) |     |
|          | 31 NB and ANTs | SK-N-SH, LAN-6, HUVEC | miR-506-3p, STAT2, CDK1, Cyclin D1 | –                  | DLX6-AS1 silencing inhibits proliferation, tumor growth, cell cycle, and glycolysis. | – (91) |     |
| IncNB1   | SEQC-RPM-seqcnb1 dataset: 493 NB tissues | BE(2)-C, IMR32, SY5Y, SHEP, HEK293T | RPL35, E2F1, DEPDC1B, ERK, n-Myc | –                  | IncNB1 down-regulation abrogates clonogenic capacity and leads to NB tumor regression. | Lower OS (92) |     |
| DEIN     | Case study of a monozygotic twin with NB | HAND2 | – | – | Both twin liver tumors had a 4q34.1 amplification of DEIN, which is strongly linked to HAND2. HAND2 functions as an essential regulator of neurogenesis. | – (93) |     |
| LINC01296| 28 patients with primary NB, R2: Genomics Analysis and Visualization Platform for 88 NB patients | – | – | – | Over-expression of LINC01296 was associated with age>18 month and advanced INSS stage. Moreover, LINC01296 over-expression is correlated with larger tumor size, elevated serum lactate dehydrogenase level, and serum neuron-specific enolase level. | Poor prognosis and OS (94) |     |
| SNHG16   | 40 patients with NB, GSE62564 dataset: 498 NB patients | SH-SY5Y | – | – | SNHG16 down-regulation inhibits proliferation, migration, and induces cell cycle arrest at the G0/G1 phase. SNHG16-related RNA binding proteins partake in controlling mRNA metabolic processes, gene silencing, mRNA transport, RNA splicing, and translation. | Poor OS and EFS (95) |     |
|          | 76 NB tissues | SK-N-AS, SK-N-SH, SK-N-AS-R, SK-NSSH-R | miR-338-3p, PLK4, MRP1, p-glycoprotein | PI3K/AKT | In cisplatin-resistant NB tissues and cells. SNHG16 is up-regulated, while miR-338-3p is down-regulated. | – (96) |     |
|          | 48 NB and 38 ANTs | SK-N-SH, IMR-32, SK-N-AS, SK-N-DZ, HUVEC | HOXA7, miR-128-3p | – | SNHG16 silencing represses proliferation, migration, and invasion but boosts apoptosis. The Knock-down of SNHG16 or HNF4α impedes proliferation, migration, invasion, and EMT. | – (97) |     |
|          | 30 NB and 30 ANTs | SKNB-E-2, SK-N-SH, HEK293, LAN-5 | miR-542-3p, HNF4α | RAS/RAF/MEK/ERK | The knock-down of SNHG16 diminishes migration, invasion, autophagy, and tumor growth. | Lower OS (98) |     |
|          | 45 NB and ANTs | LAN-1, SHEP, SKN-SH, IMR-32, HUVEC | miR-542-3p, ATG5 | – | The knock-down of SNHG16 diminishes proliferation, migration, invasion, autophagy, and tumor growth. | – (99) |     |
| MIAT     | – | Neuro2A | caspase-3, miR-211, GDNF | – | MIAT overexpression lowers the apoptosis rate. | – (100) |     |
| SNHG7    | – | – | miR-653-5p, STAT2 | – | SNHG7-miR-653-5p-STAT2 loop is involved in regulation of NB progression. Silencing of SNHG7 reduced cisplatin resistance and suppressed cisplatin-induced autophagy. | – (101) |     |
|          | 26 NB and ANTs | SK-N-AS, LAN-6, HUVEC | miR-329-3p, MYO10 | – | SNHG7 knock down repressed migration, invasion, and glycolysis. | Poor prognosis and OS (102) | Poor OS (103) |
|          | 45 NB and ANTs | SH-SY5Y, SK-N-SH, NB-1, SK-N-AS, HUVEC | miR-323a-5p, miR-342-5p, CCND1 | – | SNHG7 knock-down lessens proliferation, migration, and invasion rates. RMRP expression is markedly increased in patients with advanced neonatal NB versus early stages. | Poor OS (104) |     |
| RMRP     | 44 cases of neonatal NB and ANTs | NB-1, SK-N-AS, HEK293T | miR-206, TACR1 | ERK1/2 | RMRP knock-down lessens proliferation, migration, and invasion rates. RMRP expression is markedly increased in patients with advanced neonatal NB versus early stages. | Poor OS (105) |     |
| SNHG1    | – | SK-N-DZ, SK-N-BE(2)C, SK-N-AS | MATR3, YBX1, HNRPPL | – | SNHG1 significantly elevates ribonucleoprotein complex biogenesis, RNA processing, and RNA splicing. MYCN amplification up-regulates SNHG1. | Poor OS and EFS (106) |     |
|          | GSE62564 dataset: 493 NB patients, – | SK-N-DZ, SK-N-SH, SK-N-BE(2)C, SK-N-AS, SK-N-F1 | rMHCN | – | – | – (107) |     |

