Genetic Predisposition to Solid Pediatric Cancers

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Progresses over the past years have extensively improved our capacity to use genome-scale analyses—including high-density genotyping and exome and genome sequencing—to identify the genetic basis of pediatric tumors. In particular, exome sequencing has contributed to the evidence that about 10% of children and adolescents with tumors have germline genetic variants associated with cancer predisposition. In this review, we provide an overview of genetic variations predisposing to solid pediatric tumors (medulloblastoma, ependymoma, astrocytoma, neuroblastoma, retinoblastoma, Wilms tumor, osteosarcoma, rhabdomyosarcoma, and Ewing sarcoma) and outline the biological processes affected by the involved mutated genes. A careful description of the genetic basis underlying a large number of syndromes associated with an increased risk of pediatric cancer is also reported. We place particular emphasis on the emerging view that interactions between germline and somatic alterations are a key determinant of cancer development. We propose future research directions, which focus on the biological function of pediatric risk alleles and on the potential links between the germline genome and somatic changes. Finally, the importance of developing new molecular diagnostic tests including all the identified risk germline mutations and of considering the genetic predisposition in screening tests and novel therapies is emphasized.

Keywords: genetic predisposition, germline variants, cancer predisposition genes, pediatric tumors, cancer susceptibility, germline-somatic interaction, SNP, next generation sequencing

INTRODUCTION

Genomic sequencing studies have highlighted that pediatric cancers typically have few somatic mutations but a higher prevalence of germline alterations in cancer predisposition genes (1). The contribution of germline variants in pediatric tumors has been estimated between 8 and 12% (2, 3). Genetic variants are generally classified on the basis of their clinical effect: pathogenic variant means any sequence change that, differing from the consensus wild-type sequence, directly contributes to the development of the disease; likely pathogenic variants, instead, are genetic changes with a high likelihood of being disease-causing, but additional evidence is expected to confirm their clinical significance. Variant classification can arise from different methodologies and algorithms, which can assign different weights to collected data. However, studies cited in the present review generally refer to the American College of Medical Genetics and Genomics (ACMG) guidelines for variants interpretation (4). In this process, multiple categories of data (such as frequency in affected and unaffected populations, computational prediction tools, functional studies, and...
gene- or disease-specific information) are taken into account and combined to determine a variant pathogenicity classification.

It is also important to note that genetic variants can be detected through different genomic approaches and the type of identified alteration depends on the nature of the assay used. Large-scale genomic analyses such as whole-exome sequencing (WES) or whole-genome sequencing (WGS) can identify uncommon, moderate penetrant variants. Since WES investigates only the coding regions of the genome, it has proved very useful in detecting most of the causative variants of Mendelian diseases (5, 6). Furthermore, it has recently been used also to identify rare and uncommon causative mutations of complex diseases (7). On the other hand, WGS can capture nearly all known genetic variations, including those falling in regulatory elements, with much more uniform coverage of the genome, but it does not allow to detect mosaic variants with low clonality or variations causing DNA repetitions (8). Common, low-penetrance genetic variants, instead, are mostly identified by genome association study (GWAS), which assesses genotype–phenotype associations through testing of variants across genomes of many individuals, based on data obtained using numerous technologies, mostly WGS or genome-wide single-nucleotide polymorphism (SNP) arrays. Consequently, GWAS limitations are linked to the technology on which it is based: e.g., SNP array-based GWAS rely on pre-existing genetic variant reference panels (9). Finally, besides SNP array, copy-number variations (CNV) can be identified also through CGH array. Anyway, array methods cannot be used to detect single base pair changes, indels, balanced chromosome rearrangements, and low-percent mosaicism (10).

Recently, in addition to germline pathogenic and/or likely pathogenic variants in known cancer-predisposing genes, it has been estimated that a high percentage (61%) of children, adolescent and young adult patients with solid tumors carry germline pathogenic and likely pathogenic variants in new candidate genes, including PRKN, SMACAL1, SMAD7, and TMPRSS3 (3). The detection of cancer predisposition can lead to clinical benefits for patients, both for the molecular diagnosis and for the presence of specific biological features, as well as to eventually refine therapeutic choices. We provide an overview of the most significant knowledge of germline predisposition for the main pediatric solid tumors, which are central nervous system tumors (medulloblastoma, ependymoma and astrocytoma), neuroblastoma, retinoblastoma, Wilms tumor, osteosarcoma, rhabdomyosarcoma, and Ewing sarcoma, altogether accounting for 34.8% of all childhood cancers (Figure 1). Each tumor description is organized into two subsections: “familial cancer” and “sporadic tumor.” Familial cancer means a form of cancer that has higher incidence in families than in the general population due to rare, high-penetrance genetic variants. In this group, we also included rare genetic syndromes that are not usually considered as cancer syndromes but that predispose to the development of solid pediatric tumors. The second group, sporadic tumor, is referred to cancers which do not run in families and are intended as multifactorial diseases whose onset
can be attributed to the combined effect of environmental and genetic factors. In sporadic cancers, genetic factors can be categorized into two types: uncommon, moderate-penetrance genetic variants, which for the studies considered in this review show a frequency lower than 1–0.001% in the general population and are not so rare as those associated with familial cancer, and common, low-penetrance genetic variants.

The knowledge of genetic mutations responsible for syndromic disorders associated with the risk of developing pediatric cancer has greatly increased over the past years (11). Indeed, several tumor predisposing syndromes are the underlying cause of at least 8.5% of cancers in pediatric patients (12). Thus, the role of general practitioners and pediatricians in recognizing the major cancer genetic-associated syndromes, in making appropriate referrals for genetic counseling and testing when indicated, is crucial for a specific monitoring and management of the patient.

