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Germline Variants in Pediatric Cancer : Based on Oncogenic Pathways

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Pathogenic germline variants (PGVs) are increasingly recognized as critical elements in pediatric cancer predisposition. Determining the pathogenicity of germline variants is a dynamic process, with advancements in next-generation sequencing and expanding genome databases reshaping our understanding of cancer genomics. This article reviews the role of PGVs in key oncogenic pathways, including RTK (receptor tyrosine kinase)/RAS/MAPK (mitogen-activated protein kinase), PI3K (phosphatidylinositol 3-kinase)/AKT (v-akt murine thymoma viral oncogene homolog 1), WNT (wingless-type), and Hedgehog signaling, highlighting their associations with specific cancer predisposition syndromes and neurosurgical implications. Most PGVs are inherited in an autosomal dominant pattern and are frequent in tumor suppressor genes, while autosomal recessive conditions like Ataxia-telangiectasia and Fanconi anemia are less common. Germline variants in proto-oncogenes such as *PTPN11*, *KRAS*, and *HRAS* are associated with RASopathies, including Noonan and Costello syndromes, which show variable cancer risks. Similarly, *PTEN* PGVs, linked to Cowden syndrome, and *DICER1* PGVs, responsible for DICER1 syndrome, exemplify the diverse clinical presentations and risks of pediatric cancer predisposition syndromes. Medulloblastoma, a pediatric-specific brain tumor, shows an increasing proportion of PGVs, with approximately 12% of all medulloblastomas harboring PGVs in *APC*, *PTCH1*, *SUFU*, and *ELP1* in the WNT-activated and sonic hedgehog-activated subtypes. Emerging evidence suggests that approximately 8.5–20% of pediatric cancer patients harbor PGVs, with a substantial proportion arising *de novo*. Routine germline screening for pediatric cancer patients is increasingly recommended, as many PGVs lack family history. Programs like STREAM (Solid Tumor REsearch And Magic) in Korea underscore the importance of comprehensive pediatric genome databases for personalized precision medicine. As neurosurgeons are frequently the first to encounter central nervous system tumor manifestations, a robust understanding of genomic medicine is essential. This review emphasizes the need for international collaboration to develop actionable insights into pediatric cancer genomics, ultimately improving diagnostic, therapeutic, and preventive strategies.

Key Words : Germ-line mutation · Medulloblastoma · Basal cell nevus syndrome · Noonan syndrome · Costello syndrome · Cowden syndrome.

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GENERAL ASPECTS AND IDENTIFYING PATHOGENIC GERMLINE VARIANTS (PGVs)

Determining the pathogenicity of a certain germline variant is a dynamic process due to the growing and updated evidences in large genome databases[35,38]. What is currently classified as a variant of uncertain significance may later be reclassified as a pathogenic or likely pathogenic variant. In general, clinically significant germline variants are referred to as pathogenic or likely pathogenic variants. In this manuscript, I will use the term PGV, which encompasses the two pathogenic/likely pathogenic classes of the American College of Medical Genetics (ACMG) guidelines[48].

The majority of PGVs causing cancer predisposition syndromes show an autosomal dominant inheritance pattern and involves mutations in tumor suppressor genes. Autosomal recessive cancer predisposition syndromes, such as Ataxia-telangiectasia and Fanconi anemia, exist but are less prevalent, as they require the inheritance of both mutant alleles. A study investigating 871 PGVs found that 659 occurred in 66 tumor suppressor genes, while 33 occurred in five proto-oncogenes[28]. A PGV in a tumor suppressor gene is likely to be a loss-of-function mutation, whereas an oncogene requires a gain-of-function mutation. When a PGV in a tumor suppressor gene is present, loss of heterozygosity (LOH) due to deletion of the wild-type allele or a somatic mutation, can lead to cancer development, as explained by the well-known two-hit hypothesis[28,34].

Interestingly, PGVs in renowned proto-oncogenes associated with pediatric cancers, such as *H3-3A, CTNNB1*, and *PI3KCA*, manifest as neurodevelopmental disorders or systemic overgrowth disorders rather than cancer predisposing syndromes[11,13,44]. This may be due to the fact that many proto-oncogenes are essential for normal cell growth and developmental process. Known proto-oncogenes that cause cancer predisposition include *MET, HRAS, KRAS, PTPN11* which are involved in the RTK (receptor tyrosine kinase)/RAS/MAPK (mitogen-activated protein kinase) pathway.

