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Cancer predisposition analysis and post-disclosure behaviors after screening in Japanese children

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Abstract

Germline pathogenic variants in cancer predisposition genes are found in approximately 10% of children with cancer, yet data regarding result disclosure and subsequent clinical actions in Japan remain scarce. To evaluate the frequency of germline pathogenic variants in children and to assess post-disclosure clinical actions, including surveillance and cascade testing in Japan. We retrospectively analyzed 188 patients diagnosed with cancer before age 20 and treated at the University of Tsukuba Hospital. Targeted sequencing panels were applied, supplemented by multiplex ligation-dependent probe amplification or direct sequencing when indicated. Variants were classified according to ACMG/AMP guidelines. Pathogenic or likely pathogenic variants were disclosed to patients and families upon consent, followed by counseling on surveillance and cascade testing. Germline pathogenic variants were identified in 20 patients (10.6%), most frequently in *DICER1, TP53, SMARCB1*, and *RB1*. Carriers more frequently had a family history of cancer and secondary malignancies ($p = 0.001$ and $p = 0.028$, respectively). Results were disclosed in 15 patients; among them, 9 initiated surveillance and cascade testing was performed in 7 families. Surveillance was not implemented when patients had died before disclosure or had not reached the recommended age. Families generally accepted the findings and participated in surveillance, consistent with Western reports. This study is the first in Japan to describe disclosure practices and subsequent actions following germline testing in pediatric cancer patients. Rates of surveillance and cascade testing were comparable to those reported internationally. These findings support incorporating germline testing into standard pediatric oncology care.

Introduction

Survival outcomes in pediatric cancer have improved markedly, and approximately 80% of patients now achieve long-term survival.[1] Beyond treating the primary disease, increasing attention has been directed toward long-term comorbidities and genetic cancer predisposition.[2] Previous studies have reported that 8%–15% of children with cancer carry germline variants in cancer-predisposition genes,[3–6] although prevalence varies substantially by cancer type and ethnicity.[3–10] With advances in genomic analysis and its broader clinical availability, genetic medicine has rapidly expanded in recent years. However, because pediatric cancers are rare, the extent of germline testing implementation and the current state of genetic medicine remain insufficiently characterized, with many aspects still unexplored. From a clinical management perspective, understanding a patient's genetic background, including the risks of developing specific diseases or symptoms, can enable better medical care. Conversely, awareness of genetic findings that appear to predetermine future health may have complex psychological, familial, and social implications. Therefore, when considering germline testing for each patient, it is important to recognize that result disclosure may entail not only benefits but also potential harms. Moreover, patients' attitudes and responses toward genetic medicine are likely to vary considerably depending on social systems, cultural background, religion, and healthcare infrastructure.

In Sweden, nationwide whole-genome sequencing has been performed for pediatric central nervous system (CNS) and non-CNS solid tumors.[9] Potentially pathogenic variants were identified in 11% of patients, and clinically significant findings that could guide surveillance strategies or therapeutic adjustments were obtained in 7%. In addition, several patients were newly diagnosed with primary immunodeficiency, leading to hematopoietic stem cell transplantation. However, details regarding whether surveillance was implemented or cascade testing of relatives was conducted were not reported.[9] At Memorial Sloan Kettering Cancer Center, potentially pathogenic variants were detected in 13%–18% of pediatric solid tumor cases,[3] of whom 76% attended a genetics clinic and 21% underwent cascade testing of relatives. In Japan, the National Cancer Center reported that 9% of patients with relapsed or refractory solid tumors carried germline pathogenic variants.[8] However, to date, no study in Japan has described the disclosure of germline testing results in pediatric cancer patients, nor has any report provided detailed information on subsequent actions such as cascade testing, implementation of surveillance, or modifications of clinical management following disclosure.

In this study, we conducted targeted gene analysis in Japanese pediatric cancer patients to determine the prevalence of germline pathogenic variants and to describe result disclosure, subsequent surveillance, and cascade testing. Genomic medicine has rapidly become integrated into pediatric oncology practice, driven by increasing accessibility and decreasing cost. Awareness of cancer predisposition among pediatric cancer patients is important not only for pediatric oncologists but also for general pediatricians, as such knowledge can help enhance the quality of patient care.

