

DNA copy number alterations in central primitive neuroectodermal tumors and tumors of the pineal region: an international individual patient data meta-analysis

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Abstract Little is known about frequency, association with clinical characteristics, and prognostic impact of DNA copy number alterations (CNA) on survival in central primitive neuroectodermal tumors (CNS-PNET) and tumors of the pineal region. Searches of MEDLINE, PubMed, and EMBASE—after the original description of comparative genomic hybridization in 1992 and July 2010—identified 15 case series of patients with CNS-PNET and tumors of the pineal region whose tumors were investigated for genome-wide CNA. One additional case study was identified from contact with experts. Individual patient data were extracted from publications or obtained from investigators, and CNAs were converted to a digitized

format suitable for data mining and subgroup identification. Summary profiles for genomic imbalances were generated from case-specific data. Overall survival (OS) was estimated using the Kaplan–Meier method, and by univariable and multivariable Cox regression models. In their overall CNA profiles, low grade tumors of the pineal region clearly diverged from CNS-PNET and pineoblastoma. At a median follow-up of 89 months, 7-year OS rates of CNS-PNET, pineoblastoma, and low grade tumors of the pineal region were 22.9 ± 6 , 0 ± 0 , and 87.5 ± 12 %, respectively. Multivariable analysis revealed that histology (CNS-PNET), age (≤ 2.5 years), and possibly recurrent CNAs were associated with unfavorable OS. DNA copy number profiling suggests a close relationship between CNS-PNET and pineoblastoma. Low grade tumors of the pineal region differed from CNS-PNET and pineoblastoma. Due to their

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high biological and clinical variability, a coordinated prospective validation in future studies is necessary to establish robust risk factors.

Keywords Chromosomal imbalances · Prognostic markers · Comparative genomic hybridization · Brain tumor

Introduction

Central nervous system primitive neuroectodermal tumors (CNS-PNET) are a heterogeneous group of WHO grade IV lesions (Supplementary Table 1). They comprise 3–7 % of brain tumors in children and young adults [1, 2] and are associated with a dismal prognosis [3, 4]. Histologically, these highly proliferative lesions are currently divided into CNS-PNET or supratentorial PNET, respectively (synonym PNET not otherwise specified, PNET NOS), CNS neuroblastoma, CNS ganglioneuroblastoma, medulloepithelioma, and ependymoblastoma [5]. CNS-PNET and medulloblastoma share a similar histology and are often solely distinguishable by their supratentorial versus infratentorial location. Further, pineoblastoma, a WHO grade IV tumor of the pineal gland [5], is filed in some studies as CNS-PNET although pineoblastoma forms a group of neoplasms of the pineal region together with pineocytoma, pineal parenchymal tumor of intermediate differentiation, and papillary tumor of the pineal region [5]. The classification of malignancies within the group of embryonal tumors has changed considerably in the last four editions of the WHO classification of tumors of the CNS (Supplementary Table 1). Tumor classification systems are increasingly complemented by molecular genetic profiling data, especially in hematologic neoplasias [6]. However, for the various subtypes of CNS-PNET, such data are still scarce and large series are missing. Profiling of regional copy number abnormalities (CNA) by genomic hybridization techniques is a robust methodology for whole genome data analysis. Principal techniques include the different variants of chromosomal and array-based comparative genomic hybridization (cCGH/aCGH; [7–10]) and single-color oligonucleotide array technologies [e.g., genomic single nucleotide polymorphism (SNP) arrays].

In contrast to data from gene expression measurements, CGH data is easily adaptable across multiple datasets to perform a meta-analysis. Methods to assess genomic CNAs are standardized and reproducible as demonstrated in previous reports (e.g., [11, 12]). Some earlier reviews have reported on specific types of aberrations or were focused on the descriptive analysis of certain classes of malignancies [13, 14].

