Cancer Predisposition Syndromes in Children: Who, How and When Should Genetic Studies Be Considered?

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Abstract

Early detection of cancer predisposition syndromes (CPS) is crucial to determine optimal treatments and follow-up, and to provide appropriate genetic counseling. This study outlines an approach in a pediatric oncology unit, where 50 randomly selected patients underwent clinical assessment, leading to 44 eligible for genetic testing. We identified 3 pathogenic or likely pathogenic variants in genes associated with CPS and 6 Variants of Uncertain Significance (VUS) potentially associated with cancer development. We emphasize the importance of a thorough and accurate collection of family history and physical examination data and the full coordination between pediatric oncologists and geneticists.

Introduction

Unlike adult cancer, which is more commonly secondary to aging, environmental exposures and lifestyle habits, childhood cancer is remarkably different. No prominent causative factors have been identified except for rare cases involving cancers attributed to viral infections, radiation, oncological and immunosuppressive therapy. Recent studies have identified a cancer predisposition syndrome (CPS) in 10% of children with cancer[1-5]. The frequency of germline variants is different between tumor types but appears to be more significant in some malignancies such as central nervous system tumors and paraganglioma[6,7].

In routine pediatric oncology practice, detecting these syndromes can be challenging. There is a paucity of information regarding which patients should be studied, when screening should be performed (e.g., at diagnosis, at the end of the treatment), and which specific test should be done, if whole exome sequencing (WES), trio-whole exome sequencing or gene panels[8]. Moreover, interpreting the genomic results (based on established criteria[9]) can be overwhelming for clinicians.

Recent publications have reviewed the importance of early recognition of these syndromes[10-12] and clinical screening tools have been proposed to help identify the patients who carry higher risk. Particularly useful are the classic Jongmans criteria[13] and the recent McGill Interactive Pediatric OncoGenetic Guidelines (MIPOGG)[14-16].

Genetic studies may not be universally accessible within all healthcare systems. Consequently, it is crucial to prioritize the selection of patients eligible for such studies. Heterogeneous strategies are observed in various institutions, achieving similar outcomes[17-23].

There has yet to be a consensus on the best time to carry out the genetic study, whether at diagnosis, in the middle of, or at the end of treatment. The most crucial advantage of performing the CPS study at

diagnosis is adjusting the patient's treatment to perform personalized medicine. Avoiding radiotherapy in particularly sensitive patients (e.g., Li Fraumenni patients[24,25]), or choosing targeted therapy specific to the patient's syndrome (e.g. immunotherapy in patients with constitutional mismatch repair deficiency[26]), are some advantages of performing this study early. Nevertheless, delaying the family cancer appointment could provide an opportunity for more comprehensive information on treatment-related toxicity and family medical history.

There is no consensus on which genetic study to perform, whether a WES or a gene-targeted panel focusing on known genes associated with CPS[8]. Before the application of next-generation sequencing (NGS), single-gene analysis of specific high-risk genes was performed, a time-consuming and expensive approach. The widespread availability and implementation of NGS significantly enhance the efficiency of identifying individuals with CPS.

We present our experience in the recent years detecting patients with CPS by multigene panel analysis. We highlight the importance of dedicating a specific appointment with families to obtain a thorough and accurate clinical history and to increase the efficiency of the process.

Methods

Study design and participants

Ethical approval was obtained through the regional scientific ethical committee. Within the Pediatric Oncology department at HM Oncology Center (CIOCC), HM Monteprincipe, all children with a malignancy, who had finished their treatment were invited to participate in the study. Patients who already had a diagnosis of a CPS as an early approach in the acute phase or based on family history were excluded. A pediatric oncologist trained in genetic counseling explained the procedure, as well as its benefits and limitations. Informed consent was obtained from the patient (if age-appropriate) and/or their parent/legal guardian.

Consented patients underwent a comprehensive cancer susceptibility assessment with a pediatric oncologist, involving thorough physician examinations, extensive three-generation family history, and collection of tumor and somatic mutation data if available. Data were collected based on established risk factors associated with CPS and were recorded in a standardized form (Table 1). The malignancies included as frequently associated with CPS are described in the supplementary file (Table 1 of supplementary material).