Most cancer susceptibility genes are involved in fundamental biological pathways such as cell-cycle control, chromatin remodeling, or DNA repair. Therefore, alterations in these genes compromise the normal control of cell growth and lead to a substantial increase in the risk of developing cancer. Another element of great interest discussed here is the presence of cooperation between germline and somatic alterations, which can represent an early tool for evaluating the clinical outcome and for the stratification of patients in risk subgroups. We also discuss evidence that points to a need for more collaborative investigations in identifying driver events in pediatric cancers.

**CENTRAL NERVOUS SYSTEM TUMORS**

Central nervous system (CNS) tumors represent the most frequent types of cancer in children aged 0–14 years, with a mortality rate of 0.72 per 100,000 population (13). The three most frequent tumors are medulloblastoma (MB), ependymoma (EP), and astrocytoma (AS) (Figure 2).

**Medulloblastoma**

MB is an embryonal tumor of cerebellum (14) that affects children under the age of 14, with an average onset of about 6–8 years (Figure 2) and with a 5-year overall survival for standard-risk patients of 70–85% (14). It is classified into four genetic and molecular groups: the first two groups, WNT-activated (MB\_WNT) and Sonic Hedgehog activated (MB\_SHH), are named for the...
signaling pathways that play prominent roles in the pathogenesis of those subgroups, while, since less is known about the biology of the remaining two subgroups, they are numerically designated as “Group 3” and “Group 4” (14). Damaging germline mutations in known cancer-predisposing genes play an important role in two main subgroups, MBWNT and MBSHH, in which genetic testing is highly recommended (15). MBWNT is characterized at somatic level by activating mutations in exon 3 of β-catenin (CTNNB1) and monosomy of chromosome 6, while MBSHH by amplification of GLI2 and MYCN, as well as loss of 17p (16).

**Familial Medulloblastoma**

To date, only germline mutations in *ELP1* have been found in two independent families with MBSHH (17). Although inherited or familial MB is extremely rare, there are few rare inherited syndromes that are associated with increased risk of developing this tumor (Table 2). Germline mutations of *PTCH1* and *SUFU*, by causing activation of the SHH signaling pathway, predispose to MBSHH in Gorlin syndrome, an autosomal dominant disease caused by mutations in *PTCH1* (67, 124). In Turcot syndrome, a rare disorder characterized by the association of colonic polyposis and primary brain tumors, germline mutations of *APC* predispose to the development of MBWNT (114). In MBWNT, activation of the WNT pathway is due to somatic mutations of *CTNNB1* in most of tumors but it is also observed in patients with only germline mutations of *APC*, stressing the importance of genetic predisposition in high-risk patients (15, 114). Germline mutations in *BRCA2* and *PALB2*, associated or not associated with Fanconi anemia, have been found in MBSHH (58, 125) and are often observed in association with somatic homologous recombination repair defects (15). The role of germline mutations in *TP53* in MB is still widely debated today. *TP53* germline mutations affect MB prognosis differently according to the different subgroups: germline mutations in MBSHH are associated with poor prognosis, while both germline and somatic mutations in MBWNT are associated with better prognosis. This may be due to a different origin of the MB itself (14). Patients with germline *TP53* mutations can have tumors characterized by catastrophic DNA chromothripsis and are often associated with Li–Fraumeni syndrome (LFS), a cancer predisposition disorder caused by germline mutations of the tumor-suppressor p53 (71). Other MB-associated syndromes are Bloom’s syndrome (31), ataxia telangiectasia (18), and Greig’s cephalopolysyndactyly syndrome (14, 40, 45, 85, 122) (Table 2).

**Sporadic Medulloblastoma**

The association between MB and genetic syndromes explains most of the genetic predisposition to MB. However, sporadic forms are known in literature and are partially explained through uncommon, moderate penetrant mutations identified by whole-exome sequencing (WES) or whole-genome sequencing (WGS), or common, low-penetration genetic variants identified by genome wide association study (GWAS) (Table 1 and Table 3).

**Uncommon, Moderate-Penetrance Variants**

In a study on 1,022 MB patients, novel partial or total *APC* deletions were found (15). These mutations were not associated with any familial syndrome and predisposed to MBWNT. In

**Table 1** Rare, high-penetrance, and uncommon, moderate-penetrance variants in genes predisposing to pediatric tumors and main biological pathways.

| Pathways                          | Gene(s)     | Tumors                  | References |
|-----------------------------------|-------------|-------------------------|------------|
| Collagen chain polymerization     | COL7A1      | NB, RMS, WT             | (3)        |
| Cytoskeletal and adhesion signaling | GJB2       | AS, CNS tumors, EWS, OS, RMS | (3, 126) |
| DNA base excision repair (BER)    | ERCC2       | AS, OS                  | (127–129) |
| DNA double-strand break repair (DSB) | BRCA1     | AS, CNS tumors, EWS, OS, RB | (3, 126, 129) |
|                                   | BRCA2       | AS, NB, MB, RMS         | (2, 3, 15, 58, 125, 126) |
|                                   | CHEK2       | CNS tumors, EWS, NB, OS, RB, RMS, WT | (3, 129, 131, 132) |
|                                   | BAP1        | RB                      | (3)        |
|                                   | BLM         | EWS, MB                 | (15, 130) |
|                                   | BRIP1       | EWS, MB, OS             | (2, 3, 15, 129, 130) |
| DNA mismatch repair system (MMR)  | MSH2        | WT, OS                  | (2, 3)     |
|                                   | MSH6        | RB, RMS, WT             | (3, 133)   |
|                                   | PMS2        | AS, CNS tumors, EWS     | (2, 3, 127, 130) |
| DNA repair                        | FANCA       | AS, MB                  | (15, 126) |
|                                   | FANCC       | EWS, MB                 | (2, 15, 130) |
|                                   | FANCI       | RMS                     | (133)      |
|                                   | FANCL       | OS                      | (2, 129)   |
|                                   | FANCM       | OS                      | (2, 129)   |
|                                   | ATR         | RMS                     | (3)        |
|                                   | MUTYH       | AS, EWS                 | (2, 127)   |
|                                   | RAD51       | WT                      | (3)        |
|                                   | RECOL4      | OS                      | (129)      |
| Genome stability and regulation of cell cycle | ALK | Familial/sporadic NB | (2, 3, 134, 136) |
|                                   | ATM         | EWS, MB, OS, RB, RMS    | (3, 15, 129, 133) |
|                                   | RB1         | OS, familial/sporadic RB | (2, 3, 129, 135, 136) |
|                                   | TP53        | AS, EWS, MB, NB, RMS, OS, WT | (2, 3, 15, 127, 129–131, 133, 135, 137–139) |
| Metabolic pathways                | HMBS        | CNS tumors              | (3)        |
|                                   | FAH         | OS                      | (129)      |
|                                   | SDHA        | NB                      | (3)        |
| Protein interaction at synopsis    | PTPRD       | Advanced/metastatic EWS | (140)      |
| Protein translation and modification | KIF1Bβ     | Familial NB             | (141)      |
| RET signaling and G-protein signaling, H-RAS regulation pathway | ERBB4 | NB | (3) |
|                                   | NF1         | AS                      | (126)      |
|                                   | RET         | EWS                     | (2, 130)   |