Methods

Patients

Patients diagnosed with cancer before the age of 20 between 1991 and 2025 who received treatment or long-term care at the University of Tsukuba Hospital from 2015 to 2025 were included. Patients were considered eligible if their participation was deemed appropriate by the treating physician, the study was explained, and informed consent was obtained. In most cases, written informed consent was provided by patients and/or their guardians. For some patients, analysis was conducted under an opt-out framework through public disclosure of an information document. Among the study population, 20 patients with rhabdomyosarcoma, 38 with brain tumors, and 6 with pleuropulmonary blastoma had previously been included in genomic analyses reported elsewhere.[4, 5, 11] Germline genomic analysis was conducted, and post-disclosure behaviors, including cancer screening and cascade testing, were assessed.

Ethical Approval:

This study was conducted in accordance with the principles of the Declaration of Helsinki. The protocol was approved by the Institutional Review Board of the University of Tsukuba Hospital (Approval No. H27-

167). Written informed consent was obtained from patients and/or their legal guardians in most cases. For some participants, an opt-out procedure through public disclosure

Genomic analysis

Genomic deoxyribonucleic acid (DNA) was extracted from non-tumor samples (such as peripheral blood or oral swabs) using standard procedures described previously.[12] For patients from whom sufficient DNA was obtained, targeted sequencing was performed using one of seven panels available at the time of analysis, encompassing 39–138 genes (Supplementary Table 1). Primers for targeted sequencing were designed with the AmpliseqDesigner™ (Thermo Fisher Scientific, Waltham, MA, USA), and sequencing was performed with the IonPGM™ system (Thermo Fisher Scientific) according to the manufacturer's instructions.

In selected cases, additional Multiplex Ligation-dependent Probe Amplification (MLPA) analysis was performed based on family history and/or specific cancer diagnosis, such as *SMARCB1* for atypical teratoid rhabdoid tumor (ATRT) or *TP53* for multiple primary cancers and adrenocortical carcinoma. MLPA was performed according to the manufacturer's instructions.[13] One patient with pleuropulmonary blastoma was analyzed only for *DICER1* exons by direct sequencing because an adequate DNA sample could not be obtained for targeted sequencing.

Variant classification process

Variants were excluded if they met any of the following criteria: allele frequency in the general population ≥0.0001; variant allele frequency <0.32; sequencing depth <20; classification as benign, likely benign, or of uncertain significance in ClinVar;[14] location outside exon or splice site regions; Combined Annotation Dependent Depletion (CADD)[15] score <20; prediction as benign by Sorting Intolerant From Tolerant (SIFT)[16] or tolerated by Polymorphism Phenotyping (PolyPhen);[17] or synonymous substitution. All remaining candidate variants were manually reviewed using Integrative Genomics Viewer (IGV),[18] and those with plausible evidence of presence were confirmed by Sanger sequencing. The pathogenicity of confirmed variants was assessed according to the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) guidelines.[19] Truncating variants consistent with the clinical phenotype, as well as those annotated as pathogenic or likely pathogenic in ClinVar, were classified as pathogenic.

Process of genetic result disclosure

For variants classified as pathogenic or likely pathogenic, results were disclosed to patients and/or their guardians only after consent to receive such information was obtained. Disclosure was conducted by a clinical geneticist, who explained the potential clinical implications of the variant and the likelihood of its presence in relatives. The preferences of patients and families regarding surveillance by geneticists or pediatric oncologists and continued follow-up in a genetics clinic were then confirmed. For those who

consented, surveillance and follow-up visits were implemented, and cascade testing was offered to family members who sought counseling at genetic clinics.

Statistical analysis

Categorical variables were compared between patients with and without pathogenic variants using the chi-square test or Fisher's exact test, as appropriate. Age at diagnosis was compared using the Mann–Whitney U test. A two-sided p value < 0.05 was considered statistically significant.