Family History
Two or more neoplasia in family members before the age of 18 (including index case). Parents or siblings with cancer before

TABLE 1. Data collected in the familial cancer appointment.

If the patient met at least one criterion (listed on Table 1), blood samples were collected from the child and both parents. A targeted exome sequencing based on a panel of 110 genes frequently associated with childhood cancer was performed on the patient. The genes studied are shown in the supplementary file (Table 2 of supplementary material).

In each patient, we additionally gathered the same data (physical exam and family history) directly from the patient's medical record before this scheduled visit ("pre" data). Our objective was to assess whether the structured approach, in a dedicated medical appointment, and consistent data collection by the same oncologist or a trained associate, influenced the study's selection criteria outcomes.

Retrospectively, we have validated our selection criteria by comparing them with the results we would have obtained with one of today's most widely used tools, MIPOGG[14-16].

Whole exome sequencing

Genomic DNA from the proband's blood was isolated with an automatic system (MagnaPure, Roche). A library was prepared using Comprehensive Exome Panel technology (Twist Bioscience), sequenced on the

NovaSeq 6000 SystemTM (Illumina) and designed with the Comprehensive Exome Panel technology (Twist Bioscience) to capture over 20,000 genes, achieving more than 99% coverage of genes included in the RefSeq, CCDS, and GENCODE databases, encompassing over 85% of gene-mediated disease-related alterations and flanking splicing regions (5-20 bp). The library size is 41.2 MB. These processes were carried out at Nimgenetics laboratory.

Data alignment and calling with the reference genome (GRCh38/hg38) in the target regions (Twist_Exome_RefSeq_targets_hg38.bed) was performed with DRAGEN^{TM} software version 07.021.572.3.6.3. Variant annotation was carried out using custom software developed using NIMGenetics database and free publicly available sources. The analysis focused on identifying variants in exonic regions or splicing regions (at least 5 bp), including missense or nonsense mutations, synonymous mutations, small insertions or deletions (indels) with an allele frequency (VAF) greater than 30% of the reads. Identified variants were cross-referenced with specific databases like ClinVar for known phenotype associations and population frequency databases (dbSNP, gnomAD, 1000 Genome Project, or NHLBI-ESP 6500 exomes) to annotate variants commonly found in the general population (at least 1%). Pathogenicity of variants was estimated using CADD and a combination of prediction systems from the dbNSFP database (SIFT, PolyPhen2, MutationTaster, MutationAssessor, LRT, FATHMM, and MetaSVM) for missense mutations.

The impact of mutations in splicing regions on mRNA processing was evaluated using SpliceSiteFinder and MaxEntScan prediction systems. Nucleotide position conservation was assessed using UCSC score ranges from the PhyloP tool. The association of identified variants with OMIM syndromes was evaluated. The nomenclature and classification of variants follow the guidelines of the Human Genome Variation Society and the American College of Medical Genetics and Genomics. Geneticists and clinicians jointly interpreted the data in a multidisciplinary assessment process before issuing the final report.

Results

Description of the cohort

A random sample of 51 patients who had already finished treatment in our unir were approached for participation in this study. Acceptance was 98% with just one family refusing to participate. The 50 initial patients (ages ranging from 2 months to 22 years) were recruited from October 2019 to April 2022.

A detailed clinical description of the cohort is summarised in Table 2. The malignancies or hematologic problems are detailed in Table 3.

Total number of patients	**N**	**%**
	50	100
Sex		
Female	20	40
Male	30	60
Age at diagnosis	Median age (7,09 years)	Median age (7,09 years)
0-5 years	24	48
6-10 yr	12	24
11-15 yr	9	18
16-22 yr	5	10
Diagnosis		
Hematologic tumor	**9**	**18**
Solid tumor	**41**	**82**
Treatment		
Systemic treatment	21	42
Combined (Systemic+radiotherapy)	21	42
Radiotherapy	2	4
None	6	12

TABLE 2. Epidemiology. Systemic treatment includes chemotherapy, immunotherapy, immunosuppressive treatment, and hematopoietic stem cell transplantation. Non-systemic or radiotherapy refers to patients with surgical approaches exclusively.