Due to the low incidence of CNS-PNET and pineoblastoma, only a few CGH studies have been reported in

Fig. 1 Delineation of 3 distinct clinicogenetic subgroups. **a** Regional copy number imbalances for individual cases were plotted separately by overall diagnostic assignment [yellow gain, blue loss, blue tumors of the pineal region except pineoblastoma, light blue pineoblastoma, pink central primitive neuroectodermal tumors (CNS-PNET)]. Individual profiles were arranged by hierarchical clustering inside their groups. **b** Histograms of genomic gain and loss frequencies (color legend corresponding to (a))

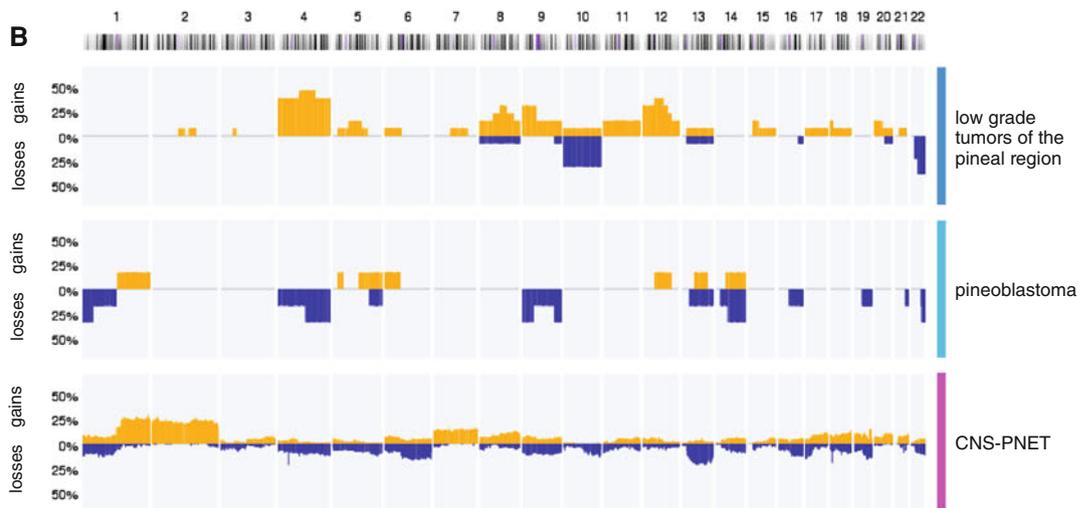
these tumors [2, 15–17]. So far, results have suggested that CNS-PNET are genetically heterogeneous with frequent and diverse CNAs and that CNA patterns are distinct from those observed in medulloblastoma [2, 15–17].

For the present study, we performed an individual patient data (IPD) meta-analysis—a specific method of systematic review [18] offering advantages for meta-analysis [19, 20]—of genomic imbalances in CNS-PNET and tumors of the pineal region. The collected data are made available through the “Progenetix” molecular-cytogenetic database (www.progenetix.org: [14, 21, 22]).

Methods

Search strategy, and selection criteria

We did a modification of the Cochrane Highly Sensitive Search Strategy for prognostic studies [20] combined with predefined search terms in MEDLINE, Pubmed, and EMBASE without language restriction [23, 24]. The process of the study retrieval, in- and exclusion of studies/patients is displayed in the flow chart (Supplementary Fig. 1) according to the PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement. The search was limited to articles published after the original description of CGH [7] until July 2010. Key words were: “medullo(-)blastoma(s)”, “primitive neuroectodermal tumor(u)r(s)”, “neuroectodermal tumor(u)r(s) primitive” “pnet (s)”, “medullo(-)epithelioma(s)”, “ependymoblastoma(s)”, “ganglioneuroblastoma(s)”, “pinealoma”, “pineocytoma(s)”, “pineoblastoma(s)”, “pineal tumor(u)r(s)”, “pineal parenchymal tumor(u)r(s)”, “mixed transitional pineal tumor(u)r(s)”, “mixed transitional pineal tumor(u)r(s)”, “atypical teratoid rhabdoid tumor(u)r(s)”, “rhabdoid tumor(u)r(s)”, “AT(/)RT” and “rhabdoid”, “supratentorial neoplasm(s)” or “neuroblastoma(s)” and “central nervous system neoplasm(s)”; and “cgh” or “comparative genomic hybridization” or “snp” or “SNP” or “genomic array(s)” or “copy number” or “dna microarray(s)” or “amplification”. Additionally to the search queries, we followed references from the selected articles and assessed each abstract. Minimal requirements for inclusion of a patient to the study were the availability of case-specific genomic copy number data with whole genome coverage, the unambiguous diagnostic classification of CNS-PNET/tumor of the pineal region, and matching available or inferred locus information.