(Continued)
the same study, 1% of patients (classified as MBBH) had TP53 mutations but only 5/11 patients showed family history of cancer, emphasizing the role of TP53 germline mutations in predisposing to sporadic MB. Notably, germline missense, frameshift, or non-sense mutations in the DNA-binding domain of TP53 were found to be associated with a series of events at the somatic level such as rearrangements, chromothripsis, and loss of heterozygosity in MBBH patients, whereas germline mutations in SUFU and PTCH1 co-occurred with somatic loss of heterozygosity (15) (Table 4). These results further provide evidence that novel associations between germline variants and specific somatic events, beyond those reported by Knudson in 1971, can play a role in carcinogenesis. Indeed, recent body of literature supports the hypothesis that specific germline variants determine which somatic events and mutations are generated and selected in cancer cells during tumorigenesis (179).

MB can also arise in patients with germline mutations in other known cancer genes such as ATM, FANCA, FANCC, NBN, WRN, BLM, and BRIP1 and in candidate genes like CHEK2, CREBBP, RAD51, ERCC2, and ERCC4. All of these genes are involved in cell-cycle regulation and DNA repair (15). Frameshift, protein-truncating, and missense mutations occurring in GPR161, a gene never previously associated with MB, were found in 6 MBBH cases (143) that, at the somatic level, showed loss of heterozygosity with retention of the mutated allele, confirming its role as driver gene in MBBH. GPR161 functions are essential for embryonic development and for the proliferation of granular cells (143). Germline mutations in ELPI have been very recently found to predispose to MBBH and to be associated with two consecutive somatic events: loss of the 9q arm, with consequent loss of the wild-type copy of PTCH1 and ELPI, and a second independent mutation event in PTCH1 (17) (Table 4). This study, importantly, showed that 40% of MBBH patients carry disease-predisposing mutations and that genetic predisposition to proteome instability may be a determinant in the pathogenesis of pediatric brain cancers (17) (Table 1).

**Common, Low-Penetrance Variants**

To date, there are no relevant GWAS conducted to identify common variants associated with MB. Only one study has been performed in a small sample including 244 MB cases and 247 control subjects from Sweden and Denmark, but no locus reached the significance threshold (154). The most significant locus was 18p11.23 including PTPRM (154). A different approach that starts from the most frequently mutated genes in MB such as CCND2, CTNNB1, DDX3X, GLI2, SMARCA4, MYC, MYCN, PTCH1, TP53, and KMT2D was proposed to identify MB-associated common variants (162). Eight variants, located in CCND2, PTCH1, and GLI2, associated with the risk of developing MB (162) (Table 3). However, these findings need further validation in independent cohorts of cases and controls.

Microsatellites are tandem repeats of 1–6 base pairs, and their variability is associated with numerous tumors, including MB. In a recent work, starting from WES and WGS data, the authors developed an algorithm able to identify a signature of 43 microsatellites that distinguished with high-sensitivity and specificity MB subjects from controls in two independent sets of MB cases and controls (180). Interestingly, *in silico* analyses revealed that genes harboring these microsatellite loci had cellular functions important for tumorigenesis (180).

