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Case report

Central neurocytoma: SNP array analyses, subtel FISH, and review of the literature

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ABSTRACT

The central neurocytoma (CN) is a rare brain tumor with a frequency of 0.1-0.5% of all brain tumors. According to the World Health Organization classification, it is a benign grade II tumor with good prognosis. However, some CN occur as histologically "atypical" variant, combined with increasing proliferation and poor clinical outcome. Detailed genetic knowledge could be helpful to characterize a potential atypical behavior in CN. Only few publications on genetics of CN exist in the literature. Therefore, we performed cytogenetic analysis of an intraventricular neurocytoma WHO grade II in a 39-year-old male patient by use of genome-wide high-density single nucleotide polymorphism array (SNP array) and subtelomere FISH. Applying these techniques, we could detect known chromosomal aberrations and identified six not previously described chromosomal aberrations, gains of 1p36.33-p36.31, 2q37.1-q37.3, 6q27, 12p13.33-p13.31, 20q13.31-q13.33, and loss of 19p13.3-p12. Our case report contributes to the genetic knowledge about CN and to increased understanding of "typical" and "atypical" variants.

1. Introduction

Central neurocytoma (CN) is a rare tumor of the central nervous system with an incidence of 0.1-0.5% of all brain tumors [1]. It is classified as a usually benign grade II tumor according to the World Health Organization classification of 2016 [2] and associated with favorable outcome [3]. In some cases, central neurocytomas show histopathological "atypical" and increasing proliferation, resulting in poor clinical outcome [4]. Mostly patients in their third decade are affected without any differences in gender [1,3]. CN is located predominantly in third or lateral ventricles, often in relation to the foramen of Monroe [5,6]. Due to the intraventricular location obstructive hydrocephalus is one of the first symptoms [7] followed by seizures, headache, nausea, memory, and visual disturbances [1,3,8].

Since oligodendroglioma, neuroblastoma, and neuroyctoma share histological similarities, allelic loss of 1p and 19q, such as amplification of *MYCN* (2p24) has been investigated and controversially discussed [9,10], Mrak et al. reported one case of an atypical neurocytoma with oligodendroglial-like histopathology and loss of heterozygosity (LOH) of 1p/19q [12], whereas Fujisawa et al. did not detect any allelic losses of 1p/19q in CN by FISH analysis [13]. Also, Tong et al. did not show significant occurrence of oligodendroglioma-like and/or neuroblastoma-like genetic changes in CN due to lack of LOH in 1p or 19q and MYCN amplification [10]. Only a limited number of genetic studies

Abbreviations: CGH, comparative genomic hybridization; CN, central neurocytoma; cn-LOH, copy neutral loss of heterozygosity; CNV, copy number variation; EGFR, epidermal growth factor receptor; EMA, epithelial membrane antigen; FISH, fluorescence in situ hybridization; GFAP, glial fibrillary acidic protein; H&E, hematoxylin and eosin staining; HPF, high power field; IC, interphase cells; IDH, isocitrate dehydrogenase; MAP-2, microtubule associated protein 2; MRI, magnetic resonance imaging; MUC1, mucin 1, cell surface associated; PTEN, phosphatase and tensin homolog; RBFOX3, specific neuronal marker: RNA binding fox-1 homolog 3; SNP-A, single nucleotide polymorphism array; UPD, uniparental disomy

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Table 1
Overview of identified chromosomal aberrations in central neurocytoma.