Upon identifying PGVs in pediatric cancer patients, genetic counseling is necessary. Genetic counseling involves interpreting the results, predicting the clinical course of the patient, assessing the risk of cancer occurrence, performing cancer screening, conducting genetic testing for family members (along with subsequent cancer screening if necessary), and providing counseling for family planning.

Data supports that younger age and early-onset cancers are more likely driven by germline variants, while late-onset cancers are predominantly influenced by acquired somatic mutations[47]. Suspicion of a cancer predisposition syndrome may arise during patient evaluation. Jongman et al.[31] have suggested criteria for considering cancer predisposition and referral for clinical genetic testing. This includes presence of 1) a family history of early-onset or rare cancer, 2) specific tumor types associated with cancer predisposition syndromes, 3) multiple tumors in a patient, 4) other congenital anomalies, and 5) excessive treatment toxicity from cancer therapy (Table 1). A study utilizing criteria similar to those of Jongman demonstrated that 18.5% of patients who met one criterion exhibited PGVs, while 63.6% of patients meeting two criteria presented PGVs[61].

Table 1. Jongmans criteria for considering cancer predisposition[31]

Relevant family history
2 or more malignancy in age ≤18 years, including the patient
First degree relative with cancer in age ≤45 years
2 or more second degree relative with cancer in age ≤45 years, on the same side of family
The parents have familial connections
Specific tumor types (adrenocortical carcinoma, atypical teratoid/rhabdoid tumor, choroid plexus carcinoma, hemangioblastoma, pleuropulmonary blastoma, pineoblastoma, etc.)
Patient with 2 or more malignancies (bilateral, multifocal, metachronous)
Other congenital anomalies (skeletal, organ related), abnormal growth, intellectual disabilities, etc.
Excessive treatment toxicity from cancer therapy

EMERGING IMPORTANCE OF GERMLINE VARIANTS IN THE NEXT-GENERATION SEQUENCING (NGS) ERA

Before the advent of NGS, germline cancer predisposition syndromes were diagnosed based on clinical phenotype and family history. With the application of NGS, our knowledge of the cancer genome and associated germline variants has expanded significantly. Due to the rarity of pediatric cancers and the need for personalized precision medicine, efforts to build comprehensive pediatric genome databases of tumor and germline data are actively ongoing on a nationwide basis in

many countries[63,69-71]. In Korea, a pediatric solid tumor genome database program named STREAM (Solid Tumor REsearch And Magic), has been established since 2023. This program includes 1) integrated genomic analysis : whole-genome, transcriptome, and methylome sequencing of tumor tissue along with matched germline sequencing, 2) high-throughput drug screening, and 3) multidisciplinary discussion at molecular tumor-board. The purpose of this program is to build a personalized, precision medicine platform that will enhance the diagnosis and treatment of pediatric solid tumor patients.

Zhang et al.[73] analyzed 1120 pediatric cancer patients and revealed that 8.5% of the cases harbored PGVs. Notably, among the patients with PGVs, 40% had no family history suggestive of a cancer predisposition syndrome. Another recent study reported that 64% of cancer predisposition syndrome in children were *de novo* cases[62]. The proportion of PGVs among pediatric cancer patients appears to be increasing, with more recent reports indicating rates of 12% and even up to 20%[1,18]. These findings could influence clinical decisions, driving the recent trend towards performing routine germline screening for pediatric cancer patients[26]. Our preliminary data from the STREAM program includes 192 pediatric solid tumor patients. Brain tumors were the most common, representing 94 patients (48.9%). Among the 192 patients, 28 patients (14.5%) had germline mutations, and 20 patients (10.4%) were pathogenic variants according to the ACMG guideline. The genes identified were *TP53, VHL, NF1, SMARCB1, SDHD,* and others (Fig. 1).