**Other Brain Tumors**

EP originates from the walls of the ventricular system (79), arises between 0 and 4 years (Figure 2) (79), and has a 5-year overall survival of about 60% (181). EP is diagnosed in ∼33–53% of patients with type 2 neurofibromatosis, with high occurrence of truncating mutations in NF2 (97). EP has recently been associated with Kabuki syndrome, with mutations in KMT2D (70) and rarely occurs in Turcot and MEN1 syndromes with mutations in MSH2 and MEN1, respectively (79) (Table 2). To date, large studies on common variants and sporadic forms are lacking (Table 1). AS is classified into several forms including pilocytic, anaplastic, diffuse, and glioblastoma (182). Pilocytic AS is the most common form in children and young adults, with an average age at onset between 0 and 9 years (13) (Figure 2) and a 5-year survival of 94.1% (13). Regarding the genetic predisposition, one large study reported germline...
| Syndrome/disease                          | Inheritance pattern | Gene/s associated | Tumor | Frequency               | References |
|------------------------------------------|---------------------|-------------------|-------|-------------------------|------------|
| Ataxia telangiectasia                    | AR                  | ATM               | MB    | Extremely rare          | (18)       |
| ATR-X syndrome                           | AR                  | ATR-X             | OS    | Extremely rare          | (19)       |
| Balter–Gerold syndrome                   | AR                  | RECQL4            | OS    | Extremely rare          | (20, 21)   |
| Beckwith–Wiedemann syndrome              | Imprinting, AD      | CDKN1C            | NB    | 4–21%                   | (22, 23)   |
|                                          |                     | KCNQ1OT1          | RMS   | 7.5%                    | (24–28)    |
|                                          |                     | 11p15 or H19 loci | WT    | 7–30%/20%               | (29, 30)   |
| Bloom syndrome                           | AR                  | RECL3 (BLM)       | MB    | Extremely rare          | (31)       |
|Bohring-Opitz syndrome                    | AD                  | ASXL1             | WT    | 7%                      | (35, 36)   |
| CCHS/hirschsprung syndrome               | AD                  | PHOX2B            | NB    | 10–20%                  | (37–39)    |
| Constitutional mismatch repair deficiency| AR                  | MSH2, MSH6, MLH1, PMS2 | MB | 11.6%                  | (33, 40)   |
| Costello syndrome                        | AD                  | HRAS              | NB    | 17%                     | (41)       |
|Curry–Jones syndrome                      | Unknown             | GLI3              | MB    | Extremely rare          | (45, 46)   |
|Diamond–Blackfan anemia                   | AD                  | Unknown           | OS    | <1%                     | (33, 47–50)|
|Denys–Drash syndrome                      | AD                  | WT1               | WT    | 90%                     | (51)       |
|DICER1 syndromes                          | AD                  | DICER1            | RMS   | Rare                    | (52–54)    |
|Familial paraganglioma/pheochromocytoma syndrome | AD                | SDHB              | NB    | Rare                    | (55)       |
|Fanconi anemia                            | AR                  | BRIP1, BRCA2, PALB2 | NB | rare                   | (57)       |
|                                          |                     | BRCA2, PALB2      | MB    | 25%                     | (58, 59)   |
|                                          |                     |                   | WT    | >20%                    | (60–62)    |
|Frasier syndrome                         | AD                  | WT1               | WT    | 5–10%                   | (63)       |
|Gorlin syndrome                           | AD                  | PTCH1             | RMS   | Rare                    | (64, 65)   |
|                                          |                     |                   | WT    | <5%                     | (65, 66)   |
|                                          |                     | PTCH1             | MB    | <2%                     | (67, 68)   |
|                                          |                     | SUFU              |       | 30–40%                  |            |
|Hyperparathyroidism-jaw tumor syndrome    | AD                  | CDC73 (HRPT2)     | WT    | <5%                     | (60)       |
|Isolated hemihypertrophy                  | AD                  | 11p15 locus       | WT    | 6%/<5%                  | (69)       |
|Kabuki syndrome                           | AD                  | KMT2D             | EP    | Extremely rare          | (70)       |
|Li–Fraumeni syndrome                      | AD                  | TP53              | MB    | 14%                     | (68, 71)   |
|                                          |                     |                   | NB    | rare                    | (72)       |
|                                          |                     |                   | OS    | 12%                     | (73–76)    |
|                                          |                     |                   | RMS   | 80%                     | (75, 77)   |
|                                          |                     |                   | WT    | <5%                     | (79, 78)   |
|MEN1 syndrome                             | AD                  | MEN1              | EP    | Rare                    | (79)       |
|Mosaic variegated aneuploidy syndrome     | AR                  | BUB1B             | RMS   | High                    | (80, 81)   |
|                                          |                     | BUB1B, TRIP13     | WT    | >20%                    | (60, 80, 82, 83)|
|Mulleby nanism syndrome                   | AR                  | TRIM37            | WT    | <5%                     | (29, 84)   |
|Nijmegen breakage syndrome                | AR                  | NBS1              | MB    | Extremely rare          | (85)       |
|                                          |                     | NBS1              | RMS   | Rare                    | (86, 87)   |
|Noonan syndrome                           | AD                  | PTPN11, KRAS      | NB    | 17%                     | (88)       |
|                                          |                     | SOS1              | RMS   | Rare                    | (89–93)    |
|Noonan-like syndrome                      | AD                  | CBL               | RMS   | Extremely rare          | (94)       |
|Neurofibromatosis type I                  | AD                  | NF1               | NB    | Rare                    | (95, 96)   |
|                                          |                     |                   | RMS   | 0.5%                    | (44)       |
|Neurofibromatosis type II                 | AD                  | NF2               | EP    | 3–6%                    | (68, 97)   |
|Paget's disease of bone                   | AD                  | Unknown           | OS    | <1%                     | (98, 99)   |

(Continued)
splicing mutations in the tumor-suppressor genes MUTYH and ERCC2 and point mutations in TP53 and PMS2 (127) (Table 1). Pathogenic mutations in NF1, BRCA2, FANCA, and GJB2 have been also identified in a recent study involving 280 patients with different forms of AS (126).

### NEUROBLASTOMA

Neuroblastoma (NB) originates from neural crest cells and affects the nervous sympathetic system (183). NB exhibits unique features, such as early age of onset, high frequency of metastatic disease at diagnosis in patients over 1 year of age (Figure 2), and the tendency for spontaneous regression of tumors in infants. In high-risk cases, the survival rate is only 50% (183). NB tumors, as well as other pediatric cancers, present few recurrent somatic mutations but frequent chromosomal aberrations such MYCN amplification, 17q gain, 1p deletion, and 11q deletion (184).