Clinical and CNA data collection, data extraction, quality assessment, conversion of CNA data, and data synthesis

For CGH results specified in cytogenetic annotation formats, data were standardized to ISCN 1995 (International System for Human Cytogenetic Nomenclature, 1995) “re-visit” format based on an 862-bands karyotype and checked for semantically correct annotation using dedicated software. For genomic array data without annotated gain/loss information, clone specific data files were segmented using Progenetix website tools. Normalized data were converted to Golden Path mapped copy number status information by software implemented in the Perl scripting language [14].

In a first step, clinical and genomic data were extracted from publications by two reviewers (A.O.V.B. and M.B.). Subsequently, the original data, in particular in case of incomplete data (genomic and clinical data), for each participant were obtained and updated directly from the researcher responsible for each included study [25]. To prevent duplicate inclusions, authors were asked to indicate whether a patient had been analyzed within different studies. In addition, copy number profiles were clustered for similarity and reviewed for the occurrence of profile pairs, in order to avoid duplicate cases due to republished data. Data of three unpublished CNS-PNET patients were provided by two authors (S.P. and O.D.). Generally, two approaches to perform IPD meta-analyses are used. First, IPD meta-analyses can be performed directly, as if all data belong to a single trial/study, termed the “one-stage” approach [26]. Second, a “two-stage” approach can also be used. Each trial/study is analyzed separately using its raw data before the summary results from each trial/study are pooled and analyzed using conventional meta-analyses techniques [26]. Due to the small patient numbers of each individual case series, the “one-stage” approach was used here.

Exploratory data mining and statistical analysis

For the evaluation of regional copy number changes, non-overlapping genomic segments were generated based on the complete CNA data from all cases. For each of these intervals, case-specific involvement was evaluated and gain/loss frequencies determined. For visualization and ordering of case-specific CNA data, data matrices were produced containing imbalance status (gain, or loss) mapped to a variety of genomic intervals (from chromosomal arm level down to 1 Mb). Cases were ordered by hierarchical clustering of gain/loss matrices (unsupervised, complete linkage), and the derived case order was used for re-plotting of the original CNA annotations. CNA complexity, a relatively resolution-independent surrogate

marker of genomic instability, was determined for each case by evaluating the occurrence of gain and loss events per chromosome arm, with a maximum score of 2 per arm (i.e. occurrence of one or more of each gain and loss; modified from [27]).

To evaluate imbalance distribution in relation to diagnostic assignment, for each of the entities in our dataset, gain/loss frequencies were calculated mapped to genomic intervals on a 5-Mb level. Copy number profiles were compared by generating a heatmap of gain/loss distributions.

Cases with clinical follow-up were evaluated with respect to correlation of clinical factors and regional CNA status to OS. OS was defined as date of diagnosis to death of any cause or to the date of last visit. Cut-off values of age and CNA complexity were determined by recursive partitioning [28]. Univariable and multivariable survival analyses were performed. OS was estimated by the Kaplan–Meier method, and the log-rank test was used for comparisons of survival in different groups [29]. Univariable analyses to investigate the effect of age (continuous), and CNA complexity (continuous) on OS was done with univariable Cox regression analysis. Multivariable analyses were performed using Cox’s proportional hazards model. All statistical analyses are intended to be rather exploratory than confirmatory. *p* values are considered statistically significant when $p < 0.05$. No adjustment for multiple testing was carried out. Statistical analyses were performed using SAS (v.9.2 for Windows; SAS Institute, Cary, NC, USA), and PASW Statistics 18 for Windows (SPSS, Chicago, IL, USA).