(Continued)
| IncRNA     | Specimens                              | Cell lines                | Targets/regulators | Signaling pathway | Function                                                                 | Effect of IncRNA up-regulation on patient’s prognosis | Ref |
|------------|----------------------------------------|---------------------------|--------------------|-------------------|--------------------------------------------------------------------------|--------------------------------------------------------|------|
| GALNT8     | GSE12460 dataset; 47 NB patients        | SK-N-AS, HEK293T          | TCEA1, RBMX, MCM2, CBX3 | –                 | Suppressing the GAU1/GALNT8 cluster hinders tumor progression and growth. GAU1 recruits TCEA1 to activate GALNT8 expression. | Poor OS (107)                                      |      |
| GAU1       | TCGA dataset; 88 NB cases              |                           |                    |                   |                                                                          |                                                        |      |
| MYCNOS-01  | 88 NB samples                          | KELLY, SYSY               | MYCN               | –                 | The suppression of MYCNOS-01 or MYCN expression reduced cell proliferation and viability. |                                                         |      |
| pancEts-1  | 42 NB patients and 88 NB cases from GSE16476 dataset | NB-1643, SK-N-Be(2), NB-1691, IMR32, BE(2)-C, (SK-N-AS, SH-SYSY), Sk-N-Sh | hnRNPK, β-catenin  | –                 | PancEts-1 increases the proliferation, invasion, and metastasis of NB cells. pancEts-1 binds to hnRNPK to enhances its interplay with β-catenin and stabilizes the β-catenin. | Poor survival (109)                                  |      |
| MALAT1     | 15 normal tissues, 19 primary NB, and 28 metastatic NB tissues | NQP, SH-SYSY, NMB, SHEP21N, SKNAS, SHEP2, HEK293T | Axl, AKT, ERK1/2   | –                 | MALAT1 overexpression increases invasion and migration. |                                                         |      |
| GAS5       | –                                      | BE(2)-C, C, HUVEC         | FGF2               | –                 | MALAT1 significantly promotes cell migration, invasion, and vasculogenesis. |                                                         |      |
| HCN3       | –                                      | BE(2)-C                   | BID, Noxa, HIF-1α  | –                 | Linc01105 knock-down increases HIF-1α and promotes cell proliferation. In contrast, linc01105 and HCN3 knock-down increase the apoptosis rate. |                                                         |      |
| Inc01105   | Tumor and para-tumor tissue samples (n = 6) | BE(2)-C                  | NCYM, N-myc, NonO  | –                 | LncUSMycN up-regulates NCYM expression. |                                                         |      |
| IncUSMycN  | Versteeg dataset: 88 NB samples, Kocak dataset: 476 NB samples | IMR32, BE2C, SK-N-DZ, CHP134, Kelly, SK-N-Ri, SH-NAS, NB69, SYSY, SHEP, LAN-1 | NonO, N-Myc       | –                 | LncUSMycN increase up-regulates N-Myc RNA and NB cell proliferation. | Poor OS (86)                                       |      |
| HOXD-AS1   | GSE3446 dataset: 102 NB patients       | SH-SYSY                  | Magea9B, SN1, TMEM86A, VIPR1, CREM, TSPAN2, CNR1, CREBL1, PTGS1, ADAMS3, AMDMD2, ANG, ASNA1/retinoic acid | PI3K/Akt, JAK/STAT | Following RA treatment, HOXD-AS1 diminishes the expression of genes involved in NB progression, angiogenesis, and inflammation. |                                                         |      |
| CAI2       | 62 primary NB samples and 25 healthy controls | FS15, NMB7               | P16, ARF           | –                 | CAI2 expression is significantly higher in advanced-stage NB. | Poor OS (67)                                        |      |
| Paupar     | –                                      | N2A                      | KAP1, Pax6, ROR3, PPAN, CHE-1, ERH | –                 | Paupar regulates expression of some target genes involved in the regulation of neuronal function and cell cycle. |                                                         |      |
role of a number of SNPs within lncRNAs such as LINC00673, H19, MEG3 and HOTAIR has been evaluated in this regard (137–140). Moreover, the rs4938723 within miR-34b/c has been associated with risk of this kind of cancer (141). Notably, some studies have appraised these associations in certain subgroups of patients. For instance, the association between rs4938723 TC and CC genotypes is prominent in all age-based subgroups, both sexes, retroperitoneal tumors as well as tumors originated from other sites, and all clinical stages (141). Such detailed analyses have not been done for all assessed SNPs. Table 8 summarizes the results of studies which assessed contribution of SNPs within ncRNAs in conferring the risk of neuroblastoma.