Due to the high prevalence of *de novo* mutations and the advent of NGS, predicting PGVs from tumor somatic sequencing data has become an important tool to complement classical clinical history taking[64]. Ripperger et al.[49] have modified the Jongmans criteria by incorporating tumor sequencing results suggestive of germline predisposition. In simplified terms, somatic variants found in tumors with a variant allele frequency (VAF) of 0.4 to 0.6 could indicate true germline variants[2]. However, VAF can exceed 0.6 due to LOH and may fall below 0.3 due to clonal heterogeneity and tumor purity issues[41]. More complex considerations, such as the type of genes, specific tumor types, the actionability of the variant, and the patient's age, are factored in the clinical setting. The European Society for Medical Oncology group recommends testing for PGVs based on specific gene and age considerations. For example, PGVs in genes such as *NF1*, *MLH1/MSH2/MSH6/PMS2*, *SMARCB1*, *TSC1/2*, and *VHL* can occur across all ages. In contrast, variants in genes such as *APC*, *PTEN*, *RB1*, *TP53*, *CDKN2A*, and *SMARCA4* should be tested for PGVs in patients younger than 30 years old, as they are commonly acquired somatic variants in older patients[37].

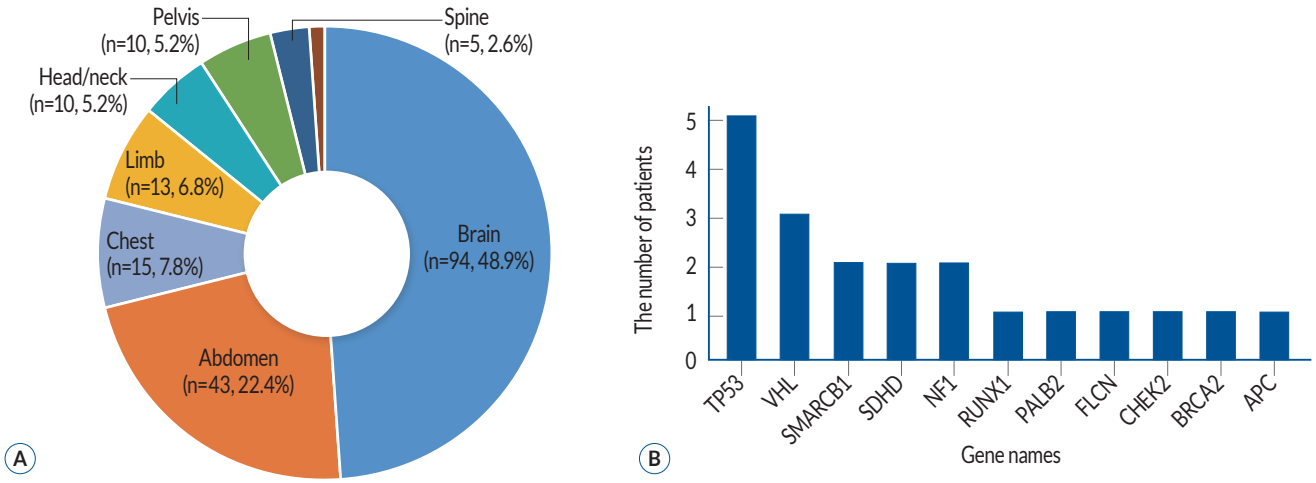

Fig. 1. Preliminary data from the STREAM program from March 2023 to March 2024. A : Tumor regions of the 192 pediatric solid tumors patients. Brain was the most common, representing 94 patients (48.9%). B : Gene distribution of the twenty patients (10.4%) having pathogenic germline variants according to the ACMG guideline. TP53 : tumor protein p53, VHL : von Hippel-Lindau tumor suppressor, SMARCB1 : SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1, SDHD : succinate dehydrogenase complex subunit D, NF1 : neurofibromin 1, RUNX1 : runt-related transcription factor 1, PALB2 : partner and localizer of BRCA2, FLCN : folliculin, CHEK2 : checkpoint kinase 2, BRCA2 : breast cancer 2, APC : adenomatosis polyposis coli, STREAM : Solid Tumor REsearch And Magic, ACMG : American College of Medical Genetics.

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PGVS IN PEDIATRIC CANCER : BASED ON ONCOGENIC PATHWAYS

The top canonical oncogenic pathways, as defined by the Cancer Genome Atlas study, include key cancer driver pathways such as p53, RTK/RAS/MAPK, PI3K (phosphatidylinositol 3-kinase)/AKT (v-akt murine thymoma viral oncogene homolog 1), WNT (wingless-type) and the cell cycle pathway[53]. Additionally, there are oncogenic pathways associated with genomic instability, which affect DNA repair, epigenetic modifiers, splicing, and other cellular processes. In terms of incidence, commonly encountered PGVs in pediatric cancer include *NF1/NF2*, *TP53*, *TSC*, *VHL*, *SMARCB1*, and mismatch repair genes, as discussed earlier in this pediatric issue.