Results

Supplementary Figure 1 illustrates the process of evaluating articles for inclusion in the IPD meta-analysis. We identified 1,220 papers by the search terms. The number of papers was reduced to 840 after removing of duplicates (by titles and abstracts). Title and abstract review resulted in the exclusion of 710 papers. Three case-specific data (one case series) were provided by two authors. We reviewed 131 papers in full, from which 15 studies, and 1 unpublished case series ($n = 3$), met inclusion criteria for this study (Supplementary Fig. 1).

Study characteristics and quality assessment

The 16 studies included here comprised 107 patients in total, after exclusion of 4 cases with ambiguous CNA profiles. From 61 patients, information about OS was available (clinical characteristics are shown in Table 1). Of those, 38 patients were profiled using aCGH and 23 patients using cCGH. The median follow-up time for

Table 1 Demographics and disease characteristics of 61 patients with central primitive neuroectodermal tumors (CNS-PNET) and tumors of the pineal region

Characteristics	Number of patients (complete follow-up; $n = 61$)
Sex	
Male	13 (21 %)
Female	17 (28 %)
N/A	31 (51 %)
Age	
Median age at diagnosis (range; years)	4.2 (0.6–66)
Histology	
CNS-PNET	46 (75 %)
Tumors of the pineal region	15 (25 %)
Tumor samples source	
Primary tumors	59 (97 %)
Relapses	2 (3 %)
Metastatic stage	
Metastases	8 (13 %)
No metastases	21 (35 %)
N/A	32 (52 %)

N/A information not available

survivors was 75 months, and the median follow-up time across all patients was 89 months. Fifteen children were aged ≤ 2.5 years and 46 patients were aged > 2.5 years. The cohort comprised all tumor entities classified as CNS-PNET in the current WHO classification when taking into account the update of earlier WHO classification in which some of these tumors were partly classified as different subgroups of embryonal tumors [5, 30] ($n = 46$), and tumors of the pineal region ($n = 15$) which included pineocytoma ($n = 4$), pineal parenchymal tumor of intermediate differentiation ($n = 3$), papillary tumor of the pineal region ($n = 5$), and pineoblastoma ($n = 3$). Mean CNA complexity was 9.4 (range, 0.00–30.00). For the purpose of statistical analysis, CNS-PNET were considered as one group and tumors of the pineal region were considered as another group.

Overall genomic imbalance patterns in central nervous system primitive neuroectodermal tumors and tumors of the pineal region

In order to evaluate the overall patterns of genomic imbalances in bona fide CNS-PNET and tumors of the pineal region, we visualized the case-specific CNAs of all tumors clustered for their overall imbalance similarities (Fig. 1a). In CNS-PNET ($n = 88$), frequent gains of chromosomes 1q4 [$n = 31$ (35 %)], 2p2 [$n = 27$ (31 %)],

and 7q3 [$n = 16$ (18 %)] as well as losses involving chromosome 13q2 [$n = 21$ (24 %)], and 6q [$n = 18$ (20 %)] could be observed among other less frequent changes (Fig. 1b). In contrast, low grade tumors of the pineal region were characterized by gains of chromosomes 4q2 [$n = 6$ (46 %)], and 12 [$n = 5$ (38 %)] as well as losses of chromosomes 10 [$n = 4$ (31 %)], and 22 [$n = 5$ (38 %)]. Interestingly, pineoblastoma ($n = 6$) displayed a pattern of genomic imbalances unrelated to the changes observed in the group of low grade tumors of the pineal region. Supplementary Figs. 2–4 illustrate gains and losses of the different disease entities.

We observed frequent gains involving chromosome 2 and losses involving chromosome 6 in ependymoblastoma as well as in medulloepithelioma (Supplementary Fig. 3b, c). Losses of chromosome 6 and 13 were typical for ependymoblastoma.

Embryonal tumor with abundant neuropil and true rosettes (ETANTR) was first described by Eberhart et al. [31], but is so far not listed as a distinct tumor entity in the 2007 WHO classification [5] and represents a CNS-PNET with “ependymoblastic” rosettes [32]. Recently, Korshunov et al. [33] demonstrated in a series of 21 ependymoblastoma and 20 ETANTR that 95 % of ETANTRs and 90 % of ependymoblastoma have the unique focal amplification at 19q13.42.

