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REVIEW

The genetic era of childhood cancer: Identification of high-risk patients and germline sequencing approaches

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Abstract

Childhood cancer is a leading cause of death by disease in children ages 5–14, for which there are no preventive strategies. Due to early-age of diagnosis and short period of exposure to environmental factors, increasing evidence suggests childhood cancer could have strong association with germline alterations in predisposition cancer genes but, their frequency and distribution are largely unknown. Several efforts have been made to develop tools to identify children with increased risk of cancer who may benefit from genetic testing but their validation and application on a large scale is necessary. Research on genetic bases of childhood cancer is ongoing, in which several approaches for the identification of genetic variants related to cancer predisposition have been used. In this paper, we discuss the updated efforts, strategies, molecular mechanisms and clinical implications for germline predisposition gene alterations and the characterization of risk variants in childhood cancer.

KEYWORDS
cancer prevention, childhood cancer, genetic predisposition

1 | INTRODUCTION

Childhood cancer is a leading cause of death by disease in 5- to 14-old children for which there are no prevention strategies. The last report of the International Agency for Research on Cancer (IACR) showed considerable variation in the incidence by age, sex and geographic regions. In high-income countries (HIC), the global incidence of childhood cancer increased up to 1% per year (Steliarova-Foucher et al., 2017). High-income countries (HIC) have improved survival rates with approximately 80% surviving 5 years after diagnosis. While in low- and middle-income countries (LMICs), where nearly 90% of children with cancer reside, limited data suggests lower estimates of overall survival (Bhakta et al., 2019). Racial and ethnic disparities in survival rates have been reported, mainly associated with socioeconomic status and access to medical care, however, the impact of genetic differences between populations is not well described (Bhatia, 2011). The causes of childhood cancer are not yet clear. Unlike adult cancer, only a few environmental factors have been associated with cancer risk including radiation, prior chemotherapy, parental exposure to pesticides (Patel et al., 2020), benzene, polycyclic aromatic hydrocarbons (PAHs) (Carlos-Wallace et al., 2016), and smoking (Metayer et al., 2016), the confirmation of their real role on cancer risk remains a

challenge, mainly due to the difficulty of recruiting a large and representative sample in order to obtain statistical significance. Next Generation Sequencing (NGS) has improved the understanding of the genetic bases of childhood cancer. While Whole Genome Sequencing (WGS) is the most comprehensive technique that identifies variants in coding and noncoding regions, Whole Exome Sequencing (WES) is a cost-effective approach, detecting up to 85% of disease-causing variants and finally, Targeted Analysis Sequencing (TAS) focuses on a panel of genes known to have strong associations with specific cancer predisposition syndromes.

Recent findings have shown that childhood tumors have 14 times lower somatic alterations than adult tumors (except patients with germline deficiencies in mismatch repair, MMR) (Gröbner et al., 2018). A possible explanation includes the fact that somatic mutations are accumulated in normal tissue during aging or as a result of environmental exposure to carcinogens, as it has been observed in tumors that have developed from premalignant lesions, which have been growing and accumulating alterations many years before diagnosis (Martincorena et al., 2018). Another hypothesis proposed is that germline mutations have greater functional impact than somatic mutations and therefore, require fewer somatic mutations to reach a critical level of alterations in cancer hallmark genes (Qing et al., 2020).

Increasing evidence is highlighting the role of germline genetic variants in childhood cancer risk. Staler and colleagues performed germline sequencing in 1201 individuals and found that 21% of patients with early-onset cancer had an inherited genetic alteration, compared with 13% of patients with young-adult cancer (Staler et al., 2020). In fact, it is estimated that pathogenic germline alterations can be present in up to 30% of all pediatric oncology patients (Walsh et al., 2014).

Elucidating the molecular bases of genetic variants and their implications in screening, diagnosis, treatment and surveillance of childhood cancer could help to improve its prevention and clinical outcomes in middle and low-income countries.