Results

Patient cohort

Genetic analysis was performed in 188 pediatric cancer patients (Table 1). The cohort included 49 patients (26%) with hematologic malignancies, 90 (48%) with solid tumors, and 49 (26%) with CNS tumors. The median age at cancer diagnosis was 6.5 years (range, 0.0–19.0). The numbers of patients with a family history of cancer and with second malignant neoplasms or predisposition-related health conditions were 47 (25%) and 7 (4%), respectively. In one patient with pleuropulmonary blastoma, DNA of sufficient quality for targeted sequencing could not be obtained. In another patient with pleuropulmonary blastoma, targeted sequencing was performed using a panel that did not include *DICER1*, and no pathogenic variant was detected. For these two patients, direct sequencing of the *DICER1* exon regions was conducted. Among patients with ATRT, six underwent additional *SMARCB1* analysis using MLPA. In 13 patients with a family history or tumor diagnosis suggestive of Li-Fraumeni syndrome, MLPA analysis of *TP53* was performed.

Pathogenic variants

Pathogenic variants were detected in 20 patients (10.6%). No significant difference was observed between genders in the prevalence of pathogenic variants. Patients with pathogenic variants tended to be younger at diagnosis, although this did not reach statistical significance (p = 0.051; Table 1). A family history of cancer and the occurrence of subsequent malignancies were significantly more frequent among patients with pathogenic variants (p = 0.001 and p = 0.028, respectively; Table 1). Pathogenic variants were most commonly detected in patients with pleuropulmonary blastoma, retinoblastoma, and CNS tumors, particularly ATRT (Figure 1). Detected genes included *DICER1* (n = 5), *TP53* (n = 3), *SMARCB1* (n = 3), *RB1* (n = 2), and *BRCA2*, *CHEK2*, *FANCI*, *MSH2*, *PTCH1*, *SLX4*, and *SUFU* (n = 1 each). Notably, the patient with an *MSH2* variant was diagnosed with fetal-onset cerebellar ATRT and also harbored a pathogenic *SMARCB1* variant. A total of 39 variants, including pathogenic, likely pathogenic, and variants of uncertain significance, were identified in 37 patients. Detailed information is provided in Supplementary Table 2.

Disclosure of genetic results

Of the 20 patients with pathogenic variants, those with heterozygous variants associated with autosomal recessive diseases were excluded from result disclosure. Genetic results were disclosed to 14 patients (70%), and surveillance screening was initiated in 9 (45%) (Table 2). Among the five patients who received disclosure but did not undergo surveillance, three had died before disclosure; one was a male infant with acute myeloid leukemia carrying a *BRCA2* variant; one was a school-aged male with a history of neuroblastoma carrying a heterozygous *ATM* variant; and in one case (case TA378), initiation of surveillance could not be confirmed.

Cascade testing

Cascade testing of family members was performed in six families (43%). Among disclosed cases in which cascade testing was not conducted, the cohort included two patients with ATRT harboring *SMARCB1* variants, one medulloblastoma patient with a *PTCH1* variant, two retinoblastoma patients with *RB1* variants, and one patient with undifferentiated sarcoma carrying a *TP53* variant. In two families, cascade testing was still under discussion at the time of manuscript preparation, and in another, its implementation status was unknown.

The mother of a patient carrying a heterozygous truncating *ATM* variant expressed mixed feelings about learning that such variants are associated with a slightly increased risk of breast cancer. However, she also conveyed gratitude for receiving this information, recognizing that it provided an opportunity for her daughter—the patient's sibling—to undergo early surveillance and potentially benefit from early detection. Cascade testing in this family remains on hold, and ongoing genetic counseling has been arranged.

In another family, the patient and relatives harboring a *TP53* pathogenic variant expressed positive views regarding the value of genetic testing, acknowledging that it could facilitate early diagnosis and cancer surveillance. Nonetheless, cascade testing was not pursued because of financial constraints.

A mother who had lost two relatives to cancers associated with an *MSH2* pathogenic variant described the result as deeply distressing but also expressed acceptance, recognizing that identifying the variant offers opportunities for early detection and treatment. She stated that, if familial risk could be known in advance, she would wish to share the information with her children and paternal relatives and encourage them to consider testing. In this family, cascade testing will be introduced sequentially to at-risk relatives as they reach appropriate ages, with ongoing genetic counseling currently in progress.

Discussion

In this study, we conducted germline genomic analysis in Japanese pediatric cancer patients and identified pathogenic variants in 10.6% of cases. Patients harboring pathogenic variants more frequently had a family history of cancer, second malignant neoplasms, or cancer predisposition–related conditions. Cascade testing was performed in 6 families (43%) among patients who received result disclosure.