### Familial Neuroblastoma

Familial NB represents 1–2% of cases, with PHOX2B and ALK as major susceptibility genes (184) (Table 1). The first identified familial gene is PHOX2B (37, 145), already associated with congenital central hypoventilation syndrome (CCHS) (185) and encoding a transcription factor driving neural crest differentiation (186). NB-exclusive mutations are mainly missense and frameshift (187). PHOX2B germline mutations account for ~10% of familial NB (188), but this gene is also mutated in 2% of sporadic cases (189). Subsequently, the major susceptibility gene was identified in ALK. Its gain-of-function mutations, which account for 75% of familial cases (134, 188), are mainly located in the kinase domain of the encoded tyrosine kinase receptor and show incomplete penetrance (190). ALK somatic mutations are also reported in 10–12% of primary sporadic NB tumors (134, 191). Additional NB-predisposing genes have not yet been discovered. Mutations in KIF1Bβ (141) and GALNT14 (192) and in 16p12–13, 4p16, and 1p loci (193–195) (Table 1) have been reported in related patients, but further validations are needed.

Children suffering from specific cancer predisposition syndromes such as LFS and others (Table 2) show an increased NB risk (22, 38, 39, 41, 56, 57, 72, 77, 88, 95, 111, 116, 121). Thus, protocols for NB surveillance need to be established.

### Sporadic Neuroblastoma

Only a small subset of sporadic NB cases has an identifiable somatic oncogenic point mutation (196, 197), suggesting that predisposing genetic factors found in GWAS studies could cooperate to increase disease occurrence (198, 199).

### Uncommon, Moderate-Penetrance Variants

Recent studies focused on uncommon germline variants, which presumably have a larger effect on predisposition compared to common ones. In different studies, pathogenic and likely pathogenic variants were identified in predisposition genes such as ALK, CHEK2, BRCA2, SMARCA4, and TP53 (Table 1) but also in candidate genes like AXIN2, PALB2, BARD1, PINK1, APC, BRCA1, SDHB, and LZTR1 (2, 135, 146, 196, 197, 200). Specifically, TP53 variants are strongly associated with NB
susceptibility (201). All the mentioned genes are involved in DNA repair and maintenance of genomic integrity (Table 1).

### Common, Low-Penetrance Variants

GWAS studies identified several NB susceptibility loci (Table 3) including CASC15 (160), BARD1 (157), LMO1 (175), HACE1, and LIN28B (155) associated with high-risk NB, whereas DUSP12, HSD17B12, DDX4, and IL31RA associated with the low-risk NB group (161, 198). Functional studies of these loci have highlighted the key role of GWAS in elucidating NB carcinogenesis. A SNP in the long non-coding RNA (lncRNA) CASC15 produces a truncated isoform, whose lower expression correlates with advanced disease (202). Loss of another lncRNA, NBAT-1, at the same locus, contributes to aggressive NB by increasing proliferation and impairing differentiation of neuronal precursors (203). Diverse functional studies have elucidated the role of BARD1 and its variants in NB development (204). Variants in the BARD1 promoter decrease the expression of the tumor-suppressor form which protects NB cells from DNA damage (205, 206), whereas variants in introns increase the expression of an oncogenic isoform, BARD1β, which stabilizes the Aurora kinases (207, 208). LMO1 decreased expression, caused by a variant in a super-enhancer which disrupts GATA binding (209), reduces NB cell proliferation. Finally, the activation of LIN28B, due to genetic variants, can enhance MYCN levels via let-7 microRNA suppression (155, 210, 211). The genetic landscape of sporadic NB has been amplified with the discovery of additional susceptibility genes including RSRC1/MLF1 and CPZ (159), SPAG16 (177), NEFL (156), and CDKN1B (170).

Reanalyses of GWAS data have discovered novel mechanisms and genetic factors that promote NB development (Table 3). Two studies clearly demonstrate a cooperation between predisposing variants and somatic aberrations in NB initiation (Table 4). Indeed, SNPs in MMP20 (167) and KIF15 (168) increase NB susceptibility in the presence of 11q deletion and MYCN amplification, respectively, whereas another study shows that specific mtDNA haplogroups can influence the risk of NB (212). We have provided evidence that SNPs in PARP1 and ILE6 might be predictive biomarkers of response to chemotherapy and prognosis (213, 214). Finally, our recent works found that NB shares risk loci with other complex diseases and tumors. Indeed, SNPs in 2q35, 3q25.32, and 4p16.2 are cross-associated with congenital heart disease (CHD) and NB (215), while 1p13.2 showed cross-association with NB and melanoma (216). Very recently, a cross-match investigation between germline alterations in pediatric patients with different solid tumors and CHD-related genes has identified that NB is among the tumors with the highest enrichment of germline pathogenic and likely pathogenic variants in these genes (3).

### Constitutional Chromosomal Abnormalities

Highly associated with NB are hemizygous deletion in 1q21.1, disruption in NBPF23 (217), and microdeletion in 16p11.2, containing SEZ6L2 and PRRT2 (218). Deletion including SLFN11, duplication of SOX4, and partial deletion of PARK2 have been identified in three different patients, respectively (219).

### RETINOBLASTOMA

Retinoblastoma (RB) is a pediatric malignancy of the neural retina, commonly initiated by biallelic inactivation of RBI (220) and affecting one (unilateral) or both eyes (bilateral). The median age at diagnosis is 12 months in bilateral tumors and 24 months...
in unilateral ones (220) (Figure 2). Patient survival is >95% in high-income countries but <30% globally (220). The first studies on RB unveiled the importance of genetics in cancer; indeed, the “two-hit hypothesis” formulated by Knudson (221) on RB1 has been paradigmatic for the understanding of tumor-suppressor genes and the study of familial cancers.

