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CHEK2 mutations in pediatric brain tumors

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This study reviews the cases of 3 pediatric patients with central nervous system (CNS) tumors found to have checkpoint kinase 2 (*CHEK2*) mutations. Germline testing, obtained in 1 case, demonstrates that the *CHEK2* mutation is germline in nature. We speculate that *CHEK2* may be playing a role in carcinogenesis, and that further reporting of similar cases may help identify a new molecular driver in pediatric CNS tumors.

Checkpoint kinase 2 (*CHEK2*) is a tumor suppressor gene that is activated following DNA damage and leads to the arrest of cellular division, activation of DNA repair, and/or apoptosis.[1,2] *CHEK2* mutations have been described in many cancers. Germline variants have been identified in association with Li-Fraumeni syndrome,[3] breast, and prostate cancers, while somatic mutations have been reported in cases of colon, male breast, kidney, ovarian, thyroid, and lung cancers.[1,2] There is a growing body of reports of *CHEK2* mutations in adult central nervous system (CNS) tumors, including pilocytic astrocytoma with anaplasia[4] and oligodendroglioma.[5] To date, there has been limited reporting of *CHEK2* mutations in pediatric brain tumors.[6]

Here, we describe 3 pediatric glial CNS tumor cases with *CHEK2* mutations, one of which is a germline mutation.

Methods

The information was obtained via a retrospective chart review of electronic medical records, and a review of pathology slides.

Patient 1

A 2-year-old male presented with a 3-month history of vomiting. Magnetic resonance imaging (MRI) demonstrated a posterior fossa mass, which was gross totally resected. Histology revealed anaplastic ependymoma, WHO grade 3 (Figure 1A). Molecular testing was not obtained. The patient was treated with local field radiation therapy at a dose of 59.4 Gy. Over the next 18 years, he had 5 recurrences of his disease. The treatment modalities included CyberKnife radiosurgery, everolimus, and 2 additional surgical resections. In light of the 2021 WHO classification of CNS tumors, the tumor was identified as a posterior fossa group A (PFA) ependymoma, with loss of H3K7me3 on immunohistochemistry. Molecular testing revealed *CHEK2* p.T367fs mutation. As of December 2019, neuroimaging demonstrates a residual enhancing nodule along the fourth ventricle. The patient is managed conservatively with serial exams and neuroimaging. There is no family history of cancer, and germline testing was declined.

Patient 2

A 12-year-old male presented with a 1-month history of nausea and vomiting followed by acute headache. MRI demonstrated a cystic posterior fossa mass; a subtotal resection was completed. Histology revealed pilocytic astrocytoma, WHO grade 1. Molecular testing was not obtained at diagnosis. The tumor progressed 3 months postoperatively and the patient underwent gross total resection. Molecular studies revealed *FGFR1*, *PIK3CA*, and *CHEK2* c.1283C>T (p.Ser428Phe) mutations. The histologic findings and molecular results supported a diagnosis of a rosette-forming glioneuronal tumor, WHO grade 1 (Figure 1B). The patient is managed conservatively with serial exams and neuroimaging.

Family history of cancer was pertinent for pancreatic, skin, colon, prostate, breast, and ovarian cancers in multiple members related to 1 parent. Thus, the patient underwent germline testing revealing a *CHEK2* c.1283C>T (p.Ser428Phe) germline mutation.

Patient 3

An 11-year-old male presented with a 1-month history of headaches, morning emesis, and ataxia. MRI demonstrated a midline cystic and solid posterior fossa mass. He underwent a gross total resection. Histology revealed pilocytic astrocytoma, WHO grade 1 (Figure 1C). Molecular testing was notable for *KIAA1549-BRAF* fusion and *CHEK2* p.T367fs mutation. One-year postoperatively, there is no evidence of residual or recurrent disease. Family history of cancer was negative and germline testing was declined.

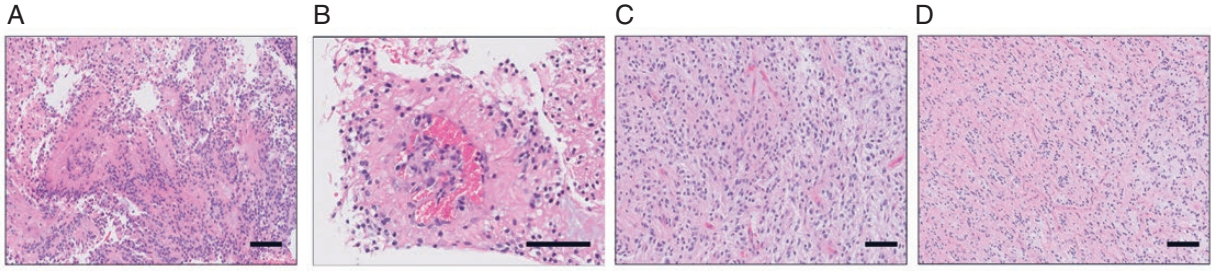

Figure 1. Neuropathologic features of checkpoint kinase 2 (*CHEK2*)-mutant pediatric central nervous system (CNS) tumors. Representative hematoxylin and eosin-stained slides for 3 *CHEK2*-mutated pediatric CNS tumors taken at 20X magnification. Panels A, C, and D are separate images from patients 1, 2, and 3, respectively. Panel B shows a representative area displaying anaplastic features (microvascular proliferation), consistent with the diagnosis of anaplastic ependymoma of patient 1. Scale bars: 200 µm (A, C, D) and 100 µm (B).

Discussion

While *CHEK2* mutations have been described in a variety of tumors, there has been limited reporting in the context of pediatric CNS tumors.[6] Here we present patients with *CHEK2* mutations in 3 types of glial pediatric CNS tumors. We hypothesize that *CHEK2* mutations are underreported and that these variants can affect diagnostic decisions, such as germline testing for tumor predisposition, and therapeutic decisions, such as using caution with radiation therapy[7,8] and investigating new targeted agents.

Given that only 1 patient underwent germline testing, it is unclear if the 2 other mutations are somatic or germline. The role of *CHEK2* requires further investigation; loss of heterozygosity with loss of the second *CHEK2* allele may have contributed to tumorigenesis, as one would expect with a tumor suppressor gene. A limitation of our study is that no loss of heterozygosity testing was performed. We are sharing our experience as we believe that further reporting of similar cases will be foundational for future studies evaluating the potential role of *CHEK2* mutations in driving pediatric CNS tumors.

Keywords

CHEK2 mutation | CNS tumors | molecular profiling | pediatrics

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Conflict of interest statement

None declared.

Authorship statement

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