2 | GENETIC PREDISPOSITION

The laws of inheritance were crucial to understand the patterns of monogenic disorders. The first genes associated with cancer predisposition were discovered in affected families by linkage analysis using the Mendelian approach; since then, several childhood tumors have been associated with cancer predisposition syndromes with both, dominant and recessive inheritance, due to alterations in DNA repair genes (Table 1).

Recent reports have shown a high frequency in germline alterations in childhood cancer patients. Jinghui Zhang et al. reported that 8.5% of 1120 patients under the age of 20 were carriers of germline alterations in *TP53, APC, BRCA2, NF1, PMS2, RB1*, and *RUNX1* genes, compared to 1% of the control group; interestingly, only 40% of carriers reported a family history of cancer (Zhang et al., 2016). Pan-Cancer analysis showed a similar frequency of alterations to that reported by Zhang, where 7.6% were associated with pathogenic germline variants in *MSH2, MSH6, PMS2, TP53, BRCA2*, and *CHEK2* genes (Gröbner et al., 2018). The highest percentage of germline alterations in childhood cancer to date, was reported by Oberg et al. (Oberg et al., 2016), where 14% of children who underwent WES were carriers of alterations in cancer predisposition genes. Although previous studies included higher number of individuals, they have some limitations: First, not all tumors types were included and some of them have shown a strong association with germline alterations (e.g., up to 55% of sarcoma patients harbored at least one pathogenic germline alterations) (Ballinger et al., 2016); second, the inheritance and origin of the alterations could not be established because the sequencing testing did not include parents or relatives and third, environmental factors were not evaluated. For these reasons, it is necessary to conduct more family-based germline sequencing studies in order to establish the origin of the alterations (father, mother or de novo), gene–environment interaction and evaluation of penetrance or expressivity.

Some ongoing research lines are coordinated mainly by the National Institutes of Health (NCI), The Children's Oncology Group (COG) and *The Société Internationale d'Oncologie Pédiatrique* (*SIOP*). In clinicaltrials.gov, there are 5 genetic studies in progress: SJFAMILY and Next Generation Sequencing of Normal Tissues Prospectively in Pediatric Oncology Patients by St. Jude Children's Research Hospital (NCT03050268 and NCT02530658, respectively), The Childhood Cancer Predisposition Study (CCPS) (NCT04511806), which is a multicenter study, DICER1 related Pleuropulmonary Blastoma Cancer Predisposition Syndrome by NCI (NCT01247597) and EXO-CARE by University Hospital, Angers (NCT03472807). The Childhood Cancer Survivor Study (CCSS) includes the evaluation of genetic variants implicated in the risk of second primary neoplasms (The Childhood Cancer Survivor Study [CCSS]), which is coordinated by the National Institutes of Health, St. Jude Children's Research Hospital and 30 other centers.

2.1 | Multifactorial inheritance

Even though Mendelian inheritance has been strongly implicated in childhood cancer predisposition, only 8–10% of tumors have been attributed to monogenic disorders, so, the challenge is to find an explanation for the remaining cases.

