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Molecular genetics and diversity of choroid plexus tumors

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Choroid plexus tumors are rare intraventricular brain tumors predominantly arising in children but also affecting adults. Chromosome-wide copy-number alterations and *TP53* mutations do occur, but in most choroid plexus tumors, driver mutations have not been identified. Here we give a brief overview of the histopathological and clinical diversity of choroid plexus tumors and their genetic and epigenetic heterogeneity. Preliminary data indicate that choroid plexus carcinomas comprise at least 2 epigenetic subgroups, one of which is associated with *TP53* mutation status. These findings strongly encourage us to further investigate the genetic and epigenetic heterogeneity in a larger cohort and to align molecular subgroup status with clinical annotations, in order to identify prognostic markers that may also aid stratification within future international trials.

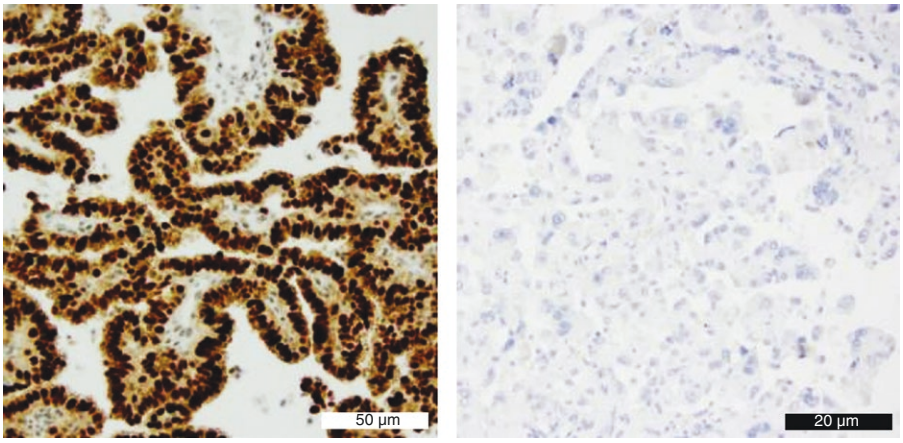
Keywords

choroid plexus tumor | choroid plexus carcinoma | DNA methylation profiling | neuropathology | prognosis | *TP53*

Choroid plexus tumors are intraventricular neoplasms derived from the choroid plexus epithelium and represent 0.2% of all central nervous system neoplasms, but 10%–20% of brain tumors occurring throughout the first year of life. Histopathologically, choroid plexus tumors comprise 3 entities: Choroid plexus papilloma (CPP, WHO grade 1), atypical CPP (aCPP, WHO grade 2), and choroid plexus carcinoma (CPC, WHO grade 3). Patients harboring CPP usually experience favorable long-term outcomes if gross total surgical resection can be achieved, whereas aCPP is associated with an increased risk of recurrence mainly in older children (≥3 years) and adults.[1] While CPP and aCPP are histologically highly differentiated neoplasms resembling non-neoplastic choroid plexus tissue, CPC is characterized by frank signs of malignancy including brisk mitotic activity, nuclear pleomorphism, high cellularity, blurring of the papillary growth pattern, and necrosis. Despite aggressive treatment protocols with surgical resection and a combination of chemotherapy and radiation, the prognosis of patients with CPC is heterogeneous with 5-year overall survival rates ranging from 36 % to 56 % and most of the survivors exhibit long-term cognitive and developmental deficits. On the other hand, some CPC patients have a remarkably favorable clinical course with long-term survival even in the absence of multimodal therapy. Here we review underlying genetic and epigenetic heterogeneity and some recent advances in the understanding of choroid plexus tumor biology.

Genetic Heterogeneity

Choroid plexus tumors are characterized by pronounced numerical aneuploidy with CPP/aCPP showing hyperdiploid karyotypes and the majority of CPC featuring widespread chromosomal losses. However, allele-specific copy-number analyses revealed a considerable heterogeneity of CPCs with a subset showing hyperdiploidy in combination with acquired uniparental disomy, but the biological relevance of these chromosomal alterations remains unclear.[2] The majority of CPC arises in children and may be associated with Li-Fraumeni syndrome, a cancer susceptibility syndrome caused by germline mutations of the *TP53* tumor suppressor gene. Li-Fraumeni patients generally have a poor prognosis not only due to CPC, but also because of an increased risk for secondary malignancies during or after treatment and treatment-induced toxicity. However, the impact of somatic *TP53* mutation status (either