Diagnosis	**50**	**100%**
Hematologic tumor	**9**	**18**
Acute lymphoblastic leukemia	**5**	
Non-Hodgkin Lymphoma	**2**	
Myelodysplastic syndrome/aplastic anemia	**2**	
CNS tumor	**10**	**20**
Medulloblastoma	2	
Ependymoma	3	
Glioma	3	
Schwannoma	1	
Glial neuroepithelial	1	
Sarcoma/Rhabdomyosarcoma	**17**	**34**
Osteosarcoma	3	
Rhabdomyosarcoma	8	
Ewing sarcoma	4	
PNET	2	
Non-CNS embryonal tumor	**10**	**20**
Neuroblastoma	7	
Nephroblastoma	2	
Hepatoblastoma	1	
Other	**4**	**8**
Lung neuroendocrine tumor	1	
Non-Langerhans cell histiocytosis	1	
Leydig cell tumor	1	
Melanoma	1	

TABLE 3 . Description of the tumors presented by our patients. Abbreviations: CNS: Central Nervous System. PNET: Primary peripheral neuroectodermal tumor.

Patient selection

We scheduled specific appointments with families to collect comprehensive information about the family's cancer history, any available molecular tumor data, and physical examination. If they met any criteria outlined in Table 1, we conducted genetic testing on the patient and their parents. Out of 50 patients, 44 (88%) met at least one criterion and underwent genetic testing, while the remaining 6 patients (12%) were excluded from the study. Results and workflow are shown in Fig.1.

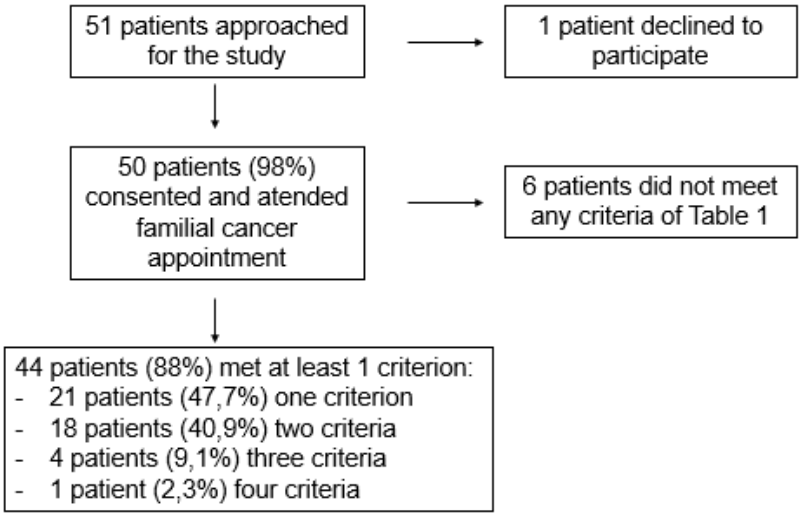

Figure 1. Workflow and results of selected patients.

Of the patients, 47,7% met only one criterion, 40,9% met two criteria, 9,1% met three criteria, and 2,3% met four criteria. 16 patients were selected by family history (32%), 31 patients (50%) were selected by tumor type (24 by tumor diagnosis and 7 by the presence of a somatic variant detected in the tumor). 14 patients (28%) met the criteria for a compatible phenotype, and 11 patients (22%) due to experiencing high toxicity during treatment.

The patients selected by mutations present in the tumor were:

- High-grade neuroepithelial tumor with variants in BAP1 and BCOR in tumor.
- Two patients with neuroblastoma and ALK somatic variant identified in the tumor.
- Patient with osteosarcoma a TP53 somatic variant identified in tumor
- Patient with medulloblastoma and a TP53 somatic variant identified in tumor
- Patient with parameningeal rhabdomyosarcoma that presents in the tumor an NF1 rearrangement and a BCOR loss.
- Patient with schwannoma and deletion of FANCL in tumor.

"Pre-data" and "post-data" information were compared. Interestingly 24% of patients did not meet any criteria on the "pre-data" evaluation (at diagnosis), but did meet at least one criterion on the specific appointment for familial cancer (post-data) (Figure2).