DISCUSSION

Recent studies have demonstrated abnormal expression of lncRNAs, miRNAs and circRNAs in neuroblastoma. Besides, some SNPs within lncRNAs and miRNAs confer risk of neuroblastoma. In vitro studies have shown the functional interactions between a number of these ncRNAs and MYCN, the oncogene that has essential roles in the pathogenesis of this type of cancer. Moreover, certain miRNAs have been shown to target tyrosine kinase receptors. For instance, hsa-miR-376c is predicted to target ALK tyrosine kinase receptor. Notably, this miRNA has been up-regulated in neuroblastoma samples of long-survivors (146). Expressions of a number of other ncRNAs have been shown to stratify neuroblastoma patients based on their risk of recurrence and clinical outcome. The observed dysregulation of ncRNAs in neuroblastoma can be explained by their association with the frequent chromosomal abnormalities in this kind of cancer. Amplification of genomic loci corresponding to these transcripts is a possible route for their up-regulation (86). Moreover, epigenetic factors participate in the regulation of ncRNAs expression in neuroblastoma, as several lines of evidence points to the role of retinoic acid and its derivatives in the reversal of such dysregulation. Consistent with these observations, ATRA has been lately shown to induce differentiation of a number of neuroblastoma cell lines or activate apoptosis in these cells (147).
MYCNOS is expected to enhance their stability and their presence in the body and enrichment in the target organs. The encapsulation of these small transcripts in nanoparticle vesicles might represent an alternative mechanism of MYCN up-regulation/amplification in clinical settings. Administration of miRNA antagonism in suppression of proliferation of MYCN-amplified neuroblastoma cells in animal models (68). However, these results have not been replicated in clinical settings. Administration of miRNA mimics in clinical settings has encountered some problems most of the being related with the distribution of these transcripts in the body and enrichment in the target organs. Encapsulation of these small transcripts in nanoparticle vesicles is expected to enhance their stability and their presence in the circulation, permitting further time for their amassment in tumor tissues (148).

Multidrug resistance is a problem in the treatment of patients with neuroblastoma. Such phenotype has been associated with a number of genetic abnormalities such as over-expression of MYCN oncogene, hyper-activation of tyrosine kinase receptors (BDNF-TrkB) or reduced expression and activity of tumor suppressor genes including p53 (148). Therefore, ncRNAs that modulate expression of these elements or function in the downstream of these molecules can also be involved in the multidrug resistance of these cells. Therefore, modulation of expression of these transcripts represents a novel modality to combat multidrug resistance in neuroblastoma.

### TABLE 5 | Down-regulated lncRNAs in neuroblastoma (NB, Neuroblastoma; OS, overall survival; EFS, event-free survival).