Therefore, the term embryonal tumor with multilayered rosette (ETMR) has been suggested for ependymoblastoma and ETANTR, a new entity with multilayered rosettes for which amplification at 19q13.42 represents a rather sensitive and specific marker [32].

In our cohort, we identified 9 tumors with such an amplification. As described previously by Li et al. [2], cases with such an amplification predominantly (8/9) also displayed gains of the whole or the major part of chromosome 2. For some additional cases with gain of chromosome 2 identified by cCGH, no high-resolution data were available. Therefore, we may not rule out an additional amplification at 19q13.42 in these cases.

Univariable and multivariable survival analysis of clinical factors and CNA complexity

To assess which parameters contribute to prognosis, we evaluated each clinical variable by univariable Kaplan–Meier analysis. Tested variables were: gender, age, histology (CNS-PNET vs. tumors of the pineal region), metastatic stage (no metastases vs. metastases), extent of postoperative residual disease (complete/gross total resection vs. residual disease ≥ 1.5 cm²), radiotherapy (no radiotherapy/local radiotherapy vs. cranio-spinal radiotherapy), chemotherapy (no chemotherapy vs. chemotherapy), CNA complexity (< 11 vs ≥ 11 as defined by recursive partitioning), tumor

sample source (primary tumor vs. relapse), and technique (aCGH vs. cCGH). Supplementary Table 2 illustrates the factors (histology, CNA complexity, and age) showing differences as assessed by univariable analysis. Patients with tumors of the pineal region had a more favorable OS when compared to patients with CNS-PNET (7-year OS: 64.7 ± 15 vs. 22.9 ± 6 %, $p = 0.007$). Of note, all three patients with a pineoblastoma and available follow-up were dead 33 months after diagnosis, whereas all other patients with low grade tumors of the pineal region had excellent outcome (7-year OS: 87.5 ± 12 %). Patients aged ≤ 2.5 years had unfavorable OS when compared to patients aged >2.5 years (7-year OS: 0 ± 0 vs. 41.3 ± 8 %, $p = 0.001$). OS rates were similar in CNS-PNET patients with and without the amplification at 19q13.42. Univariable cox regression analysis confirmed that increasing age (continuous variable) is denoting a more favorable OS [hazard ratio, 0.967 (per year); 95 % confidence interval, 0.939–0.996; $p = 0.0282$] and increasing CNA complexity (continuous variable) a less favorable OS [hazard ratio, 1.063 (per unit); 95 % confidence interval, 1.012–1.117; $p = 0.0153$]. Multivariable analysis of clinical factors and CNA complexity revealed that histology (tumors of the pineal region), age (older than 2.5 years) and CNA complexity <11 are favorable prognostic factors (Table 2).

Multivariable survival analysis of chromosomal aberrations, CNA complexity, and clinical factors

To identify which of the chromosomal aberrations might have an impact on OS, multivariable survival analyses were

applied to all 61 patients incorporating the significant clinical factors (histology and age), CNA complexity, as well as 75 different chromosomal gains and 75 different chromosomal losses in a stepwise approach, respectively. These analyses finally revealed that young age (≤ 2.5 years), histology (CNS-PNET), and recurrent gains of 3p1 ($n = 3$; 5 %), 13q1 ($n = 5$; 8.2 %), and 15q2 ($n = 8$; 13.1 %) are associated with an increased risk for unfavorable OS (Table 3).

Discussion

Over recent years, whole genome/transcriptome molecular analysis has led to the identification of divergent biological characteristics in what were considered single cancer types. In the field of pediatric neuro-oncology, medulloblastoma are now considered as a group of biologically differing entities consisting of at least 4 molecular subgroups, loosely connected through their topography (cerebellum) and partially overlapping histological appearance [34–42].