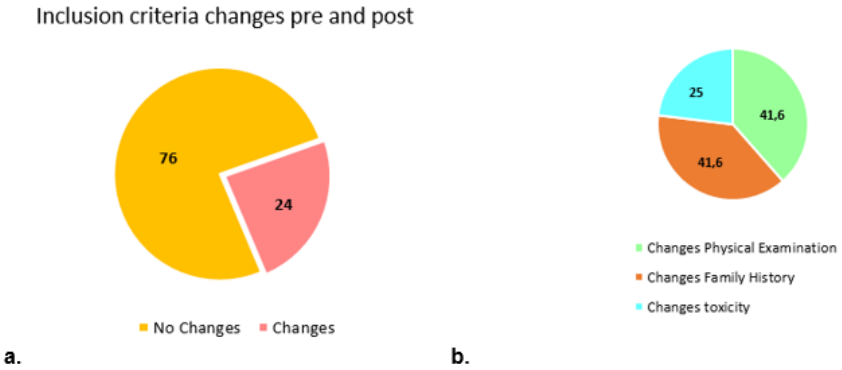

Figure 2. Inclusion criteria pre-data and post-data. a. Number of patients that change their criteria in the pre-data evaluation (diagnosis) and in the post-data (specific appointment)**. b.**Differences between the criteria met at diagnosis (pre-data) and the specific appointment (post-data).

In comparing the selection criteria with the MIPOGG tool, patients who did not meet any criteria in our study similarly did not meet criteria with MIPOGG. However, there are 9 patients whom the MIPOGG tool would not refer for genetic study, but who were investigated according to our criteria. Overall, the concordance rate was 82%.

Genetic Variants Identified

Out of the 50 patients, in 3 (6%), pathogenic or likely pathogenic genetic variants that could explain their phenotype were found. In 6 patients (12%) we identified a VUS, which after reviewing the published data on the variant/gene and the patient's clinical history, we found that the variant could be related to the patient's phenotype (Fig. 3, Table 4). Overall, variants potentially associated with cancer development were identified in 18% of the studied patients.

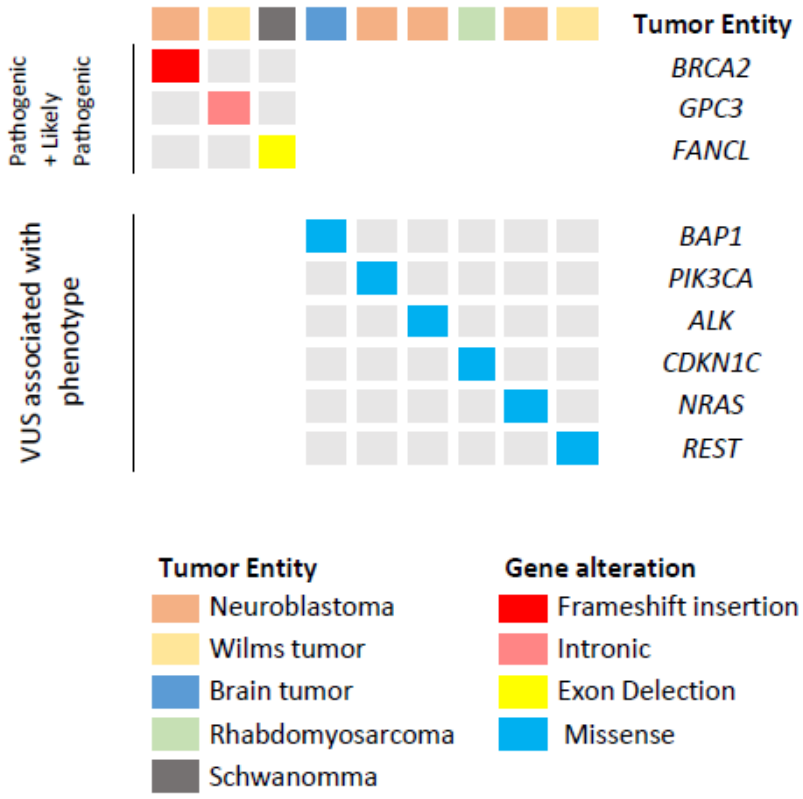

Figure 3 . Overview of pathogenic/likely pathogenic variants and VUS associated with phenotype. We identified 3 pathogenic or likely pathogenic variants in genes associated with cancer predisposition syndrome as well as 6 VUS potentially associated with the development of cancer in these patients.