Familial Retinoblastoma
Hereditary RB encompasses about 40% of all cases with most having bilateral tumors, 15% unilateral, and 5% trilateral (associated with midline brain tumor) (220). Familial RB is distinctly associated with the RB1 tumor-suppressor gene, which encodes pRB, a crucial regulator of the cell cycle. Germline mutations in RB1 are inherited in 25% of cases in an autosomal-dominant manner. A broad spectrum of inactivating RB1 germline mutations have been described, mainly nonsense and frameshifts affecting the coding region, few large deletions, and <5% silencing gene promoter (136). Penetrance and expressivity can vary within families due to partially functional RB1 alleles (222, 223) or parent-of-origin effect (224). Influence of genetic modifiers such as MDM2, MDM4 (225, 226), or MED4 (227) and polymorphisms in p53 (228), CDKN1A (169), and CDKN2A (229) could also influence RB development. Reduced MDM2 and MDM4 expression may increase the RB1 haploinsufficiency, whereas variants affecting the activity of p53 pathway effectors impact cell-cycle arrest. However, studies on larger cohorts of patients are required to confirm these findings. A small subset of hereditary RB patients is not carrier of RB1 mutations. Investigation through a clinical exome gene panel within 3 families proposed FGFR4, NQO1, ACADS, CX3CR1, GBE1, KRT85, and TYR as possible candidate genes involved in RB oncogenesis, given their association with the retinoic acid pathway (230).

RB is generally described as retinoblastoma predisposition syndrome since germline RB1 mutations lead to a high risk of second primary malignancies (231). Interestingly, RB onset is reported in 13q deletion syndrome, caused by deletion of part of the long arm of chromosome 13, where RB1 is located (123, 232) (Table 2). Patients with this syndrome show a very wide phenotypic spectrum depending on the size and the location of the deletion (123, 232, 233).

Sporadic Retinoblastoma
Sporadic RB is always unilateral. Biallelic loss of RB1 is found in 98% of cases, whereas 2% show MYCN amplification (234, 235). A significant proportion of sporadic RB exhibits somatic mosaicism for RB1 mutations (236, 237).

Uncommon, Moderate-Penetrance and Common, Low-Penetrance Variants
Susceptibility variants have been investigated mostly in patients with hereditary RB. However, given the role of the p53 pathway in RB development, polymorphisms in genes such as MDM2 (163), MDM4 (164), and CDKN1A (169) could also influence the development of the sporadic form (Table 3). Uncommon variants conferring RB risk may be present in asymptomatic individuals. Indeed, high-throughput analysis revealed that several low-frequency RB1 variants are present in the human population, including rare alleles disrupting splicing (238).

Constitutional Chromosomal Abnormalities
Mosaic and non-mosaic chromosomal deletions of 13q14 region are causative of RB (123, 239). Additionally, duplication of 1q21.1, containing the oncogene BCL9, has been reported in a patient with bilateral RB (240).

WILMS TUMOR
Wilms tumor (WT), also known as nephroblastoma, is the most common renal malignancy of childhood, with a median age at diagnosis between 2 and 3 years (241) (Figure 2). It is considered an embryonal tumor as it arises from the aberrant kidney development, due to genetic anomalies in genes essential for fetal nephrogenesis (29). WT treatment is successful with a 5-year overall survival of about 90% and 75% for localized and metastatic disease, respectively (82). It is estimated that about 10% of WT cases are caused by genetic predisposition factors, mainly represented by germline pathogenic variants or epigenetic alterations occurring early during embryogenesis (147, 242). The number of known susceptibility loci has significantly increased over the past years, even if our knowledge is still incomplete and further predisposition factors remain to be discovered. The landscape of somatic genetic alterations in WT is quite broad, with classical genetic changes involving WT1, the IGF2 locus, the WNT pathway, MYCN and TP53 but also driver mutations in several additional cancer genes including epigenetic remodelers, miRNA processing genes and transcription factors essential for nephrogenesis (29).

Familial Wilms Tumor
Several congenital malformation and cancer predisposition syndromes are associated with the risk of developing WT (Table 2). Some of the most known and characterized syndromes are associated with constitutional alterations in WT1 at 11p13.

| TABLE 4 | Germline–somatic interactions identified in genes predisposing to pediatric tumors. |
|---|---|---|---|---|
| Tumors | Gene | Frequency | Somatic interaction | References |
| MB | TPS3 | Rare | DNA chromothripsis | (71) |
| ELP1 | Rare | Loss of the 9q arm and a second independent mutation event in PTCH1 | (17) |
| NB | KIF1S | Common | Increased NB risk in presence of MYCN amplification | (168) |
| MMP20 | Common | Increased NB risk in presence of 11q deletion | (167) |
| EWS | EGR2 | Common | EWSR1-FIT1 chimera | (178) |
| NR0B1 | Common | | | (174) |

EWS, Ewing sarcoma; MB, medulloblastoma; NB, neuroblastoma.
WT1 was the first gene identified in WT and encodes a zinc-finger transcription factor, essential for renal and gonadal development (243). A syndrome frequently associated with high risk of developing WT (around 50%) is the Wilms tumor–aniridia syndrome (WAGR), caused by microdeletions of 11p13 including WT1 and PAX6 (115, 244). The second WT1-related disorder is Denys–Drash syndrome (DDS), due to missense variants in WT1 exons 8 or 9, which affect critical residues in the zinc finger domains (51). The risk of WT in children with DDS is about 90% (241). Another syndrome, phenotypically similar to DDS but with a lower risk of WT development, is Frasier syndrome (FS), caused by splicing variants that result in an imbalance of WT1 isoforms (63). The second major WT locus, identified at 11p15 (245), is also characterized by multiple germline epigenetic and genetic changes causing the overgrowth disorder Beckwith–Wiedemann syndrome (BWS). High WT risk is specifically associated with uniparental paternal disomy at 11p15 and to isolated H19 hyper-methylation that results in biallelic expression of IGF2 and over-activation of the IGF signaling pathway (30, 246). Table 2 reports other constitutional genetic mutations underlying both congenital syndromes and WT predisposition (34, 35, 61, 66, 69, 78, 80, 84, 100, 101, 110, 113).