In most patients with pathogenic variants, the results were disclosed. Following disclosure, disease-specific surveillance was initiated in nearly all cases for which such measures were deemed appropriate. Patients who did not undergo surveillance were typically those who had died before disclosure. One male infant carrying a *BRCA2* variant did not begin surveillance because he had not yet reached the recommended age for initiation at the time of disclosure.[20] Similarly, a school-aged male carrying an *ATM* variant did not undergo surveillance, as he was below the recommended age and because the oncogenic impact of *ATM* variants is considered moderate, with surveillance primarily directed toward breast cancer.[21] Importantly, patients and families generally accepted their underlying cancer predisposition and actively participated in disease-specific surveillance, recognizing its value for long-term health management. This observation is consistent with findings from Sweden, where more than 80% of patients underwent active surveillance or specialized clinical care following disclosure.[9] Cascade testing of family members was performed in approximately half of the families of patients who received disclosure, consistent with previous studies reporting that about one-third of families underwent such testing.[3] Notably, *SMARCB1* variants are frequently reported to occur de novo in patients, and cascade testing was therefore not routinely recommended at the time of disclosure in these cases.[22] In addition, in Japan, cascade testing often entails a substantial financial burden on families, which may have contributed to the limited rate of implementation.

As expected, patients carrying pathogenic variants were more likely to have a positive family history of cancer and to develop secondary malignancies (Table 1). This observation, although anticipated, represents the first confirmation of such an association in Japanese pediatric cancer patients. Previous studies in Japan have shown that patients with solid tumors who developed secondary cancers often carried pathogenic germline variants in cancer predisposition genes.[23] Our findings support these observations and further underscore the potential value of surveillance for both patients and their families.

The prevalence of germline pathogenic variants was 10.6% and varied markedly by cancer diagnosis (Figure 1). To our knowledge, this represents the first confirmation of such findings in Japanese pediatric cancer patients. Previous large-scale studies conducted in Western countries have reported that approximately 8%–13% of pediatric cancer patients harbor pathogenic or likely pathogenic germline variants.[3, 6, 10] Although the diagnostic distribution in our cohort differed from that of previously reported Japanese pediatric cancer populations,[24] the overall frequency of pathogenic germline variants was comparable. These results suggest that the prevalence of germline cancer predisposition genes among Japanese pediatric cancer patients is broadly consistent with that reported in Western populations. Similarly, the prevalence observed in patients with refractory solid tumors (9%) in a previous Japanese study[8] was comparable to our findings. Regarding the spectrum of detected genes, the predominance of *TP53*, *DICER1*, and *BRCA1/2* alterations was consistent with previous studies. However, no patients with *NF1* or *APC* variants—genes frequently reported in prior cohorts—were identified in this study.

Among patients with ATRT, approximately one-third have been reported to harbor germline alterations, most commonly in *SMARCB1.*[25] In our cohort, two of the three patients with pathogenic variants had exon deletions, consistent with prior findings. In patients with medulloblastoma, pathogenic variants were identified in three cases. Extensive genomic analyses have demonstrated that approximately 6% of medulloblastoma patients harbor germline cancer predisposition variants, with *SUFU* or *PTCH1* variants detected in about 20% of infants with the SHH subtype, findings broadly consistent with our results.[26] Notably, *SUFU* variant carriers are reported to represent nearly 30% of medulloblastoma cases, emphasizing the importance of cascade testing and family screening. In pleuropulmonary blastoma, germline *DICER1* variants have been reported in approximately 65% of patients,[27] and our study showed a comparable rate, suggesting that the prevalence of *DICER1* alterations is similar across ethnic groups. In retinoblastoma, approximately 40% of cases are bilateral and 60% unilateral. Germline *RB1* variants are detected in approximately all patients with bilateral disease or a positive family history and in about 10% of sporadic unilateral cases without family history.[28] The detection rate in our cohort was comparable to, or slightly lower than, that reported in previous studies. It has been estimated that 15%–20% of germline variants may remain undetected by sequencing alone; therefore, additional analyses such as MLPA or fluorescence in situ hybridization may improve diagnostic yield. However, none of the patients in our study exhibited clinical features suggestive of congenital anomaly syndromes such as 13q14 deletion syndrome.[29] Patients with rare entities such as pleuropulmonary blastoma and ATRT were particularly likely to harbor cancer predisposition variants. These findings highlight the importance of maintaining a high index of suspicion for underlying genetic predisposition when treating such patients.