Chromosomal aberration	Frequency	Reference Number	Year
Loss of chromosome 17	1	[15]	1993
Gain of chromosome 7	3	[12]	1997
Rearrangements of three copies of 1q with chromosomes 4 and 7	1	[13]	1999
Gains of 2p23-pter, Gain of 10q25-qter, Gain of 13q31-q33, Gain of 18q	4 4 2 3	[14]	2000
Gain of 1q44, Gains of 2p24.1, Gain of 2p22.3-p22.1, Gain of 10q23.3, Gain of 11p11.2, Gain of 11q23, Gain of 11q25, Gain of 14q32.33 Gain of 15q11-q13 Gain of 15q26	10 14 10 12 13 8 9 12 10 9	[4]	2007
Loss of 1p36.3, Loss of 1p34.3, Loss of 2q14, Loss of 5p15.2, Loss of 5q21-q22 Loss of 6p12.1-p21.1 Loss of 6q16.3-q21, Loss of 7q21.3-q22, Loss of 10p11-q11, Loss of 11p15.5, Loss of 12q23, Loss of 13q14, Loss of 13q34, Loss of 15q12, Loss of 16q23.2, Loss of 17p13.3, Loss of 17q11.2-q12, Loss of 17q21, Loss of 17q23, Loss of 19p13.2, Loss of 20pter, Loss of 20p12.1-p11.2	10 9 12 8 9 9 14 8 22 9 8 8 9 12 9 15 11 10 10 12 11 8		
Gains of 1p36.33-p36.31, 2q37.1-q37.3, 6q27, 12p13.33-p13.31, 20q13.31-q13.33	1	Present study	2019
Loss of 19p13.3-p12	1		

on CN have been performed up to date. Conventional cytogenetic analyses have revealed either normal karyotype, gain of chromosome 7, or loss of chromosome 17 [12]. Jay et al. described distal rearrangements of three copies of 1q with chromosomes 4 and 7 [13]. Comparative Genomic Hybridization (CGH) analyses of 10 cases of central neurocytoma detected frequent gains at chromosomes 2p, 10q, and 18q [14]. Another array based CGH analysis of 20 typical CN determined frequent gains at 2p24.1–22.1, 10q23.3–26.3, 11q23-25, and 18q21.3-qter. Moreover, frequent losses were mapped to 1pter-36.3, 1p34.3, 6q13-21, 12q23-qter, 17p13.3, 17q11-23, and 20pter-12.3 [4]. In addition, previous studies and our analyses showed different chromosomal aberrations (Table 1).

Systematic comprehensive genetic data on CN are very limited but necessary to provide more detailed knowledge on genetic background and molecular mechanisms of tumorigenesis.

Here, we present a case of CN with clinical and histopathological findings along with data from combined genetic analyses using high resolution genome wide single nucleotide polymorphism array (SNP-A, Affymetrix CytoScan® HD), and subtelomere FISH (ToTelVysion Multicolour DNA probes, Abbott).

2. Material and methods

2.1. Case report

A 39-year-old male patient presented with gait disturbance and visual deficiencies. MRI scan of the neurocranium revealed an occlusive hydrocephalus caused by an intraventricular tumor mass in both lateral frontal horns and the third ventricle. We performed two-step subtotal tumor resection via transventricular right and left frontal craniotomy. A ventriculoperitoneal shunt was implanted as supportive therapy to relieve symptoms of occlusive hydrocephalus. Due to a small intraventricular tumor, residual stereotactic radiation was performed subsequently. Recent MRI controls, twelve months after surgery and nine months after radiation did not show progression of the small remaining tumor in the third ventricle (Fig.1A-C). In an examination 18 months after surgery, the patient presented in good general condition without additional neurological symptoms. The initial gait disturbance and visual deficits were no longer present. He started social and occupational reintegration.

Ethics approval was obtained from the ethics committee of the University of Leipzig (Az.: 086-2008). The study was conducted in accordance to the guidelines of the Declaration of Helsinki (as revised in Tokyo 2004). The patient gave informed consent and appropriate anonymity considerations were taken into account.

2.2. Isolation and culturing of primary tumor cells

For tumor cell isolation, fresh non-necrotic surgical specimens were washed in phosphate-buffered saline (PBS) and mechanically disaggregated into small pieces which were evenly distributed in a 25 cm^2 cell culture flask (Sarstedt #83.1810) coated with AmnioMax medium (Invitrogen #17001082) and incubated at 37 °C and 5% CO_2. Tumor attachment was monitored twice a week. After tumor cell outgrowth tumor pieces were removed and cells were covered with AmnioMax. Cells were subcultivated at a confluency of about 90%.

