INTRODUCTION

Medulloblastoma (MB), a heterogeneous solid tumor of the posterior fossa, is the second most common malignant pediatric brain tumor after high-grade gliomas (Millard & De Braganca, 2016; Ostrom et al., 2015). Typically, medulloblastomas (MBs) are aggressive and metastasize within the central nervous system and, less frequently, outside the neuraxis (Millard & De Braganca, 2016). The four consensus subgroups, MB_SHH, MB_WNT, MB_Group 3, and MB_Group 4, representing the second most common type of pediatric brain cancer after high-grade gliomas. They suffer from a high prevalence of genetic predisposition with up to 20% of MB_SHH caused by germline mutations in only six genes. However, the spectrum of germline mutations in MB_SHH remains incomplete.

Methods: Comprehensive Next-Generation Sequencing panels of both tumor and patient blood samples were performed as molecular genetic characterization. The panels cover genes that are known to predispose to cancer.

Results: Here, we report on a patient with a pathogenic germline PTEN variant resulting in an early stop codon p.(Glu7Argfs*4) (ClinVar ID: 480383). The patient developed macrocephaly and MB_SHH, but reached remission with current treatment protocols.

Conclusions: We propose that pathogenic PTEN variants may predispose to medulloblastoma, and show that remission was reached with current treatment protocols. The PTEN gene should be included in the genetic testing provided to patients who develop medulloblastoma at an early age. We recommend brain magnetic resonance imaging upon an unexpected acceleration of growth of head circumference for pediatric patients harboring pathogenic germline PTEN variants.

KEYWORDS

carcinogenesis, disease susceptibility, magnetic resonance imaging, medulloblastoma, megalencephaly
MBs account for roughly 10% of central nervous system malignancies in children between 0 and 14 years of age with a worldwide age-adjusted incidence of 2.0–5.8 cases per 1,000,000 annually (Millard & De Braganca, 2016; Waszak et al., 2018). The incidence peaks in two age groups, namely in children between 3 to 4 years and 8 to 9 years of age (Millard & De Braganca, 2016; Ostrom et al., 2015). Extensive single-cell transcriptomics have revealed that MBs originate from irregularities in early brain development (Vladiou et al., 2019), which may explain why at least 70% of MBs occur in the pediatric population (Millard & De Braganca, 2016).

A recent study demonstrated that the MB_{SHH} subgroup suffers from the highest prevalence of genetic predisposition (approximately 20%) with recognized germline driver mutations in APC, BRCA2, PALB2, PTCH1, SUFU (OMIM *607035), and TP53 (Waszak et al., 2018). However, the spectrum of germline mutations in MB remains incomplete. Here, we present the first known case report of cerebellar medulloblastoma with an inactivating germline variant in the tumor suppressor PTEN (OMIM *601728). We suggest that pathogenic germline PTEN variants may predispose patients the early development of medulloblastoma and show that current treatment protocols may prove effective despite the PTEN status. We recommend brain magnetic resonance imaging (MRI) upon an unexpected acceleration of growth of head circumference for pediatric patients known to harbor such variants of the PTEN gene.

2 | RESULTS

2.1 | Ethics statement

The patient and her legal guardians conferred an informed consent for the study. The study complies with the Helsinki Declaration of 1975.

2.2 | Methods

Histological characterization of the tumor was performed at the Department of Pathology (Oulu University Hospital, Oulu, Finland). Molecular genetics studies were performed using a Next-Generation Sequencing (NGS) panel at the Laboratory of Genetics, HUSLAB (Helsinki University Hospital, Helsinki, Finland). A comprehensive hereditary cancer NGS panel of blood sample DNA was performed at the Blueprint Genetics laboratory (Helsinki, Finland). The panel includes 116 genes known to confer a hereditary predisposition to cancer.

2.3 | Case report

The index patient was referred to the Oulu University Hospital at 14 months of age due to a 2-week history of torticollis and temper tantrums. She is the first child of her parents, and the pregnancy and delivery were uneventful. Her birth weight, height and head circumference (+1.7 SD) were normal at birth. However, at the age of 2.5 weeks she presented with macrocephaly (+4.0 SD). The subsequent brain ultrasound and MRI were normal. Since the age of 5 months, her head circumference continued to grow on a +5 to +5.2 SD curve. Brain MRI was repeated at the age of 6 months and brain ultrasound at the age of 7 and 9 months. All the findings were normal. Otherwise, she developed normally and achieved walking at 12 months of age.

By admission to the hospital, the child had regressed to cruising. Macrocephaly had progressed (+6.3 SD) and MRI using a 1.5 Tesla scanner revealed a large cerebellar tumor (4.0 × 5.5 × 6.5 cm in size) with obstructive hydrocephalus (Figure 1). The tumor was suspected to represent desmoplastic-nodular medulloblastoma by nodular MRI features. Subsequently, the patient underwent immediate ventriculostomy and resection of the tumor mass. Complete resection was confirmed macroscopically and by postoperative MRI, and the child recovered as expected.

Post-surgical chemotherapy was performed according to the SKK protocol in the HIT-MED Guidance of the University of Hamburg-Eppendorf for M0 tumors (with no postoperative residual tumor or metastases), between September 2017 and August 2018. Chemotherapy included Cyclophosphamide (1,200 mg/m²), Vincristine (16.5 mg/m²), Carboplatin (3,000 mg/m²), Etoposide (2,250 mg/m²), and Methotrexate (30,000 mg/m²). The child is currently in remission at 3.5 years of age.