In this study, we described the disclosure of cancer predisposition gene variants in Japanese pediatric cancer patients, as well as subsequent implementation of surveillance and cascade testing. Concerns among patients and families about harboring an inherited cancer predisposition were evident at the time of diagnosis, and a few exhibited unanticipated emotional reactions upon disclosure. Although some experienced psychological distress when accepting their predisposition, many demonstrated a proactive and positive attitude toward living with the results, as reflected by the relatively high rate of surveillance implementation. These findings suggest that offering germline cancer predisposition testing at the time of diagnosis in pediatric cancer patients is both acceptable and potentially beneficial for future clinical management.

This study has several limitations. First, it was conducted at a single institution with a relatively small sample size, which may not fully represent the genetic landscape of pediatric cancer predisposition in Japan. Second, different targeted panels were used at various time points, and not all cancer predisposition genes were included in each panel; consequently, some variants may have been missed. Third, follow-up information regarding surveillance and cascade testing was based on available clinical records and family reports, which may have led to underestimation of actual implementation rates. Furthermore, psychosocial outcomes and the long-term impact of disclosure on patients and families were not systematically assessed.

Future research should aim to establish multi-institutional or nationwide registries to comprehensively evaluate the prevalence and clinical impact of germline variants in Japanese pediatric cancer patients. Standardization of genetic testing panels and protocols, along with systematic collection of follow-up data, will be critical for assessing the real-world benefits and challenges of genetic medicine in childhood cancer. Moreover, studies addressing psychosocial consequences, cost-effectiveness, and ethical considerations of germline testing will be essential for developing evidence-based guidelines tailored to pediatric oncology in Japan.

Conclusions

In this study, we demonstrated the prevalence of germline cancer predisposition variants in Japanese pediatric cancer patients and, for the first time, reported subsequent implementation rates of surveillance and cascade testing. The rates of surveillance and cascade testing were generally consistent with those reported in previous studies. Because surveillance for affected patients may need to continue throughout life depending on the specific gene involved, and because cascade testing extends to family members, the expansion of cancer predisposition analysis in pediatric oncology is expected to become an integral and enduring component of medical care. Continued systematic evaluation of the benefits and challenges for patients and their families will be indispensable as this field evolves. Our findings highlight the importance of incorporating germline testing into the standard pediatric oncology care in Japan.

Abbreviations

Abbreviation	Full term
ACMG	American College of Medical Genetics and Genomics
AMP	Association for Molecular Pathology
ATRT	Atypical teratoid rhabdoid tumor
CNS	Central nervous system
CADD	Combined Annotation Dependent Depletion
DNA	Deoxyribonucleic acid
IGV	Integrative Genomics Viewer
MLPA	Multiplex Ligation-dependent Probe Amplification
PolyPhen	Polymorphism Phenotyping
SIFT	Sorting Intolerant From Tolerant

Declarations

Author Contributors Statement:

Hiroko Fukushima conceptualized and designed the study, developed the methodology, performed the formal analysis, curated the data, conducted the investigation, drafted the initial manuscript, coordinated data collection, and acquired funding. Hisato Suzuki and Emiko Noguchi contributed to the study methodology and reviewed and revised the manuscript. Sho Hosaka, Ryoko Suzuki, Yuni Yamaki, Masako Inaba, and Kumie Nagatomo collected data and reviewed and revised the manuscript. Emiko Noguchi and Hidetoshi Takada supervised the study and critically reviewed the manuscript. Hidetoshi Takada also contributed to funding acquisition. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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The funder supported consumables and sequencing costs for genetic analyses. The funder had no role in the design or conduct of the study, data analysis, manuscript preparation, or publication decisions.

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documents was applied instead of written consent.

Data availability statement:

Data will be made available from the authors upon reasonable request.

Previous report: Some of the results of this study were previously reported at the annual meeting of the Japanese Pediatric Society, held in April 2025 in Nagoya.

Competing Interests: The authors have no conflicts of interest relevant to this article to disclose.