2.3. Cell preparation

Cell preparation was performed on primary tumor cell cultures using standard cytogenetic techniques (colcemid treatment, hypotonic treatment, and methanol/acetic acid fixation; according to Seabright [16,17]).

2.4. DNA isolation and molecular karyotyping using SNP array

Blood, tumor tissue, and primary tumor cells were collected and subjected to genome-wide copy number variation (CNV) analysis and assessment of copy number neutral loss of heterozygosity (cn-LOH) using SNP array (Affymetrix CytoScan® HD, ATLAS Biolabs, Berlin, Germany). Genomic DNA was extracted from blood, tumor tissue, and tumor cells according to the protocols “DNA purification from Blood or Body Fluids” and “Isolation of Total DNA from Tissues” from the QIAamp® DNA Investigator Kit (QIAGEN, Hilden, North Rhine-Westphalia, Germany). DNA quality was checked by agarose gel electrophoresis. For SNP array analyses we used the Affymetrix Chromosome Analysis Suite (ChAS 3.3.0.139) with reference data file Affymetrix CytoScanHD_Array.na32.3.v. and the copy number and LOH workflows with standard settings. We considered chromosomal aberrations ≥ 3000 kb as gain or loss and cn-LOH regions ≥ 5000 kb as representing (segmental) uniparental disomy (UPD). Pathway enrichment was analysed for all genes in affected chromosomal regions using the tool ENRICHR [18,19] with the following gene-set libraries: ARCHS4 Kinases Coexp; Reactome 2016, BioPlex 2017, WikiPathways, huMAP, NCI-Nature 2016, KEA 2015, Kinase Perturbations from GEO down, and BioCarta 2016.