It is not feasible to review all clinically significant PGVs due to their vast number and the rapidly evolving genome databases. This article will focus on PGVs not covered earlier in this pediatric issue and that are particularly noteworthy in pediatric cancer, based on their association with oncogenic pathways. Considering the scope of this journal, description of the cancer predisposition syndromes will be focused on manifestations in the central nervous system (CNS) and neurosurgical considerations. Specific PGVs in the WNT and hedgehog signaling pathways, which are associated with medulloblastoma, as well as those in the RTK/RAS/MAPK pathway, PI3K/AKT pathway, and microRNA regulation, will be discussed in this article.

PGVS IN MEDULLOBLASTOMA

WNT pathway : *APC*

The *APC* gene is a tumor suppressor and a negative regulator of the WNT signaling pathway. The APC protein functions as part of a destruction complex that targets and degrades β-catenin[39]. A PGV of the *APC* gene, combined with a second hit from somatic mutation or LOH, is required for pathogenesis[24]. PGVs of *APC* are inherited in an autosomal dominant pattern and are known as familial adenomatous polyposis 1 (FAP1) syndrome, also known as Turcot syndrome.

The penetrance of *APC* PGV is nearly 100%, with 20–30% arising as *de novo* cases[5]. Approximately 85–90% of WNT-activated medulloblastoma are caused by somatic mutations of *CTNNB1*, and *APC* PGVs are common in cases lacking *CTNNB1* mutations[45,67]. While nearly all FAP1 patients develop gastrointestinal polyposis requiring preventive colectomy, the lifetime risk of developing WNT-activated medulloblastoma remains low (1%), despite a 13-fold increased risk[7]. As a result, routine CNS imaging is not recommended for FAP1 patients[29].

The treatment of WNT-activated medulloblastoma with *APC* PGVs does not differ from that of their sporadic counterparts, and theses tumors generally have a favorable prognosis[59].

Hedgehog signaling pathway : *PTCH1*, *SUFU* and elongator complex gene, *ELP1*

PTCH1 and *SUFU* are tumor suppressor genes and negative regulators of the hedgehog signaling pathway. PGVs in these genes are inherited in an autosomal dominant pattern and are known as naevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin syndrome. NBCCS is linked to SHH (sonic hedgehog)-activated medulloblastoma, *TP53*-wildtype.

The penetrance of *PTCH1* PGVs is nearly 100%, while *SUFU* PGVs have incomplete penetrance[10]. Approximately 20–30% of PGVs in *PTCH1* and *SUFU* genes are *de novo*[14]. Common features of NBCCS include macrocephaly, facial anomalies, rib and vertebral anomalies, and basal cell carcinoma, which typically develops in the late teens[15]. While the risk of developing SHH-activated medulloblastoma is 2% in patients with *PTCH1* PGVs, patients with *SUFU* PGVs have a significantly higher risk (33%)[56]. Consequently, routine CNS surveillance is not recommended for patients with *PTCH1* NBCCS, whereas patients with *SUFU* NBCCS require contrast brain magnetic resonance imaging (MRI) every 3–4 months until the age of 3, and then annually until age 8[16].

The prognosis of SHH-activated medulloblastoma with *PTCH1* or *SUFU* PGV is reported to be better than that of sporadic cases, allowing for delayed radiation therapy in younger patients to reduce the risk of secondary malignancy[3].

Recently, PGVs in the *ELP1* gene have been identified, shedding light on the pathogenesis of medulloblastoma with PGV[68]. *ELP1*, located at 9q31.3, encodes a subunit of the elongator complex that modifies tRNA[27]. The pathogenesis involves a three-step model : 1) a PGV in *ELP1*, 2) somatic deletion of 9q, and 3) somatic mutation in *PTCH1*, located at 9q22.32, leading to biallelic inactivation of *ELP1* and *PTCH1*. PGVs in *ELP1* are present in 14% of SHH-activated medulloblastomas[68]. While *ELP1* PGVs confer an odds ratio of 33.53 for developing medulloblastoma, they exhibit low penetrance and risk (<1%) and occur only during childhood[23,57]. Due to their low penetrance

and limited phenotypic age window, routine imaging surveillance for the patient or familial genetic screening is not recommended. The prognosis of SHH-activated medulloblastoma with *ELP1* PGV is favorable[68].