WT is primarily a non-familial condition, with only about 2% of affected individuals belonging to familial pedigrees (29) (Table 1). A small proportion of familial cases are due to germline WT1 variants (149, 150) and mutations in the H19 region of 11p15 (151). Two further predisposition loci at 17q21 (FWT1) and 19q13 (FWT2) were identified by genetic linkage studies, but the causative genes still remain not fully characterized (247). Another cause of familial WT is the presence of inactivating mutations in the DICER1 miRNA processing gene, also causative of cancer susceptibility in DICER1 syndrome (55). Other recognized familial WT predisposition genes are CTR9 and REST (144, 148, 248). CTR9 encodes a key component of the PAF1 complex, implicated in maintenance of stem cell pluripotency (144), while REST encodes the REI-silencing transcription repressor, well-known for its role in repressing neural development and differentiation (249). Rare biallelic TRIP13 mutations have been found in a WES study on familial WT pedigrees (83). TRIP13 encodes a member of the spindle assembly checkpoint complex, whose inactivation leads to chromosome segregation dysfunction and aneuploidy (83). Pathogenic inactivating mutations of TRIM28 have been found in about 8% of familial WT in a sequencing study on 890 patients (147). These mutations have been found to show a strong parent-of-origin effect and a robust association with the epithelial subtype of WT (147, 250, 251). The same study reports constitutional mutations in FBXW7, NYNrin, and CDC27 as contributors to a small number of familial cases, and pathogenic mutations in TRIM28, FBXW7, and KDM3B as de novo events in children with sporadic tumors (147).

It is important to note that, to date, germline pathogenic variants have been identified only in a small proportion of familial WT cases and so that the underlying causative genetic events remain still obscure for the majority of individuals.

### Sporadic Wilms Tumor

Many genetic causes of familial and syndromic WT also contribute to sporadic cases, e.g., constitutional WT1 mutations and germline 11p15 anomalies (150, 151). It is currently estimated that in sporadic cases the number of predisposition genes is more than 20 (147). Next-generation sequencing (NGS) and GWAS approaches have allowed researchers to discover an ever-growing number of uncommon (Table 1) and common (Table 3) genetic variants associated with WT susceptibility.

### Uncommon, Moderate-Penetration Variants

Two recent WGS and WES studies have identified new pathogenic germline variants in CHEK2 and PALB2 in children with sporadic WT (131, 132). Both PALB2 and CHEK2 are involved in DNA repair pathways and are associated with breast cancer predisposition (62, 252). Germline mutations in REST and TRIM28, in addition to their role of familial WT predisposition genes, are also responsible for uncommon sporadic cases (148, 251). Additional pathogenic and likely pathogenic variants were identified in predisposition genes such as TP53, DIS3L2, and MLT1, but also in candidate genes like EP300, HDAC4, HACE1, ARID1A, NF1, MYCN, and GLI3 (131, 132, 137), that need to be validated in independent cohorts. Finally, exome and transcriptome sequencing studies have revealed constitutional mutations in the miRNA processing genes DROSHA, DGC8, Dicer1, and XPO5 (131, 137), some of which associated with the blastemal subtype of WT (137).

### Common, Low-Penetration Variants

The first WT related GWAS study was performed by Turnbull et al. (153), using a dataset of 757 affected and 1,879 controls from North America and subsequently validated in two independent replication series from UK and US populations. They identified two significant SNPs at 2p24 (rs807624 and rs3755132), in the promoter of DDX1, and one SNP at 11q14 (rs790356) located near DLG2. They also identified candidate predisposition loci at 5q14, 22q12, and Xp22, located near the genes PCSK9, TCN2, and NHS, which need further validation (153). More recently, the group of Fu and colleagues performed two candidate gene studies on Southern Chinese populations and found a significant association between WT risk and BARD1 (158) and KRAS (171) polymorphisms, respectively. However, both associations need to be validated in larger cohorts.

### Constitutional Chromosomal Abnormalities

Few chromosomal aberrations and copy-number variations (CNVs) are known to be WT predisposing genetic factors. In addition to karyotypic abnormalities affecting 11p13 and 11p15 (60), a very small number of WT patients with gain of entire chromosomes have been reported, specifically with trisomy 18 and trisomy 13 (60). Rare chromosomal aberrations have been identified at 2q (60, 253, 254) and 7q (255, 256) regions, with terminal deletions and balanced and unbalanced translocations. A constitutional de novo balanced translocation was also identified in a child with bilateral WT, affecting the tumor-suppressor gene HACE1, also reported as NB susceptibility gene. HACE1 controls growth and apoptosis and is often somatically
mutated in WT (257). Moreover, gain of MYCN (2p24), which is predominantly a somatic event, has been reported as a rare germline aberration (258). Finally, in 2020, a germline duplication of SUZ12 has been detected in a WT patient carrying other germline pathogenic variants in new candidate cancer predisposition genes (3).

**OSTEOOSARCOMA**

Osteosarcoma (OS) is the most common primary bone cancer. This tumor has a bimodal distribution with a high peak during adolescence and a smaller peak in elderly individuals (259) (Figure 2). Survival rates for children and young adults with non-metastatic disease have remained at 60–70%; however, outcome is reduced in patients with metastases (259). Unlike other childhood sarcomas, which are characterized by specific chromosome rearrangements and low mutation rate, complex genomic rearrangements are involved in OS. Indeed, OS exhibits extensive intra-tumoral heterogeneity and has a higher mutation rate (259).