TABLE 1 Childhood tumors associated with predisposition syndromes

Tumor	Predisposition syndromes	Related gene alterations
Leukemia	Fanconi anemia, Neurofibromatosis type 1, Ataxia-telangiectasia, Li-Fraumeni, Nijmegen, hereditary retinoblastoma	FANCA, FANCB, BRCA, NF1, ATM, TP53, RB1
Lymphoma	Neurofibromatosis type 1, Ataxia-telangiectasia, Wiskott-Adrich, Bloom, Nijmegen, Li-Fraumeni, Beckwith-Wiedemann	NF1, ATM, WASP, BLM, NBS1, TP53, BRCA, (CDKN1C, H19, IGF2, KCNQ1OT1).
CNS tumors	Rhabdoid tumor, Li-Fraumeni, Noonan, Multiple endocrine neoplasia type 1, Neurofibromatosis type 2, ATM, Beckwith-Wiedemann, Li-Fraumeni, Von Hippel Lindau, DICER1	SMARCB1, TP53, RAS, MEN1, NF2, ATM, (CDKN1C, H19, IGF2, KCNQ1OT1), TP53, VHL, DICER1
Neuroblastoma	Neurofibromatosis type 1, Li-Fraumeni, Beckwith-Wiedemann, Noonan	NF1, TP53, (CDKN1C, H19, IGF2, KCNQ1OT1), RAS
Retinoblastoma	Hereditary retinoblastoma	RB1
Renal tumors	Beckwith-Wiedemann, Li-Fraumeni, Denysh Drash	(CDKN1C, H19, IGF2, KCNQ1OT1), TP53, WT1
Hepatic tumors	Beckwith-Wiedemann, Li-Fraumeni, Fanconi anemia	(CDKN1C, H19, IGF2, KCNQ1OT1), TP53, FANCA, FANCB, BRCA
Malignant bone tumors	Li-Fraumeni, hereditary retinoblastoma, Beckwith-Wiedemann,	TP53, RB1, (CDKN1C, H19, IGF2, KCNQ1OT1)
Soft tissue sarcoma	Li-Fraumeni, hereditary retinoblastoma, Neurofibromatosis type 1, DICER1, Beckwith-Wiedemann	TP53, RB1, NF1, DICER1
Germ cell tumors	Denysh Drash, Cowden, Noonan, Peutz-Jeghers	WT1, PTEN, RAS, STK11
Epithelial tumors	Li-Fraumeni, Beckwith-Wiedemann, Xeroderma pigmentosum, familial melanoma	TP53, (CDKN1C, H19, IGF2, KCNQ1OT1), (XPA—XPG y ERCC5), CDKN2A

Genome Wide Association Studies (GWAS) have shown the role of common genetic variants (Single Nucleotide Polymorphism, SNP) in complex diseases. Although GWAS have been very useful in the identification of novel variant trait associations, in the discovery of new biological mechanisms and explaining the role of ethnic variation, they still have limitations for the identification of causal variants and only explain a modest fraction of the missing heritability. In fact, it is thought that discrepant findings seen in GWAS are due to real biological differences, as the genetic diversity of populations (Tam et al., 2019). One of the most important findings of GWAS studies is that several SNPs could have a cumulative cancer risk and can also be acting as genetic modifiers (enhancer or suppressor) along with disease causing variants, resulting in oligogenic and polygenetic disease, with differences in penetrance or expressivity or quantitative genetic epistasis (Figure 1) (Rahit & Tarailo-Graovac, 2020).

In the last 10 years, the number of GWAS studies has increased dramatically due to the lower cost of high throughput sequencing techniques and, thousands of variants with moderate or low penetrance have been identified and associated with cancer. Although there are fewer GWAS of childhood cancer compared with adult cancer, L.A Raynor et al. measured the differences in the Odds Ratios (ORs) between younger and adult onset cancer using data from National Human Genome Research Institute (NHRGI) Catalog of Published GWAS, the results showed that ORs in childhood and young cancer were significantly higher than in adult cancer, explaining a greater proportion of the population's attributable risk, however, further studies are needed in order to evaluate the impact of these variants on early detection, treatment and prevention (Raynor et al., 2013).

Childhood cancer presents a unique situation in which a limited amount of time has elapsed for carcinogenic factors to have caused necessary genetic mutations compared with adult malignancies. The additive effect of low-penetrance genetic variants as polymorphisms in xenobiotic metabolizing enzymes (XMEs) or the innate immune system may play a primary role in cancer development in children.