TP53 p.R282W *TP53* p.T170fs

Figure 1. p53 immunohistochemistry. Immunohistochemical staining for p53 showing accumulation in all tumor cells in a case with p.R282W *TP53* (reference transcript NM_000546) missense mutation (left), but negative staining in a case with a *TP53* frameshift mutation (p.T170fs, NM_000546, right).

heterozygous or homozygous) in CPCs is less clear. Somatic *TP53* mutations occur in 36%–60% of CPCs and have been linked to genomic instability and poorer prognosis in some cohorts. *TP53* mutations may increase the half-life of the p53 protein product and immunohistochemical staining for p53 has been proposed as a surrogate marker. However, by matching p53 immunohistochemistry with somatic *TP53* sequencing data, we also identified tumors with *TP53* mutations that did not show p53 protein accumulation on immunohistochemistry (Figure 1), suggesting that p53 immunohistochemistry might be not an ideal surrogate marker for *TP53* mutation status.

Whole-Exome Sequencing Identifies Mutations in *TP53*, *ERCC2*, and *JAK2*:

Over the past years, we have established a choroid plexus tumor biobank with a total of 458 formalin-fixed and paraffin-embedded tumor tissue (FFPE) samples (241 CPP, 118 aCPP, 99 CPC) and 43 snap-frozen samples (28 CPP, 5 aCPP, 10 CPC). Taking advantage of this biobank, we performed RNA sequencing in a series of 47 choroid plexus tumors (including 6 CPCs) and whole-exome sequencing in 25 choroid plexus tumors (including 3 CPCs).[3] While RNA-sequencing did not reveal any oncogenic gene fusion in CPCs, targeted sequencing and whole-exome sequencing revealed homozygous *TP53* mutations in 4/6 CPCs (NM_001126113: p.N235_Y236del, p.R158C, p.K164Sfs*6 and p.A347T). In addition, whole-exome sequencing showed that one *TP53*-wild-type CPC displayed a likely pathogenic variant in ERCC2 (NM_000400: c.2083C > T, p.R965C), encoding a DNA helicase involved in the nucleotide excision repair pathway. Moreover, this CPC harbored a likely pathogenic substitution in JAK2 (NM_001322204: c.114G > A, p.M38I), encoding a non-receptor tyrosine kinase frequently mutated in hematological proliferative disorders. Taken together, these results suggest that CPC might also harbor other likely pathogenic variants besides *TP53*.

Epigenetic Heterogeneity

DNA methylation-based tumor classification has emerged as a highly robust and reproducible tool to improve clinical stratification, treatment decisions, and diagnostic accuracy. Choroid plexus tumors comprise 3 clinically relevant epigenetic subgroups: supratentorial pediatric low-risk choroid plexus tumors (CPP and aCPP; "pediatric A"), supratentorial pediatric high-risk choroid plexus tumors (CPP, aCPP, and CPC; "pediatric B") and infratentorial low-risk choroid plexus tumors in adults (CPP and aCPP, "adult"). While CPPs and aCPPs branch into all 3 methylation classes, CPCs are uniformly associated with methylation class "pediatric B,"[4] emphasizing that current DNA methylation-based classification is not yet providing additional molecular layers for CPCs.[5]

DNA Methylation Profiling Reveals Novel CPC Subgroups With Association to *TP53* Status

Our database contains DNA methylation profiles from 268 CPTs (46 "pediatric A," 135 "pediatric B" and 87 cases of the subgroup "adult"). Somatic *TP53* status was available for 58 CPTs (30 CPP, 11 aCPP, and 17 CPC). The majority of CPPs were *TP53*-wild type with only 2 cases showing heterozygous *TP53* mutations (7%). One aCPP showed a homozygous *TP53* mutation, whereas the remaining 10 aCPPs were *TP53*-wild type. Among CPCs, 8 cases showed homozygous *TP53* mutations, 3 CPCs heterozygous *TP53* mutations, and 6 CPCs were *TP53*-wild type. Unsupervised t-SNE analysis of all DNA methylation profiles showed a clear segregation of samples with