| IncRNA     | Specimens | Cell line | Targets/ regulators | Signaling pathway | Function | Effect of lncRNA down-regulation on patient’s prognosis | Reference |
|------------|-----------|-----------|---------------------|-------------------|----------|-------------------------------------------------------|-----------|
| NRF-120420 | –         | SH-SY5Y   | P65, ERK, AKT, NEUROD1, NEUROG2 | –                 | The knock-down of NRF-120420 enhances cell viability but reduces the apoptosis. | –         | (125) |
| CASC15     | 220 high-risk NB samples | SK-N-BE2, SK-N-SH | – | – | CASC15 depletion improves proliferation and invasive capabilities and shifts the NB gene expression away from the differentiated neural phenotype. | Lower OS | (126) |
| NBAT-1     | Two cohorts: one with 59 and the other with 498 NB patients | SH-SY5-Y, SK-N-AS, IMR32, SK-N-BE2, hESCs, hNPCs, HEB2-9ST | SOX9, CHD7, USP36 | – | These lncRNAs regulate SOX9 expression through regulation of CHD7 stability. Loss of this synergy between these lncRNAs enhances proliferation, migration, invasion, colony formation of NB cells. | Poor OS and EFS | (127) |
| FOXD3-AS1  | 42 NB tumor samples, GSE16476 dataset: 88 cases of NB | NB-1643, SK-N-BE2, IMR32, BE(2)-C, SK-N-AS, SH-SY5Y, SK-N-SH | PARP1, OTCF | – | Over-expression of FOXD3-AS1 promotes neuronal differentiation and reduces aggressive behavior of these cells. | Poor survival | (128) |
| MEG3       | Tumor and para-tumor tissue samples (n = 6) | BE(2)-C | PMAIP1, BID, HIF-1α | – | MEG3 overexpression reduces proliferation and elevates apoptosis rate. | – | (114) |
| Linc-NeD125 | –         | BE(2)-C, D283Med, NB4, HL-60, Lan6 | BCL-2 | – | Linc-NeD125 is the host gene of miR-125b-1. Its down-regulation reduces cell proliferation and activates the antiapoptotic factor BCL-2. | – | (129) |
| MYCNOS     | –         | MYCN, MAP4, G3BP1, PKB3 | – | – | MYCNOS RNA localizes to the MYCN promoter and reduces its expression. | – | (130) |
| CASC15-S   | NCI TARGET project: 108 NB patients | SK-N-BE2, SK-N-SH, HEB2-9ST | ALCAM, NEUROD1, NEUROG2 | – | Attenuating CASC15-S elevates cellular proliferation, proliferation, invasion, and migratory capacity. | Poor OS | (126) |
| NBAT-1     | 15 NB snap-frozen tumors, 108 patients and RNA-seq data of 498 patients | SK-N-FI, SH-SY5Y, SK-N-AS, SK-N-BE(2) | NRSF, REST, SOX9, VCAN, EZH2 | – | NBAT-1 down-regulation boosts cellular proliferation and invasion and inhibits neuronal differentiation. | Poor survival | (85) |
| CASC7      | 48 NB patients | LAN-2 | mR-10a, PTEN | – | CASC7 overexpression decreases the proliferation of NB cells. | – | (131) |
| KCNQ1OT1   | Xena database: 128 NB tissues | SH-SY5Y, IMR32, HEB2-9ST | miR-296-5p, Bax | – | KCNQ1OT1 acts as a sponge for miR-296-5p. miR-296-5p inhibits Bax protein and cell apoptosis. | – | (132) |
| NEAT1      | 30 NB tissues | SK-N-SH, SH-SY5Y, IMR32, SH-N-AS | miR-183-5p, FOXP1, ERK/AKT | – | NEAT1 up-regulation lowers cell proliferation, migration, and invasion rates. | – | (133) |
Expression profile of ncRNAs has been correlated with patients’ survival. The underlying mechanism of this observation has been clarified in some cases. For instance, hsa-miR-383, hsa-miR-548d-5p, hsa-miR-939 and hsa-miR-877* miRNAs which have been down-regulated in neuroblastoma samples from long-survivors (146) target a number of genes being involved in the neuronal differentiation (149).

Taken together, the above-mentioned evidence suggests the crucial roles of ncRNAs in the regulation of important aspects of cell survival, proliferation and differentiation and their participation in the pathogenesis of neuroblastoma. Their potential as therapeutic targets for this type of cancer should be more explored in the future studies. The main limitation of studies which assessed expression of ncRNAs in...
**TABLE 7** | List of circRNAs dysregulated in neuroblastoma.

| circRNA  | Pattern of expression | Samples | Cell line | Targets/ regulators | Function | Patient’s prognosis | Reference |
|---------|-----------------------|---------|-----------|---------------------|----------|---------------------|-----------|
| circDGKB † | 30 NB tissues and 10 normal dorsal root ganglia as controls | SK-N-SH, SH-SY5Y | miR-873, GLI1, ZEB1 | circDGKB up-regulation improves the proliferation, migration, invasion, and tumorigenesis, though it reduces cell apoptosis. | Lower OS | (135) |
| circ-CUX1 † | 54 NB patients, GSE16476 dataset: 88 NB patients, oncogenic database: 117 NB and 3 normal tissues | MCF 10A, HeLa, SH-SY5Y, IMR32, SK-N-AS, BE(2)-C, SK-NMC, LoVo, PC-3, HEK293, HEK293T | EWSR1, MAZ, CUX1 | circ-CUX1 knock-down inhibits aerobic glycolysis, proliferation, progression, and aggressiveness of NB. circ-CUX1 binds to EWSR1 to enable its contact with MAZ, leading to transactivation of MAZ and transcriptional modification of CUX1 and other genes linked with cancer progression. | Lower survival rate | (136) |