Homologous recombination repair genes : *BRCA2* and *PALB2*

BRCA2 and *PALB2* are tumor suppressor genes associated with the homologous recombination process. The BRCA2 protein functions as a DNA repair protein, while PALB2 (partner and localizer of BRCA2) is a scaffold protein that mediates the recruitment of BRCA2 protein to damaged DNA loci[52,60]. Loss-of-function in these genes results in homologous recombination repair deficiency.

Although rare, PGVs in *BRCA2* and *PALB2* are associated with an increased risk for medulloblastoma, most commonly the SHH-activated subtype, with a 13.8-fold relative risk compared to controls[32,43]. Waszak et al.[67] recommend that patients with SHH-activated medulloblastoma should be screened for PGVs in *BRCA2* and *PALB2* following a negative PGV result for hedgehog signaling pathway genes.

While non-WNT/non-SHH medulloblastomas are the most common subtype, only a small proportion of these tumors are associated with PGVs. PGVs in the *BRCA2* and *PALB2* are observed in 1–2% of non-WNT/non-SHH medulloblastomas. PGVs in *BRCA2* have been associated with a 4.2-fold relative risk of developing non-WNT/non-SHH medulloblastomas[65]. Although rare, medulloblastoma with *BRCA2* and *PALB2* PGVs appear to have a favorable prognosis.

In summary, the proportion of medulloblastomas with PGV varies among subtypes. Based on literature review, approximately 12% of all medulloblastomas harbor PGVs, with the SHH-activated subtype being the most commonly involved (approximately 40%) (Fig. 2)[14,45,56,67,68].

RTK/RAS/MAPK pathway : *PTPN11*, *KRAS* and *HRAS*

PGVs in the RTK/RAS/MAPK pathway are collectively referred to as RASopathies. The most well-known RASopathy is *NF1*, a tumor suppressor gene, but the RTK/RAS/MAPK pathway gene group includes several proto-oncogenes such as *PTPN11*, *KRAS*, and *HRAS*. These RASopathies often share common clinical features, including cardiac, craniofacial, and growth manifestations[21,30]. While other RASopathies (except NF1) are not strongly associated with an increased cancer risk, both Noonan syndrome and Costello syndrome are associated with cancers[36]. RASopathy genes are generally inherited in an autosomal dominant pattern.

Noonan syndrome involves PGVs in several genes, with PTPN11 being the most common (50%), followed by *SOS1*, *RAF1*, *KRAS*, and others. More than half of Noonan syndrome arises *de novo*, with nearly 100% penetrance[50]. Noonan syndrome is associated with eightfold increased risk of cancer, although overall risk until adulthood remain relatively low (around 5%)[36]. Consequently, routine cancer imaging surveillance is not recommended[66]. In addition to malignancies such as Juvenile myelomonocytic leukemia, rhabdomyosarcoma, and neuroblastoma, Noonan syndrome is associated with low-grade glial and glioneuronal tumors and other neurosurgical conditions such as Chiari 1 malformation, craniosynostosis, and moyamoya syndrome[40,54].

Costello syndrome is diagnosed by identifying a PGV in *HRAS*. Costello syndrome typically occurs *de novo* and exhib-