XMEs include a group of Phases I and II enzymes that metabolize carcinogenic substances such as pesticides, petroleum products, and PAHs. Phase I enzymes consist of cytochrome P450 (CYP450) dependent monooxygenases that increase the hydrophilicity of lipophilic substrates through oxidative, reductive, or hydroxylation reactions. Phase II enzymes are cytosolic enzymes involved in conjugation reactions wherein hydrophilic moieties such as glutathione, nicotinamide adenine dinucleotide, and

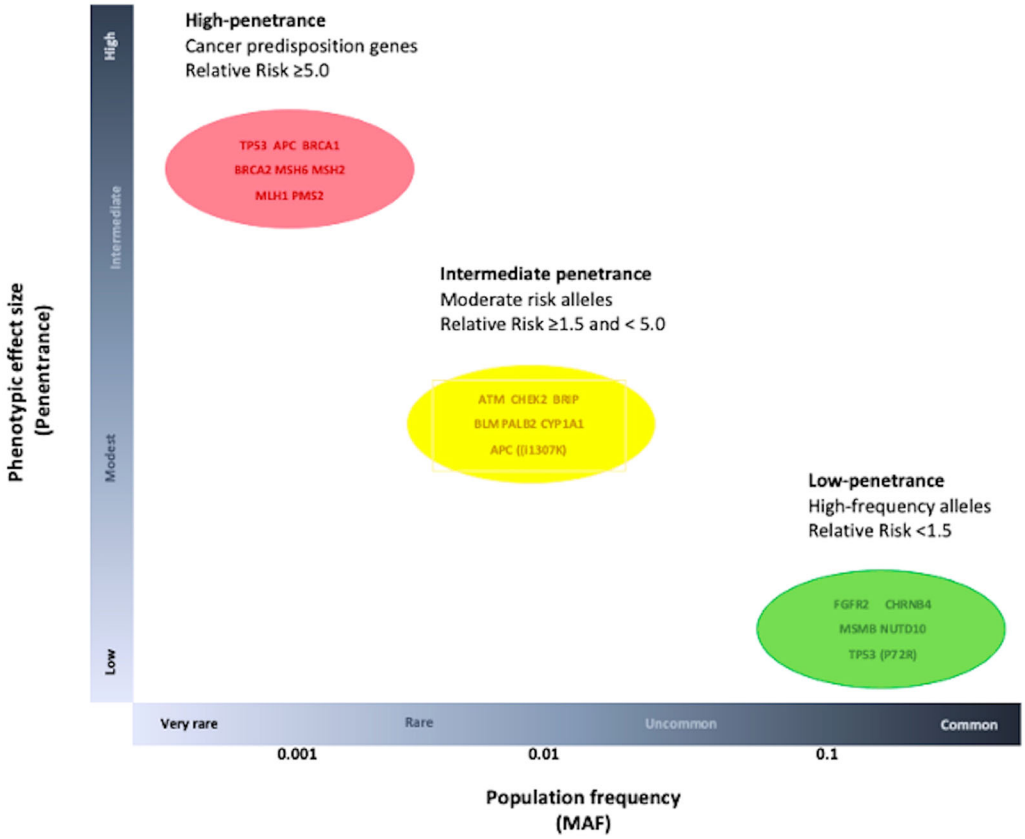

FIGURE 1 The diversity of genetic variants. Disease-causing variants in genes predisposing to cancer occur with low frequency (MAF > 0.01), and their phenotypic effect size is high. Conversely, genetic association studies have shown that common genetic variants or risk alleles (MAF > 0.01) may contribute to low to moderate risks in various tumors. (Minor Allele Frequency, MAF).

acetyl groups are attached to lipophilic substances and Phase I enzyme products, that promote subsequent excretion from the body. XME polymorphisms can have significant impacts on cancer susceptibility based on the gene, the enzyme's substrate, the tissues within which the enzyme is predominantly expressed, and the extent of subsequent genotoxicity (Swinney et al., 2006). On the other hand, dysfunction of the innate immune system could be a determinant in the susceptibility of different types of cancer because of deficiencies in leukemogenesis or host immunity response (Han et al., 2010).

The majority of research has focused on Acute Lymphoblastic Leukemia (ALL) owing to the relatively large number of cases when compared with other childhood cancers, but some relevant high-risk SNPs associated with ALL and other childhood tumors are listed in Table 2 (Plon & Lupo, 2019).