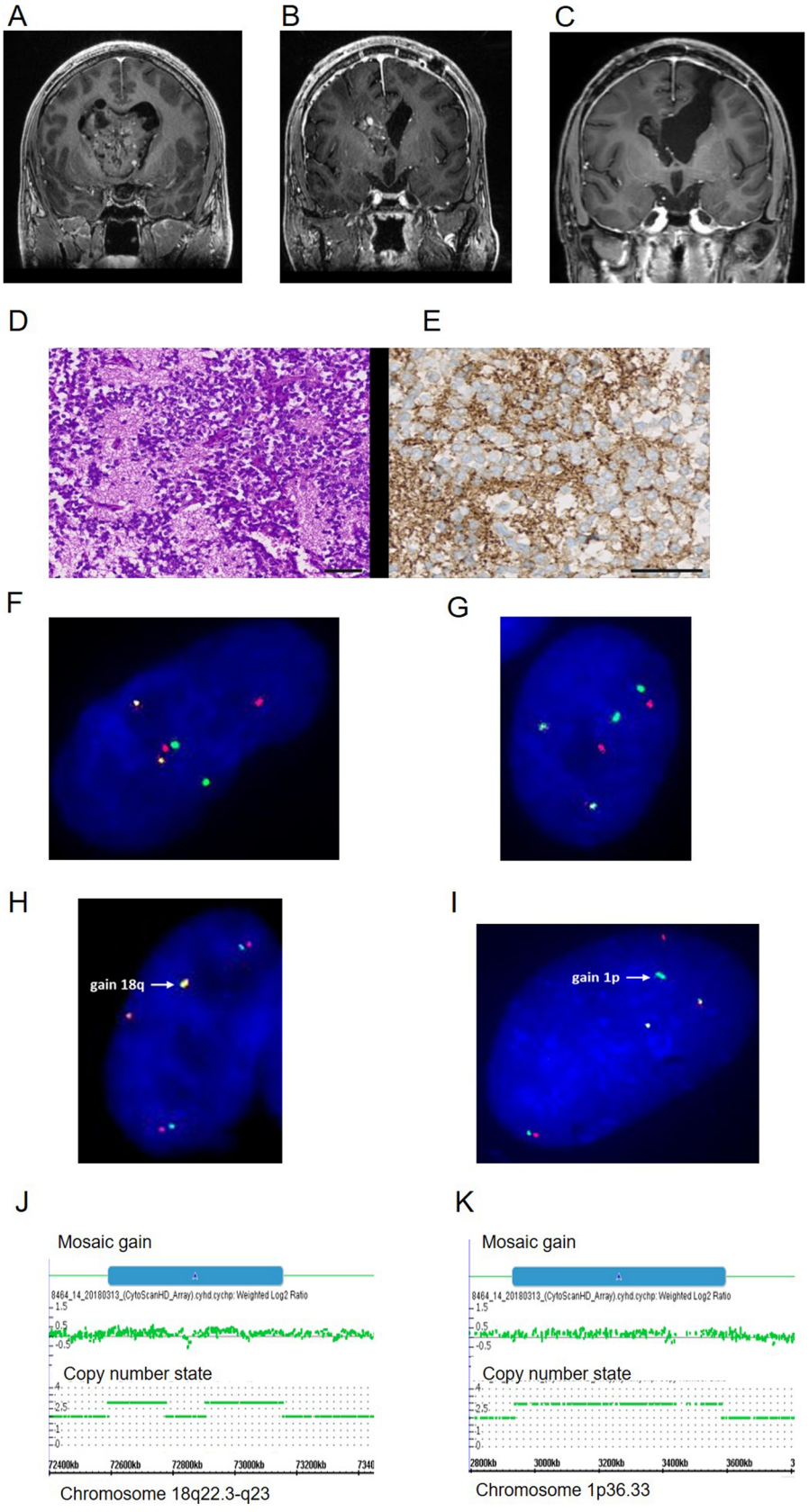

Fig. 1. Characteristics of the CN case. A-C: MRI coronal view, T1-weighted sequence after gadolinium intake. A: Intraventricular tumor mass at first diagnosis. B: Three months post surgery. C: Nine months post radiation and twelve months post surgery with stable tumor residuals. D: On H%E, the tumor displays as moderately cell-dense mass with monomorphic, central round nuclei ocassionally located in a "water-clear" cytoplasm. Multiple neuropil islands, free of cell nuclei, are visible. Mitotic figures were not detected. E: Cytoplasm and cell processes were positive for Synaptophysin. Scale bars indicate 50 µm. F-I: Subtelomere FISH of interphase cells (blue, DAPI). F: No chromosomal aberration of 18q22.3-q23 vs. H: Mosaic gain of 18q22.3-q23 (green: chromosomal regions 12p, red: 12q, yellow: 18q; arrow: gain of 18q, larger fluorescent signal in comparison to non-aberrant chromosomal region 18q). G: No chromosomal aberration of 1p36.33 vs. I: Mosaic gain of the chromosomal region 1p36.33 (green: chromosomal region 1p, gain of 1p: larger fluorescent signal in comparison to non-aberrant 1p, red: 1q, yellow: Xp). J&K: Mosaic gains (blue bars) detected by SNP-array. *J*: 18q22.3-q23. K: 1p36.33.

2.5. Subtelomere FISH

Subtelomere FISH analysis was conducted to confirm chromosomal aberrations detected by SNP array. Subtelomere FISH was performed according to manufacturer's instructions using ToTelVysion Multicolour DNA probes (#08L52-001, Abbott, Wiesbaden, Hesse, Germany) on primary tumor cells after the first surgery. The following DNA probe mixtures were used: mixture 1, probe 2, mixture 5, mixture 6, mixture

8, mixture 10, mixture 11, mixture 12, mixture 14, and mixture 15 (detailed information are given in supplemental Table 1). For each of these chromosomal regions, 100 interphase cells (IC) were analysed.