By NGS analysis, the tumor was shown to be wildtype for the PTCH1, SMO, and TP53 genes, and MYC and MYCN amplifications were excluded. However, a SUFU (c.412delinsCC, p.(Ala138Profs*32), NM_016169.3) mutation was discovered in an extended NGS panel confirming the MB_{SHH} subtype (i.e., medulloblastoma, SHH-activated and TP53 wildtype). Additional mutations were found in the KDR (OMIM *191306, c.(787C>A), p.(Pro263Thr), NM_002253.2) and PTEN (c.(18dup), p.(Glu7Argfs*4), NM_000314.4) genes. The KDR variant is classified as pathogenic (COSM353283) but is unlikely to be significant here, since the developing medulloblastoma benefits from a functioning KDR gene (Slongo et al., 2007).

Finally, genetic counselling was provided as per the HIT-MED Guidance for MB_{SHH}. A DNA sample extracted from
the patient’s blood was sent for sequencing. No known disease-causing germline variants associated with medulloblastoma were identified, including the *APC*, *BRCA2*, *PALB2*, *PTCH1*, *SUFU*, and *TP53* genes (Waszak et al., 2018). However, the panel revealed a de novo heterozygous *PTEN* frameshift variant (c.(18dup), p.(Glu7Argfs*4)) leading to a premature stop codon and representing the same mutation observed in the tumor tissue. The *PTEN* variant has been classified as pathogenic (ClinVar ID: 480383). Another patient with a germline *PTEN* variant and medulloblastoma at 1.0 years of age has previously been identified by Waszak and colleagues (Table 1) (Waszak et al., 2018). Gröbner et al. have reported two patients with germline *PTEN* variants and medulloblastoma at 19 and 23 years of age (Gröbner et al., 2018).

### 3 | DISCUSSION

We present the first known case report of a toddler carrying a pathogenic germline *PTEN* variant with macrocephaly and MB_{SHH}. While macrocephaly (+3.3 to 5.5 SD in males and +2.9 to 4.1 SD in females) is a known diagnostic feature of germline *PTEN* variants (Plamper, Gohlke, Schreiner,
mutations are druggable. Similarly, Waszak and colleagues (2019) established that germline mutations explain 5%–6% of medulloblastoma, most significantly in the APC, BRCA2, PALB2, PTCH1, SUFU and TP53 genes, with SUFU and PTCH1 mutations demonstrating a high prevalence in infant MB_SHH (Waszak et al., 2018). Their data include one pathogenic germline PTEN variant associated with MB_SHH (out of approximately 41 cases of MB_SHH with genetic predisposition) and show that familial history in MB_SHH with a germline mutation is uncommon. These data suggest that damaging germline variants in PTEN, although rare, do occur in medulloblastoma.

Because the cases of medulloblastoma that are linked with germline PTEN variants are so rare—and may thus represent coincidental association—additional evidence is required to elucidate the role of PTEN in medulloblastoma predisposition. Mechanistically, PTEN regulates a perivascular progenitor cell niche that may act as a platform for tumorigenesis (Zhu et al., 2016). The SHH and PI3K pathways converge to promote the proliferation of granule cell progenitors in the external granule layer of the cerebellum. The Pten+/− mouse model produced by Zhu and colleagues demonstrated irregular proliferation of the progenitors, which progressed to fully penetrant MB_ShH with a co-deletion of the Tp53 gene. It is possible that PTEN variants predispose to a rapidly developing medulloblastoma but require a mutation in one or several “second genes” for tumorigenesis (Gröbner et al., 2018; Zhu et al., 2016). This might explain the infrequency of medulloblastoma in patients with germline PTEN variants. Accordingly, the extended NGS panel of our patient’s tumor DNA revealed a point mutation in SUFU which has been implicated in the development of MB_SHH (Brugières et al., 2012; Waszak et al., 2018).

In conclusion, we report on a patient with macrocephaly and MB_SHH that developed before the first typical peak in medulloblastoma incidence at 3 to 4 years of age. Extensive NGS analyses revealed a pathogenic germline variant in PTEN and a second variant of the SUFU gene in the tumor DNA. Notably, remission was reached with current medulloblastoma treatment protocols despite the PTEN status. At certain countries are beginning to provide whole-genome sequencing for all newly diagnosed pediatric cancer patients (Byrjalsen et al., 2018), coincidental germline variants may confound the search for true genetic predisposition in pediatric cancer. We therefore suggest that the genetic testing of young patients with medulloblastoma should include the PTEN gene in addition to the APC, BRCA2, PALB2, PTCH1, SUFU and TP53 genes with well-defined associations to medulloblastoma to characterize the role of PTEN in the development of medulloblastoma. Genetic counseling should be provided to families where germline mutations have been revealed.

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CONFLICT OF INTEREST
No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS
AH and RN performed clinical care of the patient. All authors contributed to the design of the study, including radiological, histological and genetic analyses. JPT, AH and MSP wrote the first draft of the manuscript. All authors contributed considerable input on the preparation and writing of the manuscript.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on reasonable request from the corresponding author due to privacy restrictions.

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