Diagnosis (age)	Gene/ transcript	Chromosomal position in bp (hg19)	Chromosomal position in bp (hg19)	Nucleotide /aminoacid change	Category	Zygosity	Origin	Clinica signs/

Neuroblastoma (1 month)								
NM_-000059.3	*chr13 g.32914515*	*c.6024dup p.Gln2009Alafs*9 A/AG*	*c.6024dup p.Gln2009Alafs*9 A/AG*	*Pathogenic*	*Heterozygous*	*Mother*	*Family history of breast cancer*	
Wilms Tumor (22 y)								
NM_-004484.3	chrX g.132838281	c.1033-4225G>A T/T	c.1033-4225G>A T/T	Likely Pathogenic	Heterozygous	Mother		
Schwannoma (6y)	FANCL	chr2 : 58386860-58390670	9-14 Exon deletion	9-14 Exon deletion	Pathogenic	Heterozygous		Present as well in the tumor and detecte by MLPA
Glial neu-roepitelial Brain Tumor (2 y)								
NM_-004656.3	*chr3 g.52438516_-52438518*	*c.1201_-1203delins-GAG p.Tyr401Glu*	*c.1201_-1203delins-GAG p.Tyr401Glu*	*VUS*	*Heterozygous*	*Father*	*Presented as well in the tumor. BCOR mutation in the tumor*	
Neuroblastoma (18 months)								
NM_-006218.3	chr3 g.178916677	c.64G>A p.Val22Ile	c.64G>A p.Val22Ile	VUS	Heterozygous	Father	ALK mutation in tumor	
Neuroblastoma (15 months)								
NM_-004304.4	*chr2 g.29498276*	*c.1904A>G p.Tyr635Cys*	*c.1904A>G p.Tyr635Cys*	*VUS*	*Heterozygous*	*Mother*		
Rhabdomyosarcoma (6 y)								

NM_-000076.2	chr11 g.2906145	c.575C>G p.Pro192Arg	c.575C>G p.Pro192Arg	VUS	Heterozygous	De novo	Neuroblastoma (7 months)
NM_-002524.5	*chr1 g.115252309*	*c.331A>G p.Met111Val*	*c.331A>G p.Met111Val*	*VUS*	*Heterozygous*	*Father*	
Wilms Tumor (13 months)	REST *NM_-001193508.1*	*chr4 g.57796160*	*c.1136A>G p.His379Arg*	*c.1136A>G p.His379Arg*	*VUS*	*Heterozygous*	*Father*

TABLE 4 . Pathogenic or likely pathogenic variants and VUS associated with phenotype.

Among the 9 patients in whom we identified pathogenic/likely pathogenic or VUS likely associated with the phenotype, 8 (88.8%) met the tumor type criteria. This finding aligns with previous studies highlighting the significance of tumor type in the suspicion of a CPS[6,7].

Among the seven patients studied for tumor mutation, in two patients (28.57%) such mutation was found to be germline. This was observed in the patient with somatic variant in BAP1 and BCOR in tumor (both germline and somatic mutations were identified in BAP1), and the patient with exon deletion of FANCL in tumor (the same deletion was found in germline by MLPA).

Discussion

This study outlines an approach to investigating familial cancer within a pediatric oncology unit from October 2019 to April 2022. Before initiating this project, only patients with a substantial family history or highly distinctive phenotypes were subject to investigation. The primary change implemented in the study was the establishment of a dedicated appointment for familial cancer assessment.

Based on the results found, our study revealed that 24% of the patients demonstrated a shift in their eligibility for genetic testing when assessed at a later stage in the oncological process. This leads us to recommend scheduling a dedicated appointment for the assessment of CPS in pediatric cancer patients, considering that all the necessary data may not be available at the time of diagnosis.

The most common reason for changes in the criteria "pre-data" vs "post-data" is the physical examination and family history. This discrepancy may occur because certain phenotypic features were not initially observed at diagnosis or because the patient underwent physical changes that were not apparent during the initial examination. A similar situation arises with family history. In some cases, family history data was inaccurately reported by the families at the time of diagnosis, or new family members may be subsequently diagnosed with cancer during the patient's follow-up. The study of CPS should also be dynamic, and patients who initially do not meet the criteria should be re-evaluated as new family data becomes available.