3. Results

In histopathological examination (H&E), the sample displayed monomorphic, moderately cell-dense tissue, with central round nuclei and finely granulated chromatin, reminiscent of neuronal cells. Within the tumor multiple nucleus-free, fibrillary areas, so called 'neuropil islands' were visible (Fig. 1D). Mitotic activity was low (< 2 mitotic figures per 10 HPF). Multifocal calcifications were present, while no necrotic areas were detectable. In immunohistochemistry the tumor matrix and neuropil islands were positive for Synaptophysin (Fig. 1E) and other neuronal markers (NeuN; MAP-2). No signals were found for Chromogranin A, EMA, and a mutation-specific IDH-1 antibody (IDH1-R132 H). GFAP labelled reactive astrocytes within the tumour. According to the WHO Classification of tumors of the CNS, central neurocytoma WHO-Grade II was diagnosed.

Using genome wide human SNP array CytoScan® HD, we identified 12 chromosomal aberrations (gains and/or losses in tumor tissue and in primary neurocytoma cells, ≥ 3000 kb).

Of these, six confirmed previously described chromosomal imbalances: (mosaic) gains of 10q26.13-q26.3, 11q24.3-q25, 13q33.3-q34, 18q22.3-q23, and (mosaic) losses of 17p13.3-p13.2, and 19q13.11-q13.43 (Table 2).

Six other chromosomal aberrations have previously not been described in the literature: mosaic gains of 1p36.33-p36.31, 2q37.1-q37.3, 6q27, 12p13.33-p13.31, 20q13.31-q13.33, and mosaic loss of 19p13.3-p12 (Table 2, Fig. 1I,K).

Using subtelomere FISH (probe mixtures 1, 2, 6, 8, 10, 11, 12, 14; Supplementary Table 1) on primary neurocytoma cells, we could confirm the chromosomal imbalances detected by SNP array analyses (Fig. 1F-K).

The database "*Atlas of Genetics and Cytogenetics in Oncology and Haematology*" lists a number of genes and loci known to be involved in various tumor entities [20]. In comparison of this database with the present SNP array results, we identified 102 concordant cancer genes within genomic regions affected by gains or losses (data not shown). Of these affected cancer genes, 70 are described for solid tumors and 42 have been published in connection with brain tumors (Table 2).

We identified several possibly affected pathways by enrichment analysis, e.g. MARK4 human kinase pathway and Notch signaling pathway, which have been involved in several cancers. (Table 3).

Eight brain tumor genes were identified within the physical boundaries of the six chromosomal aberrations not previously described for CN: *MIR200A, GPC1, THBS2, FOXM1, PTBP1, VAV1, NTSR1,* and *PTK6.* These will be discussed further. According to the literature, these 8 brain tumor genes may have possible influences predominantly in focal adhesion and signal transduction pathways such as EGF/EGFR and Ras signaling pathways.

4. Discussion

Although genetic data on chromosomal aberrations are increasingly becoming available, our knowledge on characteristic genomic aberrations for better understanding of tumorigeneses or for potential therapeutic approaches is still limited due to the rareness of this tumor entity.

In addition to already known chromosomal aberrations, we identified six not previously described mosaic chromosomal aberrations in CN: gains at 1p36.33-p36.31, 2q37.1-q37.3, 6q27, 12p13.33-p13.31, 20q13.31-q13.33, and losses at 19p13.3-p12.

Gains at 1p are known in other intracranial tumors. Similar gains e.g. at 1p22.2–22.3 are described in neuroblastoma, esthesioneuroblastoma, glioblastoma, and oligodendroglioma [33,34]. However, typical chromosomal aberrations at 1p are losses. Several deletions of short arm of chromosome 1 are documented in brain tumors: like Deletions 1p13.3-1p36.33, 1p36.33-1p36.32 and 1p32.1 in neuroblastoma [35–37], frequent losses at 1p34-36 in glioblastoma [38] and 1p36 deletions in oligodendrogliomas [39].