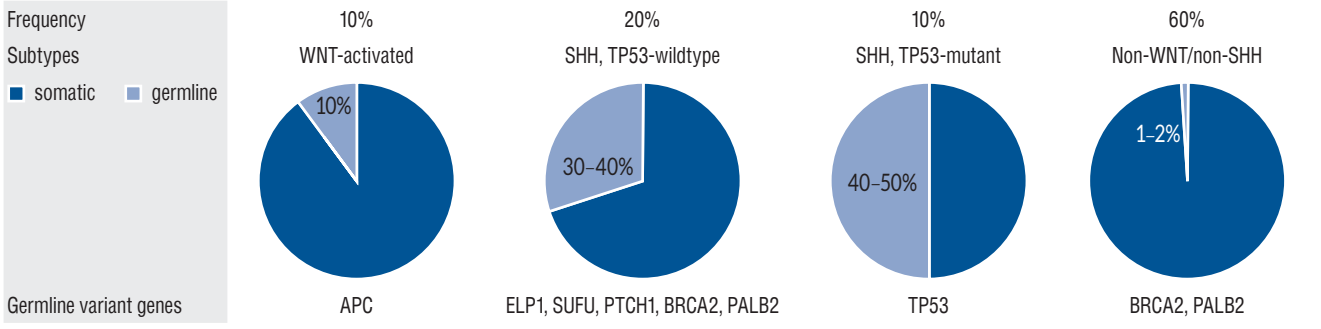

Fig. 2. Proportion of medulloblastoma cases with germline variants by subtypes and relevant genes, based on literature review[14,45,56,67,68]. Considering the frequency of medulloblastoma subtypes, approximately 12% of all medulloblastoma cases harbor germline variants. WNT : wingless-type, APC : adenomatosis polyposis coli, SHH : sonic hedgehog, TP53 : tumor protein p53, ELP1 : elongator complex protein 1, SUFU : suppressor of fused homolog, PTCH1 : patched 1, BRCA2 : breast cancer 2, PALB2 : partner and localizer of BRCA2.

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its 100% penetrance[22]. Individuals with Costello syndrome have a 42-fold increased cancer risk, with a cumulative cancer incidence of 13% by age 20[6,36]. Common malignancies include rhabdomyosarcoma, neuroblastoma, and bladder cancer, necessitating rigorous surveillance.

Treatment for these syndromes is based on clinical manifestations. Recently, promising results have been reported for managing cardiac manifestations in both Noonan and Costello syndromes using targeted inhibitors[4,19]. For solid tumors, surgical resection is necessary for diagnostic and therapeutic purpose. In Noonan syndrome patients, bleeding tendencies, especially in those with *PTPN11* PGVs, should be carefully considered before surgery[51]. A thorough history taking, including past bleeding episodes and prior surgeries should be obtained. Hematology consultation and baseline coagulopathy tests are recommended before any surgical procedures[9]. The risk of perioperative bleeding complications is approximately 6.2% in Noonan syndrome patients who have not undergone preoperative evaluation[8].

PI3K/AKT pathway : *PTEN*

The *PTEN* gene is a tumor suppressor, and the PTEN protein functions as a lipid phosphatase, which negatively regulates the PI3K/AKT pathway. Nuclear PTEN is required for cell cycle arrest, while cytoplasmic PTEN is essential for apoptosis[72]. PGVs in *PTEN* are inherited in an autosomal dominant pattern and are known as the PTEN hamartoma tumor syndrome spectrum, which includes Cowden syndrome.

The penetrance of *PTEN* PGVs is approximately 90%, with 11–48% of cases arising *de novo*[42]. A substantial proportion of *PTEN* PGVs may exhibit mosaicism[12]. Cowden syndrome carries a high risk of developing breast, thyroid, renal cell, and endometrial cancers in adulthood. In children, features such as macrocephaly and skin lesions are common. A rare intracranial