The lack of GWAS studies in childhood cancer is mainly due to the large number of individuals required and, childhood cancer only represents 1% of all cancer cases, however, GWAS meta-analysis improves the power of association and validates the consistency or heterogeneity across different datasets and populations (Evangelou & Ioannidis, 2013).

The small part of the risk of disease identified by GWAS may be due to the hypothesis of "common disease-common variants," because of this, epidemiological studies are needed in order to evaluate the interactions of lifestyle and environmental factors with low or moderate penetrance variants.

2.2 | Mother to child transmission

Although transplacental transmission of cancer to fetus is rare due to the placental barrier and fetal alloimmune response, mother to child transmission of cancer has been reported in 18 children younger than 2 years of age, presumably by the transplacental route with dissemination of maternal tumor cells to multiple organs. A recent report showed two cases of lung cancer in children probably caused by transmission of cervical tumors from the mothers, which was confirmed after histopathology and tumor-normal sequencing in children and mother's

TABLE 2 High-risk SNPs identified in GWAS of childhood cancer

Tumor	Gene /locus	Variant	Reference
Acute lymphocytic leukemia	CYP1A1	rs4646903 C > T	PMID: 18691756
	GSTM1	rs1065411G > C	PMID: 14973099
	ARID5B	rs10821936 C > A; C > T	PMID 22422485
		rs10994982 A > C; A > G	PMID 23692655
	IKZF1	rs11978267 A > G	PMID 23692655
		rs4132601 T > G	PMID 25012940
	CEBPE	rs2239633 G > A	PMID 22422485
	CDKN2A	rs3731249 C > A; C > G; C > G	PMID 26104880
		rs3731217 A > C; A > T	PMID 20453839
	GATA3	rs3824662 C > A; C > G; C > T	PMID 24141364
	PIP4K2A	rs2230469 T > A; T > C	PMID: 23996088
Neuroblastoma	CASC15/NBAT-1	rs6939340 A > G	PMID 18463370
	BARD1	rs6435862 G > A; G > C; G > T	PMID 19412175
	LMO1	rs110419 A > G; A > T	PMID 21124317
	LIN28B	rs17065417 A > C	PMID: 22941191
	HACE1	rs4336470 C > T	
	HSD17B12	rs11037575 C > T	PMID: 28435286
Ewing Sarcoma	TARDBP	rs9430161 G > T	PMID 22327514
	EGR2	rs224278 C > T	
	SRP14-AS1	rs4924410 A > C	
	CD86	rs1129055 G > A ; G > C	PMID 21563968
	20p11.22	rs6047482 T > A	PMID: 30093639
	20p11.23	rs6106336 T > G	
Wilms tumor	DDX1	rs3755132 T > G	PMID: 22544364
	2p24	rs807624 G > C; G > T	
	DLG2	rs790356 G > A	
Osteosarcoma	GRM4	rs1906953 C > T	PMID 26276359
	2p25.2	rs7591996 A > C; A > G; A > T	PMID: 23727862
	IGF2R	rs998075 A > G	PMID: 21437228
	MDM2	rs2279744 T > G	PMID 15550242
Hepatoblastoma	TP53	rs1042522 C > G	PMID: 31293648
Retinoblastoma	MDM2	rs2279744 T > G	PMID: 22180099
	CDKN1A	rs1801270 C > A; C > T	PMID: 24045412
Germ cell tumors	BAK1	rs210138 A > C; A > G	PMID: 28295819
	GAB2	rs948662 A > C; A > G	

tumors, confirming the usefulness of this tool to diagnose cancer transmission (Arakawa et al., 2021).

2.3 | Gene–environment interaction (GxE)

Besides high-dose radiation and prior chemotherapy, there are few environmental factors that have been associated with childhood cancer risk (OR > 2); factors such as birth weight, parental age, and congenital anomalies are consistently associated, while exposures to alcohol, coffee, tobacco, vitamins, and electromagnetic fields during preconception, pregnancy and postnatal periods have shown inconsistent results (Spector et al., 2015). Therefore, the phenotype is the result of gen-environment interactions and some features depend on only one gen, but some depend on several genes.