In this study, we revealed genetic aberration not previously described in CN, mosaic gain of 12p13.33-p13.31, which is described in neuroblastoma [40,41] and glioblastoma. [33]. Amplified chromosomal regions at 12q22-qter and 12p13 are shown in low grade gliomas [42]. In glioblastoma different imbalances of chromosome 12p occur frequently, e.g. loss of 12q13-q15 [38], 12q13.3-12q14.1 and 12q15 [43].

. Loss of 1p/19q is reported to be a common early event in the tumorigenesis for oligodendroglioma [39]. Mrak et al. identified loss of 1p/19q in a single case of atypical extraventricular neurocytoma [9]. Studies of Rodriguez et al. revealed low frequent co-deletion of 1p/19q in high mitotic extraventricular neurocytoma, suggesting an aggressive behavior of this tumor subtype [44]. In contrast to this report, the majority of studies revealed absence of 1p/19q co-deletion in CN [9–11] concordant to our results, assuming distinct tumorigenesis of CN compared to oligodendroglioma. Although no co-deletion 1p/19q was detected, the single mosaic loss at 19q13.11-q13.43 may influence the further pathogenesis of this tumor entity. More investigation on an extended cohort will be necessary to give a more comprehensive statement concerning the influence of losses at 19q on clinical outcome.

Another genetic aberration not described in CN is gain of 20q13.31-

Table 2
Overview of identified chromosomal aberrations and brain tumor genes by SNP-array analyses.

Chromosomal Region	Aberration	Physical Position Start (bp)	End (bp)	Length (kb)	Described Brain Cancer Genes*	Confirmation FISH	Literature
1p36.33-p36.31	Mosaic Gain	849,466	5,714,961	4,865	*MIR200A*	Yes	No
2q37.1-q37.3	Mosaic Gain	237,245,786	242,783,384	5,538	*GPC1*	Yes	No
6q27	Mosaic Gain	167,434,048	170,919,482	3,485	*THBS2*	Yes	No
10q26.13-q26.3	Mosaic Gain	126,447,367	135,427,143	8,98	*ADAM12, DOCK1, MKI67*	Yes	Yes [14]
11q24.3-q25	Mosaic Gain	128,613,887	134,938,470	6,325	*FLI1, OPCML*	Yes	Yes [4]
12p13.33-p13.31	Mosaic Gain	2,101,963	5,743,209	3,641	*FOXM1*	Yes	No
13q33.3-q34	Mosaic Gain	110,082,073	115,107,733	5,026	*ING1, IRS2*	Yes	Yes [14]
17p13.3-p13.2	Mosaic Loss	1,365,960	5,085,061	3,719	*HIC1, MYBBP1A, TRPV1, MIR21*	Yes	Yes [4]
18q22.3-q23	Mosaic Gain	71, 074,189	78,014,123	6,94	–	Yes	Yes [14]
19p13.3-p12	Mosaic Loss	260,911	24,221,956	23,961	*PTBP1, VAV1*	Yes	No
19q13.11-q13.43	Mosaic Loss	33,659,247	58,673,597	25,014	*ACTN4, AKT1S1, AKT2, ATF5, AXL, BCL2L12, CIC, DYRK1B, EMP3, FPR1, FXYD3, KLK7, KLK9, MARK4, MIR125A, MIR150, MIR373, PEG3, PLAUR, SLC1A5, TGFB1, ZNF146*	Yes	Yes [18]
20q13.31-q13.33	Mosaic Gain	55,819,139	62,915,555	7,096	*NTSR1, PTK6, TNFRSF6B*	Yes	No

* Described brain cancer genes are located within the physical boundaries of detected chromosomal aberrations.

Table 3
Pathway enrichment analyses (comparison of all genes within the detected aberrant chromosomal regions vs all genes of the annotated in the respective database).