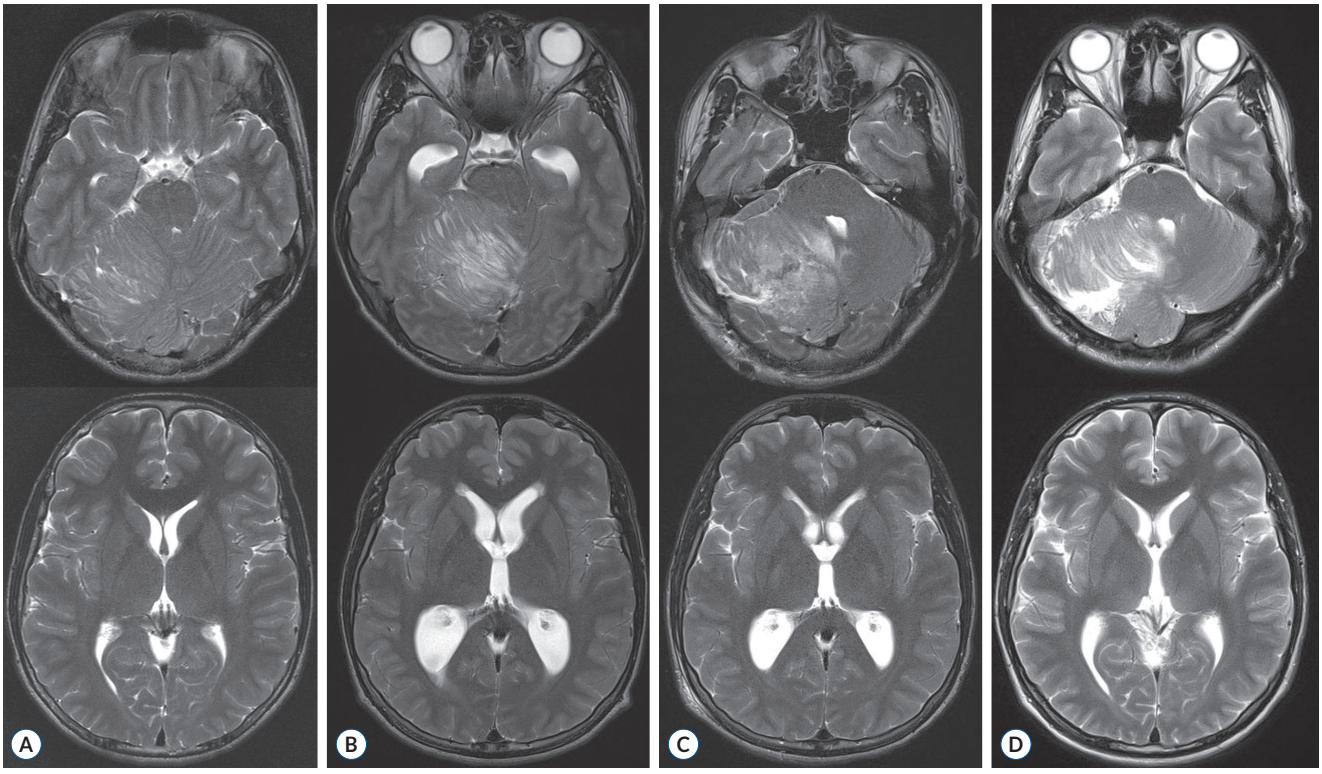

Fig. 3. Our experience with a patient with pediatric-onset cerebellar dysplastic gangliocytoma (Lhermitte-Duclos disease) without evidence of other features of PTEN hamartoma tumor syndrome (Cowden syndrome). A : An 11-year-old boy was diagnosed with cerebellar dysplastic gangliocytoma following nonspecific headache. There was no relevant family history or other clinical features. The patient was followed up due to nonspecific symptoms. B : Five years later, the patient presented with worsening headaches and tremors. Magnetic resonance imaging revealed ventriculomegaly. C : Surgical debulking was performed to relieve cerebrospinal fluid pathway obstruction. Partial resection was done, and pathology confirmed dysplastic gangliocytoma. D : At the 5-years postoperative follow-up, the patient remained stable. No other malignancies were noted at the last follow-up, at age 30.