The study of GxE can improve the discovery of genetic variants associated with childhood cancer and the environmental effects on genetically susceptible children. There are 3 main designs for GxE interaction studies,

TABLE 3 Study designs on GxE interactions

Study	Pros	Cons
Family-based	Can evaluate Mendelian transmission of alleles Low bias due to population stratification	It is difficult to collect genetic information on parents (especially for late-onset disease) or find appropriate sibling controls
Case-control	Ideal for studying rare diseases with common exposures	Selection bias (i.e., controls do not represent the population in which the cases occurred)
Cohort	Allow the collection of time- dependent exposure information before disease develops	Require enormous sample sizes or long follow-up More expensive and longer

their advantages and disadvantages are summarized in Table 3.

Few research centers have initiated studies for GxE interactions in childhood cancer. Recently, Medina-Sanson et al. conducted a case-control study of 478 children with ALL and 248 controls, the analysis showed that NAT2 rs1799929 TT SNP confers high-risk to ALL under exposure to fertilizers, insecticides, hydrocarbon derivatives, and parental tobacco smoking (OR 1.96, 95% CI 1.55−2.49), due to a low N-acetylation activity in the metabolism of xenobiotics, although this OR may vary in different populations. GxE is very important in public health, since it allows to improve environmental regulations, identification of high-risk individuals and applying preventive measures (Medina-Sanson et al., 2020).

2.4 | Germline sequencing in clinical settings

Cancer diagnostics in children raises overwhelming questions in parents as "Why did my child get cancer?" "Are my other children at risk to get cancer?," which in most cases remain unanswered. In the past few years, the introduction of NGS in clinical routine practice has been essential in the diagnosis, management and treatment of human disease. Initially, children have not been considered for genetic testing due to the lack of preventive and surveillance recommendations available to guide clinical management of alteration carriers; however, organizations as the American College of Medical Genetics and Genomics (ACMG), American Association of Pediatrics (AAP), American Society of Human Genetics (ASHG) and American Society of Clinical Oncology (ASCO) have established both diagnostic (confirmation of a genetic syndrome) and screening (children without cancer with close relatives with a known predisposition condition) recommendations in children, as long as the genetic testing (in clinical limited genes) contributes with their medical management and surveillance (Johnson et al., 2017).

It is recognized that 75% of children that meet clinical criteria for genetic cancer syndromes are carriers of pathogenic germline alterations (Coury et al., 2018), for this reason, genetic counseling is crucial to identify high-risk individuals and for the implementation of risk reduction strategies and decision making. Pre- and posttest counseling allows the clarification of possible risks and benefits, since some NGS tests as WES may reveal several variants with uncertain significance (VUS) or incidental findings as the risk of nononcologic disease.

Some factors as lack of family history of cancer, recessive or de novo germline alterations and penetrance and variable expressivity, difficult the identification of children who are carriers of cancer predisposition alterations, hence, the clinical recognition of high-risk children could be the best approach for childhood cancer prevention. After a systematic review of pediatric cancer predisposition syndromes, Jongmans et al. developed an easy-to-use tool for the identification of children with cancer who may benefit from genetic counseling; if one patient meets at least one of the five criterion (cancer family history, specific childhood neoplasms, metachronic or synchronous tumors, congenital anomalies and excessive treatment toxicity), the pediatric oncologist can refer the child for evaluation by a clinical geneticist and, if applicable, a genetic confirmation test (Jongmans et al., 2016). A few months later, experts from the Cancer Predisposition Working Group of the Society for Pediatric Oncology and Hematology added a sixth criterion, that the genetic tumor analysis reveals a defect suggesting a germline predisposition (Ripperger et al., 2017). Although this tool is not recommended for children without cancer, the application in pediatric oncology depends on the results of a large-scale validation including different populations.