In terms of the percentage of patients in whom a pathogenic or likely pathogenic variant has been identified, our study revealed such variants in 6% of patients in our cohort. This percentage is lower than reported in the literature[1-5], most likely attributed to excluding of patients with specific phenotypes.

Screening all children with cancer is of significant research interest, however it is accompanied by the trade-off of the cost and reduced chances of identifying pathogenic variants in patients who do not meet any risk criteria. This, in turn, presents challenges in managing the uncertainty associated with VUS. In the context of our research, we have observed that it is prudent to exclude patients with a strong suspicion of a particular syndrome. Conducting a WES in such cases may be unnecessary, as they can be studied more selectively. Moreover, these selective studies tend to be more cost-effective and are typically covered by the patient's insurance. For the remaining patients, we have implemented clinical screening, which considers factors such

as family history, physical characteristics, and, most importantly, the type of tumor. The type of tumor has been shown to be the most influential factor in detecting CPS.

Selecting patients by a clinical screening aligns with existing literature, notable supported by the 2022 review conducted by Rossini et al[17], which discusses various strategies for studying familial cancer in pediatrics. The authors concluded that the most efficient approach is to study patients selected using any of the clinical tools described[10,13,14,17.]

In terms of determining the most effective genetic approach, whether WES, trio-WES, a multigene panel, or single gene analysis, there are limited studies available for comparing their advantages and specific indications[8].

The clinical approach is crucial, and if a specific syndrome is suspected, a single gene analysis is the preferred option. We recommend a multigene panel for clinical use due to its comprehensive gene coverage and targeted information retrieval. WES and whole genome sequencing should be reserved for research purposes, patients with unclear cancer or multisystem phenotypes, and those with negative or inconclusive results from previous single-gene or multigene testing. Certainly, if resources are available, the most comprehensive information can be obtained through WES, ideally complemented by pairing the results with tumor sequencing.

There is some controversy regarding the detection of mutations in genes associated with the development of cancer in adulthood. In the study by Sylvester et al[5], which compiles the results from six different cohorts of pediatric patients investigated for the presence of CPS, various approaches are employed. In all cases, genes related to adult-onset cancer, such as BRCA2, MSH2 and MSH6, are examined. In the combined analysis of the 6 cohorts, 0.4% of patients were found to carry pathogenic or likely pathogenic variants in BRCA1 and 0.5% in BRCA2[5]. The tumors most frequently associated included medulloblastoma, neuroblastoma (as in the case of our patient), and acute lymphoblastic leukemia. Concurrently with the identification of BRCA2 in our patient, a 30-year-old maternal aunt, that had not been previously referred to genetic testing, was diagnosed with breast cancer. Cascade testing was then performed, and the mutation was identified in the mother, who was informed of the results, leading to the entire family to undergo genetic counseling.

We advocate for a collaborative approach to the study of CPS, involving pediatric oncologists and geneticists. The continuity of care through regular check-ups in pediatric cancer patients, allows for timely updates on any occurrences of new tumors in the family. Geneticists are crucial in guiding the approach to cancer predisposition studies and interpreting genetic tests. Genetic counseling and the long-term follow-up of patients and their families with CPS should be a collaborative effort involving pediatric oncologists, geneticists, and adult oncologists.

Conclusions

The role of the pediatric oncologist in collaboration with geneticists is fundamental in the study of familial childhood cancer. We recommend genetic testing by NGS (WES or target panel exome) in all patients if possible. If it is not possible to test all patients, the care team should ensure that all patients meeting any risk criteria for having a CPS are tested. Only in cases of high clinical suspicion of a particular syndrome, a targeted gene study is an option.

A thorough and accurate family history and a comprehensive physical examination for syndrome-related data are critical in identifying patients who are candidates for CPS risk screening. Dedicating a specific appointment to this topic may increase the likelihood of identifying these patients. This appointment may be more practical not at the time of initial diagnosis, but later in the course of the disease, when the initial concerns of the patient and the family have been addressed.

Declaration of interest statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Acknowledgements

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