**TABLE 8** | Polymorphisms within non-coding RNAs and risk of neuroblastoma.

| IncRNA/ miRNA | Number of clinical samples | SNP ID | Nucleotide change | OR (95%CI) | p-value | Description | Reference |
|---------------|---------------------------|--------|-------------------|------------|---------|-------------|-----------|
| LINC00673     | 700 cases and 1516 controls | rs11655237 | C>T | 1.58 (1.06-2.35) | 0.024 | Patients with the T allele are considerably more prone to develop NB. A substantial association exists between rs11655237 CT/TT and NB risk in subgroups of males, adrenal gland tumors, and patients with stage IV disease. Separated and combined analyses indicated no associations between these polymorphisms and NB susceptibility. Only female children with rs3024270 GG genotypes had a raised NB risk. | (137) |
| HOTAIR        | 393 NB patients and 812 healthy controls | rs2839698, rs3024270, rs217727 | G>A | 1.61 (1.04-2.50) | 0.032 | Patients with rs11752942 G allele are negatively related to NB risk. Carriers of rs11655237 T allele are prone to NB. These associations were found in females and among patients with tumors in the retroperitoneal or mediastinal region. | (138) |
| MEG3          | 392 NB children and 783 controls | rs7158663, rs4081134 | G>A | 1.36 (1.01-1.84), clinical stage III+IV: 1.47 (1.08-1.99) | 0.014 | Patients with rs4081134 AG/AA genotypes were significantly prone to develop NB among subgroups with age >18 months and stage III+IV. Carriers of these two polymorphisms were more prone to NB. These associations were found in children more than 18 months and with clinical stages of III-IV. | (142) |
| CAC15-S       | 250 primary NB, 20 NB cell lines | rs9296534 | T>A | 1.63 (1.4-1.89) | 1.24×10^{-12} | This polymorphism is located upstream of CASC15-S and spans regulatory chromatin and dense transcription factor binding site. This genomic area has an enhancer-like activity that is disturbed by NB risk allele. | (126) |
| HOTAIR        | 393 NB and 812 healthy controls | rs12826786, rs874945, rs1899663 | C>T, C>T, C>A | 1.98 (1.14-3.42), 1.91 (1.10-3.32), 1.87 (1.05-3.32) | 0.015, 0.022, 0.033 | These polymorphisms are markedly associated with increased NB risk. In stratification analyses, these associations are more dominant in females and among patients with tumors in the retroperitoneal or mediastinal region. | (140) |
| LINC00673     | 393 NB and 812 healthy controls | rs11655237 | C>T | NB risk: 1.51 (1.06-2.14), stage IV disease: 1.60 (1.12-2.30) | 0.021 and 0.011 respectively | Carriers of rs11655237 T allele are prone to NB. Associations were found in patients with adrenal gland tumors and stage IV disease. | (143) |
| uc003opf.1    | 275 patients and 531 controls | rs11752942 | A>G | 0.74 (0.55-0.99) | 0.045 | Patients with UC003OPF.1 A allele are negatively related to NB risk and are more prominent in females, subjects with tumors in the mediastinum or early-stage. Besides, rs11752942 G is associated with decreased levels of LRFN2 transcripts. | (144) |
| CASC15 and NBAT1 | 36 NB patients and 36 NB cell lines | rs6939340 | A>G | – | – | This polymorphism results in lowered expression of CASC15 and NBAT1. Lowered NBAT-1 expression in high-risk tumors relates to rs6939340. | (127) (85) |
| NBAT1         | 51 high-risk primary tumors and NB cell lines | rs6939340 | A>G | – | P < 0.05 | | |
| Lnc-LAMC2-1:1 | 393 NB and 812 healthy cases | rs2147578 | C>G | 1.33 (1.01-1.75) | 0.045 | rs2147578 rises NB susceptibility. Children under 18 months and females have increased NB risk. Lnc-LAMC2-1:1 diminishes NB risk. The stratified analysis demonstrates that rs4938723 TC/CC carriers are less prone to NB. Such association was found in both age subgroups, both sexes as well as all tumor sites and stages. | (145) (141) |
neuroblastoma is lack of longitudinal assessment of expression of these transcripts to unravel temporal changes during the course of disease. Conduction of this type of studies would facilitate approval of the diagnostic and prognostic power of ncRNAs.

AUTHOR CONTRIBUTIONS
MT and SG-F wrote the draft and revised it. OR, KHT, and MH performed the data collection, designed the tables and figures. All authors contributed to the article and approved the submitted version.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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