Pathway database	Pathway	Chromo-some region	Physical position (bp)	Enrichment p-value**	Enrichment q-value***	Involvement in brain cancer*
ARCHS4 Kinases Coexp	MARK4 human kinase	19q13.32	45,079,288 – 45,305,283	8.24e-21	4.103e-18	Glioblastoma; anaplastic astrocytoma [21]
ARCHS4 Kinases Coexp	GSK3A human kinase	19q13.2	42,230,186 – 42,242,625	9.113e-18	1.135e-15	Glioblastoma [22]
Reactome 2016	Gene expression			1.865e-9	1.2e-6	Glioblastoma [23]
WikiPathways	Oxidation by Cytochrome P450			1.349e-4	5.206e-2	Cancer initiation and progression [24]
BioPlex 2017	TRIM37	17q22	58,982,638 – 59,106,921	6.312e-3	1.000e0	Glioblastoma [25]
NCI-Nature 2016	Beta2 integrin cell surface interactions			7.851e-2	9.998e-1	Tumor progression and metastasis [26]
huMAP	ACTL6A	3q26.33	179,562,880 – 179,588,408	4.147e-2	9.997e-1	Glioblastoma [27]
WikiPathways	Notch Signaling Pathway			1.044e-1	9.999e-1	Oligodendroglioma [28] Glioblastoma [29]
BioCarta 2016	Hypoxia and p53 in the Cardio-vascular system	17p13.1	7,661,779 – 7,687,550	1.044e-1	9.999e-1	Glioblastoma [30]

Legend: Chr.: Chromosomal; * examples for involvement in brain cancer; ** p-value calculated according to the Monte Carlo simulation [31]; *** q-value calculated according to the Benjamini-Hochberg-procedures [32].

q13.33. Inda et al. were able to identify gains of 20q13 in a study of 32 glioblastoma patients. Within this chromosomal region, *MYBL2* is located [33]. This proto-oncogene plays a central role in regulation of cell proliferation, cell apoptosis, and differentiation during tumorigenesis. Overexpression of *MYBL2* is associated with poor prognosis for some tumor entities [45]. Therefore, detailed genetic knowledge could be helpful to check a potential atypical behavior in CN.

MYCN, PTEN, IGF2, PDGF, and *NRG* are known cancer genes in CN. Overexpression of *MYCN* is described in CN, such as medulloblastoma and neuroblastoma. It plays a role in neuronal proliferation and inhibition of neuronal differentiation [46,47]. The tumor suppressor gene *PTEN* also shows overexpression in CN. *PTEN* is responsible for inhibition of cell migration, spreading, and focal adhesions [48]. The P12K9/AKT-signaling-Pathway could be influenced by *PTEN* [49]. Lee et al. suggest that *PTEN* and *MYCN* are responsible for incomplete neuronal differentiation in CN [50].

5. Conclusion

In summary, our data confirm frequent chromosomal aberrations in CN, such as gains of 10q and 18q. Not previously described chromosomal aberration was detectable with gains of 1p, 2q, 6q, 12p, 20q and losses at 19p. Gain of 20q linked with overexpression of *MYBL2* is associated with poor prognosis for some tumor entities. Although no codeletion 1p/19q was detected in our study, single mosaic loss at 19q13.11-q13.43 may suggest poorer outcome, since single loss of 19q is associated with a severe prognosis in glioblastoma multiforme. However, 18 months after initial surgery, this patient recovered completely from symptoms regarding occlusive hydrocephalus. Currently, he is without sequela and started social and occupational reintegration.

Detailed genetic knowledge on a larger number of CN cases could be helpful to identify potential atypical behavior or suggest a distinct molecular pathogenesis of CN compared to neuroblastoma and/or oligodendroglioma. Genetic analyses of an extended cohort of CN is necessary to elucidate new candidate genes and chromosomal regions to define pathogenetic and prognostic factors for this rare tumor entity.

Declaration of conflicts of interest

Declarations of conflicts of interest: none.

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All relevant data are within the paper. Additional data are available upon request from the corresponding author.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.prp.2019.03.025.

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