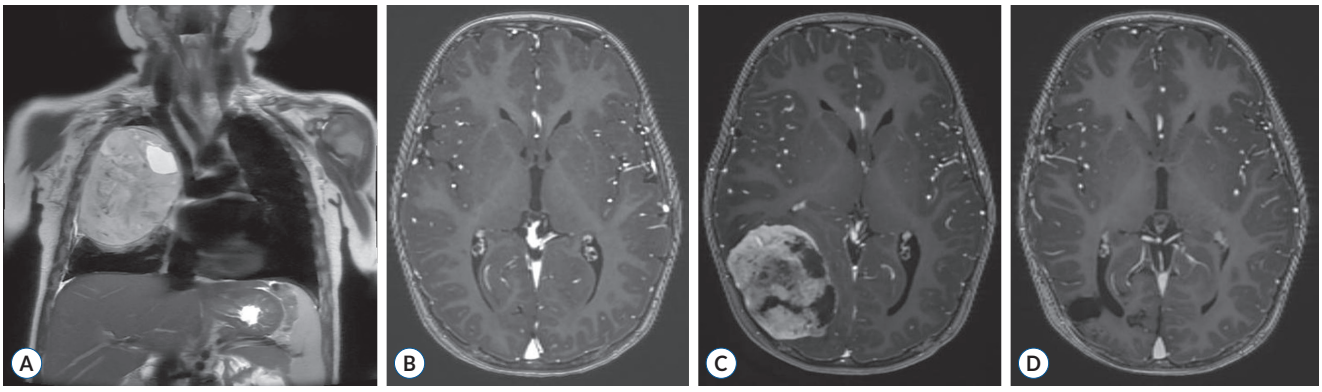

Fig. 4. A patient with *DICER1* syndrome. A : A 24-months-old boy presented with pneumonia-like symptoms and underwent surgical removal of a right upper lobe lung mass. He was diagnosed with pleuropulmonary blastoma (PPB), and next-generation sequencing of the tumor tissue revealed a *DICER1* splicing variant with a variant allele frequency of 34.9%. Germline sequencing confirmed the presence of the same variant. B : A brain magnetic resonance imaging was performed due to high risk of brain metastasis associated with PPB, but the results were negative. C : At 40 months of age, 5 months after completing chemotherapy, the patient complained of headaches, and a large brain tumor was diagnosed. Gross total resection of the tumor was performed, and pathology confirmed metastatic PPB. D : At a 6-month postoperative follow-up, no recurrence or new lesions were noted. The patient remains stable and is undergoing chemotherapy.

tumor, dysplastic cerebellar gangliocytoma, also known as Lhermitte-Duclos disease, is pathognomonic for Cowden syndrome. However, while adult-onset dysplastic cerebellar gangliocytoma is associated with *PTEN* PGVs, the pediatric-onset dysplastic cerebellar gangliocytoma is not associated with *PTEN* PGVs, suggesting different pathogeneses[74].

Since pediatric-onset dysplastic cerebellar gangliocytoma is not pathognomonic for Cowden syndrome, patients and caregivers can be reassured about the low probability of a *PTEN* PGV unless other features suggestive of a cancer predisposition syndrome are present (Fig. 3)[25].

MicroRNA regulation : *DICER1*

The *DICER1* gene is a tumor suppressor, and the DICER1 protein acts as an endoribonuclease, essential for the production of microRNAs. Disruption of microRNA-mediated gene expression regulation leads to tumorigenesis[17]. Along with a PGV, a second hit of somatic mutation is required for pathogenesis. *DICER1* PGVs are inherited in an autosomal dominant pattern and are known as DICER1 syndrome.

The penetrance of *DICER1* PGVs is reduced, with a 5% risk of cancer development by age 10 and a 20% risk by age 50[58]. Approximately 80% of *DICER1* PGVs are inherited, while 20% arise *de novo*. Common phenotypes include pleuropulmonary blastoma, thyroid gland tumor, ovarian tumor, and cystic nephroma, which predominantly occurs in childhood. Rare CNS manifestations include pituitary blastoma, pineoblastoma, embryonal tumor with multilayered rosettes (ETMR), and primary intracranial sarcoma[20,33]. The malignancy potential in DICER1 syndrome is variable, and additional alterations may contribute to tumorigenesis[46].

The most common CNS manifestation is metastasis of pleuropulmonary blastoma, which occurs in 11% of affected patients (Fig. 4). Given the high rate of metastasis, short-term surveillance for CNS metastases is recommended until 36 months following the diagnosis of pleuropulmonary blastoma[55,65]. Since other primary CNS tumors are rare, routine surveillance imaging is not recommended for asymptomatic patients[55].

CONCLUSION

With the expanding use of NGS and continuous updates to genome databases, the identification and clinical application of PGVs in cancer genomics are becoming increasingly important. Given the substantial proportion of *de novo* variants, paired germline sequencing should be adopted. Due to the rarity and diversity of pediatric cancer etiologies, sufficient genome databases cannot be established by individual researchers, institutions, or nations alone. The role of worldwide working groups is critical in advancing pediatric cancer research. As neurosurgeons often encounter patients with CNS tumor manifestations, it is essential to understand the concepts of genomic medicine.

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AUTHOR'S DECLARATION

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Informed consent

This type of study does not require informed consent.

Author contributions

Conceptualization : JWK; Data curation : JWK; Formal analysis : JWK; Funding acquisition : JWK; Methodology : JWK; Project administration : JWK; Visualization : JWK; Writing - original draft : JWK; Writing - review & editing : JWK

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