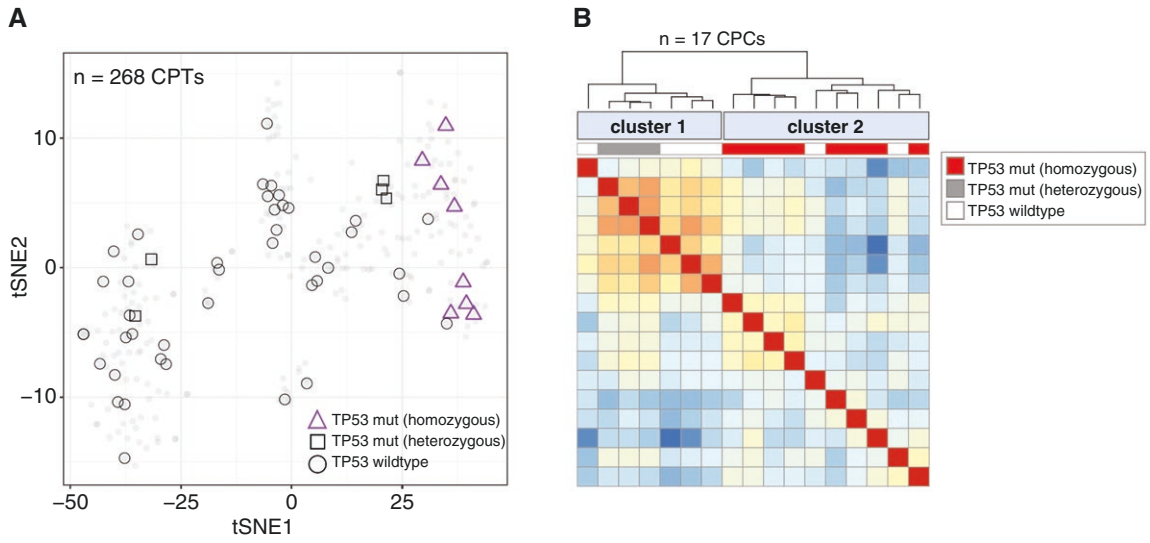


Figure 2. Epigenetic heterogeneity of choroid plexus carcinoma (CPC). (A) Unsupervised t-SNE analysis of 268 CPT DNA methylation profiles showed a clear segregation of samples with homozygous *TP53* mutations and some of the samples with heterozygous mutations tended to group together. (B) Unsupervised hierarchical clustering analysis of the 17 CPCs showed 2 major clusters with clear segregation according to *TP53* status.

homozygous *TP53* mutations and some of the samples with heterozygous mutations (Figure 2A). Subsequent hierarchical clustering analysis of the 17 CPCs with known *TP53* status demonstrates 2 distinct clusters (Figure 2B). While cluster 1 contains 4 *TP53*-wild type and 3 *TP53*-heterozygous CPCs, all 8 CPCs with homozygous *TP53* mutations clustered with methylation cluster 2 ($P = .001$, Chi-square test).

Conclusions

Choroid plexus tumors represent a diverse group of tumors. Homozygous pathogenic *TP53* alterations play an important role especially in the biology of CPCs, whereas only 7% of CPPs showed heterozygous *TP53* variants and 1/11 aCPP displayed a homozygous pathogenic *TP53* mutation. Our data indicate that CPCs may comprise at least 2 epigenetic subgroups, one of which is associated with *TP53* mutation status. These preliminary findings strongly encourage us to further investigate the genetic and epigenetic heterogeneity in a larger cohort and to align molecular subgroup status with clinical annotations to identify useful prognostic markers for patients with CPCs. In the long term, the results are expected to improve risk stratification that may be implemented in an international therapy optimization study.

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Conflicts of interest statement

The authors have no conflicts of interest to disclose.

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References

1. Thomas C, Ruland V, Kordes U, et al. Pediatric atypical choroid plexus papilloma reconsidered: Increased mitotic activity is prognostic only in older children. *Acta Neuropathol.* 2015;129(6):925–927.
2. Ruland V, Hartung S, Kordes U, et al. Choroid plexus carcinomas are characterized by complex chromosomal alterations related to patient age and prognosis. *Genes Chromosomes Cancer.* 2014;53(5):373–380.
3. Thomas C, Soschinski P, Zwaig M, et al. The genetic landscape of choroid plexus tumors in children and adults. *Neuro Oncol.* 2021;23(4):650–660.
4. Thomas C, Sill M, Ruland V, et al. Methylation profiling of choroid plexus tumors reveals 3 clinically distinct subgroups. *Neuro Oncol.* 2016;18(6):790–796.
5. Thomas C, Metrock K, Kordes U, Hasselblatt M, Dhall G. Epigenetics impacts upon prognosis and clinical management of choroid plexus tumors. *J Neurooncol.* 2020;148(1):39–45.