Molecular studies in rare tumor entities are severely limited due to the low number of cases included in single series, as well as conceptual and technical heterogeneity of the studies. To our knowledge, our study is the first IPD meta-analysis assessing the genomic and clinical features in CNS-PNET and tumors of the pineal region and their impact on OS. In this study, we show that CNS-PNET and pineoblastoma are divergent in their CNA profiles when compared with low grade tumors of the pineal region. For the cases analyzed here, recurring CNA observed only in low grade tumors of the pineal region were, e.g., gains on

Table 2 Multivariable analyses of clinical prognostic factors ($n = 61$) for overall survival (OS)

Parameter	Comparison	Sample size	HR OS	95 % Confidence interval	<i>P</i> value
Histology	Non CNS-PNET	15	0.312	0.109–0.891	0.0296
	CNS-PNET	46			
Age group (years)	>2.5	46	0.386	0.197–0.757	0.0056
	≤ 2.5	15			
CNA complexity	≥ 11 CNA	23	1.790	0.943–3.400	0.0752
	<11 CNA	38			

CNS-PNET Central primitive neuroectodermal tumor, *Non CNS-PNET* tumors of the pineal region, *CNA* copy number aberrations, *HR OS* Hazard ratio overall survival

Table 3 Multivariable analyses of clinical factors and recurrent chromosomal aberrations (forward stepwise selection; $n = 61$) for overall survival

Parameter	Sample size	Hazard ratio overall survival	95 % Confidence interval	<i>P</i> value
Age (≥ 2.5 years)	46	0.295	0.141–0.619	0.0012
Histology (tumor of the pineal region)	15	0.120	0.029–0.498	0.0035
seg3p1_gain	3	8.759	1.778–43.159	0.0077
seg13q1_gain	5	4.128	1.192–14.303	0.0253
seg15q2_gain	8	4.338	1.614–11.665	0.0036

4q2, 9p, 12p, and 8q2 as well as deletions of chromosome 10. In contrast, recurring CNA only found in pineoblastoma were deletions on 4q, chromosome 9, and 1p3. Based on our results, CGH analysis might be of help—in addition to neuroradiological and histopathological evaluation—to differentiate between CNS-PNET, pineoblastoma, and lower WHO grade tumors of the pineal region. While detection of the listed aberrations may be indicative for assignment to one of the diagnostic groups, development of a CNA-based classifier will ideally require larger numbers of genome profiles.

We found evidence that younger age at time of diagnosis is a negative prognostic factor for OS, confirming several previous studies reporting on poor outcome of young children with CNS-PNET/pineoblastoma [3, 43]. Timmermann et al. [3] reported on OS and progression-free survival rates after 3 years of 17.2 and 14.9 %, respectively. Administration of radiotherapy was the only significant prognostic marker (15 out of 29 patients were not irradiated) in this study [3] suggesting that omitting the radiotherapy in young children—with the goal to reduce neurologic sequelae—might at least explain partly the extremely poor outcome of young children with CNS-PNET/pineoblastoma.

In our cohorts, CNS-PNET and pineoblastoma shared an unfavorable prognosis. Small numbers of pineoblastoma (3 out of 61 patients) may limit the comparison of those two tumor entities. Based on the literature, there is some evidence that patients with pineoblastoma may do better than patients with CNS-PNET [44, 45]. Patients with low grade tumors of the pineal region had a favorable outcome (7-year OS: 87.5 ± 12 %) confirming that those tumor entities need a less aggressive treatment than CNS-PNET/pineoblastoma.

CNS-PNET and tumors of the pineal region share a complex karyotype with frequent CNAs [46]. In our series of 107 patients, low grade tumors of the pineal region showed relative frequently absence of CNAs (4/13), less frequently in pineoblastoma (1/6), and CNS-PNET (2/88).

Recently, a new entity of CNS-PNET termed ETMR has been suggested for a subgroup of CNS-PNET (ependymoblastoma and ETANTR) for which amplification at 19q13.42 represents a rather sensitive and specific marker [32]. Korshunov et al. [33] identified in the great majority of ependymoblastoma and ETANTR the focal amplification at 19q13.42 whereas such an amplification was not observed in a large series of other pediatric brain tumors [32]. As we report about cCGH and aCGH data, the frequency of tumors with amplification at 19q13.42 (Supplementary Fig. 6) should be interpreted with caution as detection of the amplification at 19q13.42 might be missed when tumors are profiled by conventional cCGH, which has a spatial resolution limited of several megabases.