For clinical application, genetic testing must be performed in laboratories that meet high-quality standards, trained staff and good laboratory practices. All panels must undergo standardization and rigorous validation protocols that show the accuracy and methodological limitations (Chen et al., 2009).

Some commercial panels with clinical validation available for genetic test of childhood cancer are: Hereditary Pediatric Cancer Panel (Blueprint Genetics) (Blueprint Genetics Hereditary Pediatric Cancer Panel) which detects

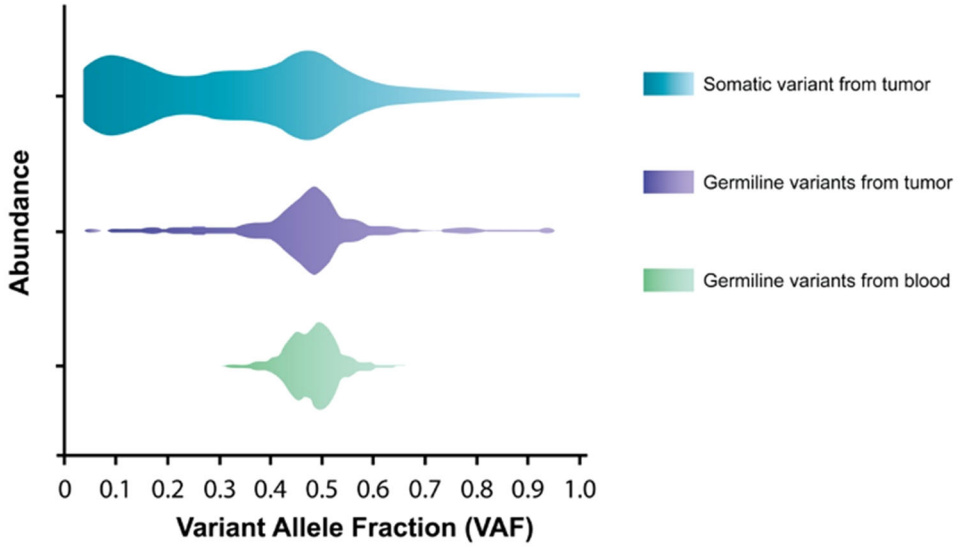

FIGURE 2 Comparison of the allelic fraction of somatic and germline variants in tumor and normal samples. Variants found in tumor sequencing with an allele fraction between 40% and 60% are often interpreted as germline when matching blood- or saliva-derived DNA sequencing data is not available. A paired approach sequencing reduces the workload for variant filtering and annotation and shortens the time to clinical report.

SNVs, INDELs, CNVs in 71 genes; Pediatric Solid Tumors, Pediatric Nervous System/Brain Tumors and Pediatric and Hematologic Malignancies Panels (INVITAE) that includes 53, 34 and 16 genes respectively by full exome sequencing ± 20pb of adjacent intronic sequences (Invitae Pediatric Genetics). Institutions such as The Memorial Sloan Kettering through Kids Clinical Genetics Service and The Pediatric Cancer Predisposition Screening Program (MSK Kids) and Pediatric Cancer Genetic Risk Program of Dana Farber Boston Children's Center (Pediatric Cancer Genetic Risk Program of Dana-Farber Boston Children's Center) offer genetic testing for several genetic syndromes.

3 | CANCER PREDISPOSITION ON THE BASIS OF GENOMIC FINDINGS WITHIN THE TUMOR

Somatic sequencing has allowed the identification of new tumor specific and nonspecific driver genes, as well as gene signatures for some childhood tumor types (Gröbner et al., 2018; Ma et al., 2018). In high-income countries, its use in clinical practice has increasing, which has allowed improvements in diagnosis, risk stratification and treatment decisions (Surrey et al., 2019).