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Figures

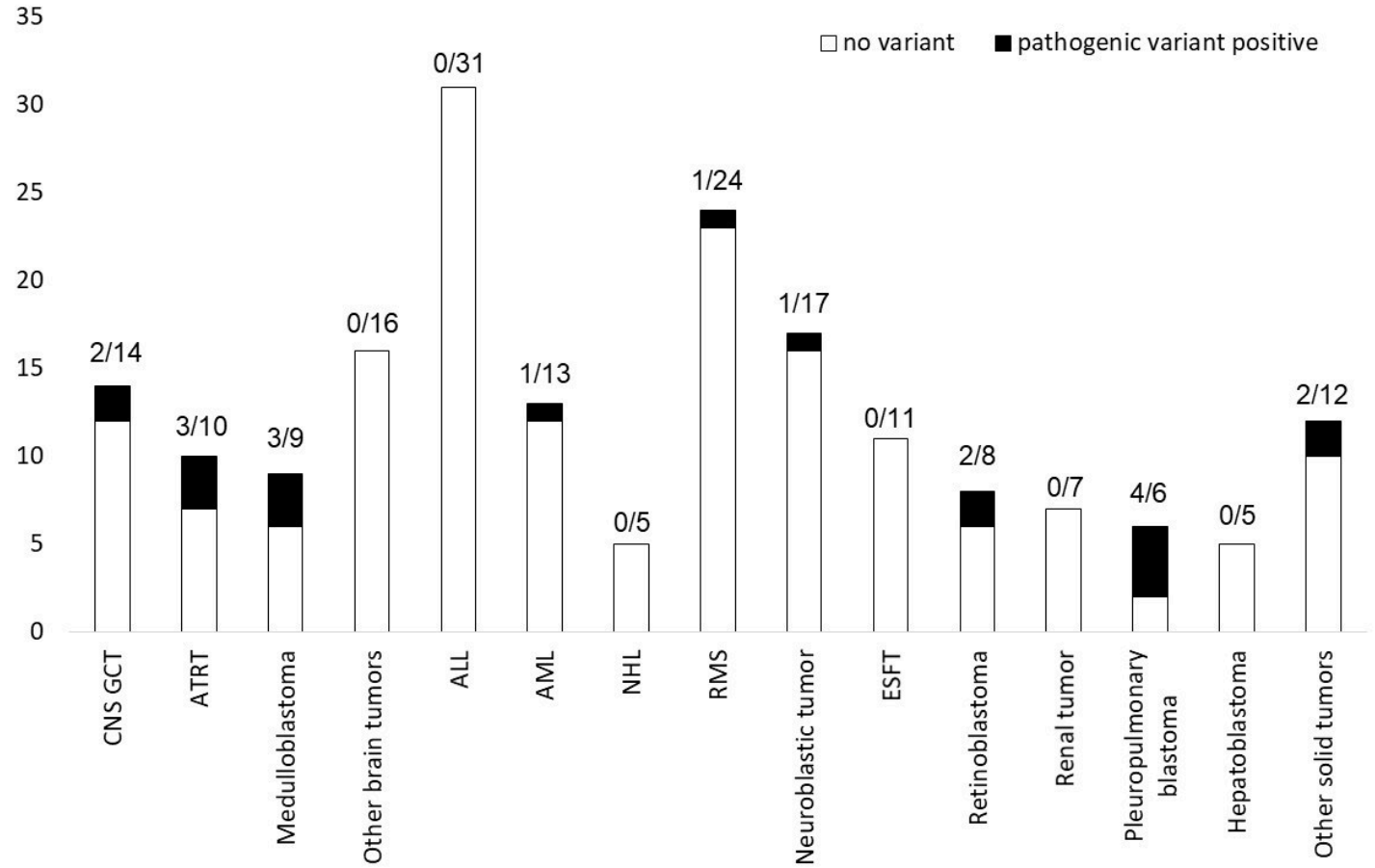


Figure 1

Prevalence of pathogenic and likely pathogenic germline variants across diagnostic categories.

The numbers of enrolled patients and the proportions harboring pathogenic or likely pathogenic germline variants are shown for each diagnostic category. The prevalence of germline variants was lower among patients with hematologic malignancies and higher among those with solid or brain tumors.

Abbreviations: CNS GCT, central nervous system germ cell tumor; ATRT, atypical teratoid/rhabdoid tumor; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; NHL, non-Hodgkin lymphoma; RMS, rhabdomyosarcoma; ESFT, Ewing sarcoma family of tumors.

Supplementary Files

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