Patients with 19q13.42 amplified tumors had a relatively poor OS (6/7 patients with available follow-up died of disease). Of note, the analysis of the prognostic impact of the amplification at 19q13.42 is limited in our cohort, because—as mentioned above—this amplification might be missed in tumors analyzed with cCGH.

Our results provide evidence that high CNA complexity is an unfavorable prognostic marker in our cohort. Because of high frequencies of genomic imbalances as well as heterogeneous patterns and frequencies of CNAs, CNA complexity appears to be a good measure for overall genomic instability which may reflect aggressiveness of a certain tumor. In light of this, specific recurrent genomic imbalances which have been identified as CNAs with potential impact on OS in our analyses [e.g., in the 61 patients: gain of seg3p1 ($n = 3$), seg13q1 ($n = 5$), seg15q2 ($n = 8$)], need to be validated—ideally in large future studies—for their prognostic value.

After the search cut-off date imposed by the IPD meta-analysis criteria, another study was published recently focusing on CNS-PNET/pineoblastoma only in pediatric patients [17]. By evaluating the genomic array data which are available from NCBI's Gene Expression Omnibus (<http://www.ncbi.nlm.nih.gov/geo/>; accession number GSE12370), we were able to generate CNA profiles for 38 patients (8 of whom had pineoblastoma, and 30 had a CNS-PNET; CGH data from 35 CNS-PNET cases were listed, 5 recurrent tumors were paired with a primary sample from the same patient) and 1 CNS-PNET cell line. Here, as in our IPD meta-analysis, pineoblastoma exhibited CNA profiles roughly comparable to subsets of cases identified as CNS-PNET as shown in the Supplementary Fig. 5 a, b.

The approach of an IPD meta-analysis—a specific method of systematic review based on a systematic search—is in our opinion both necessary and efficient to increase the patient number in rare tumor diseases. By using IPD, we may overcome many of the limitations of systematic reviews (e.g., poor quality of data can be improved by updating the information). We used common inclusion and exclusion criteria for each individual case. In addition, we have performed a quality assessment of genomic data by reassessment of each individual case by two researchers (M.B. and H.C.). Methods to assess genomic CNAs are standardized and reproducible as demonstrated in previous reports (e.g., [11, 12]). Moreover, by including unpublished data [25], we aimed to reduce the risk for publication bias [20]. Of course, the inclusion of a larger number of unpublished cases would have been desirable, and a “pooling” of such data has an exceptional value for rare diseases. Of note, IPD meta-analyses usually take longer than conventional systematic review, and obtaining IPD is time-consuming [20]. Therefore, it is not possible to include all very recent studies, and many IPD

meta-analyses are conducted on a cyclical basis with data collection, quality assessment, analyses, and dissemination of results taking place every few years [18], because by the time of the final analysis of the pooled data new cases are already available. We acknowledge some limitations of our study which is based on original data produced over a time period of several years. As shown in Supplementary Table 1, the WHO classification of tumors of the CNS has changed during this period. Moreover, in recent years, the staging has improved, as have surgical procedures and non-surgical treatment options of patients with CNS-PNET and tumors of the pineal region. Regarding genomic analysis methods, high-resolution profiling by genomic copy number arrays or whole genome sequencing could provide a higher sensitivity for the detection of hitherto undetected CNA. However, the main limitations in identifying robust CNA markers with prognostic value are in the limited number of samples and associated clinical datasets available for such analyses.

In summary, CNS-PNET and low grade tumors of the pineal region are characterized by differences in CNA profiles. In this respect, pineoblastoma fit readily into the genomically heterogeneous group of CNS-PNET with a complex karyotype. Although not necessarily displayed by each individual case, typical CNA profiles underline the differing biological background of these entities. Our results provide evidence that young age, high CNA complexity, and potentially also several specific CNAs may have an impact on OS.

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Conflict of interest None.

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