The results of childhood tumor sequencing have also allowed the identification of both targetable mutations and the suggestion of genetic variants associated with cancer predisposition syndromes. In fact, recent reports have shown that the genomic findings within the tumor could be a more powerful strategy for the identification of underlying cancer predisposition syndromes than the clinical or familial history (Postema et al., 2017). Some indicators such as a variant allele fraction between 0.4 to 1 or the identification of a pathogenic or founder mutation in cancer predisposition genes may increase the suspicion of an underlying hereditary cancer syndrome.

MacFarland and collaborators identified 210 concerning variants for cancer predisposition syndromes in 141/1023 patients who underwent somatic tumor sequencing. A total of 26 variants in 41 patients were confirmed to be constitutionally present; among patients tested, 23/41 (56.1%) were diagnosed with a cancer predisposition syndrome and interestingly, some had not been previously referred to genetic counseling (MacFarland et al., 2019).

Some authors have described the benefits of matched paired tumor-normal sequencing tests, which include the reduction of the number of germline variants that often are filtered out in somatic sequencing depending on their population frequency or some computational filters that may also mask germline variants associated with cancer predisposition genes, allowing improvement of the accuracy of variant reporting to refine diagnoses, aid in a treatment decisions, and refer patients and families to genetic counseling when indicated. Schienda and collaborators showed how the integration of germline sequencing with molecular tumor profiling in a subset of children with solid malignancies enrolled in the Genomic Assessment Improves Novel Therapy (GAIN) consortium (Clinical Trials ID: NCT02520713) could improve clinical interpretation and enhance the identification of germline variants with

significant hereditary risks (Schienda et al., 2021). They found that 66% of SNVs identified in the tumors were reported as pathogenic, likely-pathogenic or variants of uncertain significance in germline sequencing and only 29% of them were present solely in the tumor sequencing data, and thus determined to be of somatic origin. Additionally, 35.1% of true somatic mutations had VAFs inside the accepted range of germline origin (0.4–0.6); in contrast of true germline variants had a VAF that was either 0.6 or below 0.4 in the tumor only sequencing data (Figure 2).

4 | PERSPECTIVES

Although inherited genetic variants discovered by high-throughput sequencing have provided important insights about the causes of childhood cancer, there are still critical gaps in knowledge. Most of disease-causing genetic variants are under-discovered due to sequencing limitations in genomic regions such as intragenic/intergenic loci or, lack of disease-causing evidence, computational prediction and functional assays. In fact, one of the biggest challenges in genetic counseling is discussing uncertain test results, either an inconclusive test result or variants of uncertain significance (VUS), which represent the majority of variants identified by NGS technologies. In fact, it is strongly recommended to follow-up on VUS every semester to verify changes in their classification. The low- and middle-income countries present additional challenges in the implementation of somatic and germline NGS panels. First, there are few local regulations for laboratories that perform molecular genetics and genomics testing in cancer. Second, there are few laboratories that meet the international regulations of institutions such as The College of American Pathologist, CAP or The American College of Medical Genetics and Genomics, ACMG, and third, the number of available FDA approved or cleared tests are limited. These have several implications including a high-cost and long turnaround time (TAT) (Ascencio-Carbajal et al., 2021; Entidad Mexicana de Acreditación AC; Valdespino Gómez & Balbín Felechosa, 2016).

The establishment of childhood risk-factors and their validation in large scale population studies, family-based sequencing, the discussion of variants in multidisciplinary groups of experts and the evaluation of risk factors in prenatal, pregnancy and postnatal period, will improve the knowledge of the genetic basis and the origin of childhood tumors.

AUTHOR CONTRIBUTIONS

Oscar Alonso-Luna: conceptualization; investigation; writing-original draft; visualization. **Gabriela E Mercado-Celis**: conceptualization; writing–review & editing; supervision; visualization. **Jorge Melendez-Zajgla**: conceptualization; writing–review & editing; supervision; visualization. **Marta Zapata-Tarres**: writing–review & editing. **Elvia Mendoza-Caamal**: writing–review & editing.

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DATA AVAILABILITY STATEMENT

These data were derived from the following resources available in the public domain: https://pubmed.ncbi.nlm.nih.gov

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