**Familial Osteosarcoma**

OS is a sentinel cancer in many heritable cancer predisposition syndromes, including autosomal dominant cancer predisposition syndromes such as LFS (73–75) and Diamond–Blackfan anemia (47–50) (Table 2). Furthermore, recessive cancer syndromes associated with OS are Rothmund–Thomson syndrome (102–105), Baller–Gerold syndrome (20, 21), RAPADILINO syndrome (106, 107), Werner syndrome (118–120), Bloom syndrome (32), and ATR-X syndrome (19). OS has also been seen to arise in Paget's disease of bone (98, 99).

**Sporadic Osteosarcoma**

Targeted gene sequencing and WGS and WES studies have identified uncommon variants in tumor-suppressor and cancer predisposition genes (Table 1), while candidate gene, pathway studies, and GWAS have discovered common variants in genes involved in several key pathways for OS development (259) (Table 3).

**Uncommon, Moderate-Penetrance Variants**

In 2015, a sequencing on 765 germline DNA samples showed the presence of uncommon TP53 germline variants that could contribute to OS development; 3.8% of these variants were associated with LFS, and 5.7% were uncommon exonic variants of uncertain clinical significance (138). Another sequencing study on 1120 cases found 7/39 OS patients carrying pathogenic and likely pathogenic variants in TP53, RB1, APC, MSH2, and PALB2 (2). In 2016, a targeted exon sequencing on 1162 patients with sarcoma found that >50% of all patients carried pathogenic variants in TP53, BRCA2, ATM, ATR, and in ERCC2 (128). Among 11% of patients with OS, one patient showed a probable pathogenic variant in ERCC2. In the same work, an excess of functionally pathogenic variants in ERCC2 was found to enhance cell sensitivity to cisplatin, commonly used in the treatment of OS (128). Recently, a sequencing study of 1244 OS patients showed that 28% of patients carried pathogenic and likely pathogenic variants in OS susceptibility genes, identifying new candidates (CDKN2A, MEN1, VHL, POT1, and ATRX) that require further confirmation in independent cohorts (129).

**Common, Low-Penetrance Variants**

In 2013, the first GWAS study on 941 cases and 3291 controls of European ancestry, identified two risk loci, one at 6p21.3 (rs1906953) mapping in intron 7 of GRM4, and the other at 2p25.2 (rs751996) in an intergenic region (173). Subsequently, a GWAS study on OS metastasis at diagnosis identified rs7034162 at 9p24.1 (in NFIB) associated with metastasis (176). Functional investigations showed that reduced NFIB expression, due to the risk allele of the rs7034162 SNP, promoted an increase of OS cell migration, proliferation, and colony formation (176). In 2016, a case–control study identified that, for SNPs in genes associated with inter-individual variation in leukocyte telomere length (LTL) (ACYP2, TERC, NAF1, TERT, OBFC1, CTC1, and RTEL1), the allele associated with longer LTL increased OS risk, mainly rs9420907 in OBFC1 (165). These findings were confirmed in 537 OS cases belonging to California Cancer Registry (166).

**Constitutional Chromosomal Abnormalities**

Next to the heterogeneous somatic CNV scenario present in OS, in a study conducted on 54 patients with childhood tumor, two large germlinal CNVs were identified in 2 OS patients: dup4q13.33 of 476 kb containing STATH, CSN1S2B, CAB51, CSN1S1, CSN2, HTN3, HTN1, CSN1S2A, C4orf40, ODAM, FDCSP, and CSN3; and dup18q21.33 of 600 kb containing RNF152, CDH20, and PIGN (240). In 2020, a duplication of DDX10 in an OS patient with a germline variant in GJB2 has been reported (3).

**RHABDOMYOSARCOMA**

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in childhood and represents a high-grade neoplasm of skeletal myoblast-like cells. Currently, 5-year overall survival of pediatric RMS exceeds 70% (260). The two major histological subtypes are embryonal (ERMS, 67%) and alveolar (ARMS, 32%) (261). ARMS is uniformly distributed among the different age groups (Figure 2) and has a worse prognosis; ERMS has a bimodal distribution (the first peak in early childhood and the second one in early adolescence) and has a better outcome (260, 262) (Figure 2). At somatic level, ARMS is often associated with fusion of FOXO and PAX3 or PAX7, while ERMS does not show such translocations, but it is characterized by loss of heterozygosity at 11p15.5 as well as mutations in TP53, NRAS, Kras, HRAS, PIK3CA, CTNNB1, and FGFR4 (263). Since a small but substantial fraction of ARMS patients do not harbor one of these translocations, and tumors from those patients are biologically and clinically similar to ERMS, the disease classification has been further refined dividing RMS into “fusion-positive” RMS (FPRMS) and “fusion-negative” RMS (FNFRMS) subtypes.
Familial Rhabdomyosarcoma

Although RMS is primarily sporadic (264, 265), it arises in several syndromes. Cancer predisposition syndromes appear to be more frequent in patients with ERMS than in those with ARMS (260). Among syndromes commonly associated with RMS and reported in Table 2 (24–27, 42, 43, 52–54, 64, 75, 80, 81, 86, 87, 89–92, 94, 96), a high RMS risk is associated with RASopathies-like type I neurofibromatosis (NF1) (deletions in NF1), Costello syndrome (HRAS mutations), and Noonan syndrome (germline variants activating RAS-MAPK pathway), highlighting the tight dependence of RMS on the RAS pathway, which results to be activated in 40% of sporadic ERMS (263, 266, 267). In particular, up to 25% of children affected by Costello syndrome shows high RMS risk (43, 268). In addition, children who have a first-degree relative with cancer, particularly if the cancer occurred at a young age (<30 years), show an increase in RMS risk, especially of ERMS (269).

Sporadic Rhabdomyosarcoma

Unlike OS and Ewing sarcoma, GWAS studies for RMS have not been published (260) and few studies identified uncommon germline variants associated with tumor susceptibility (2, 52, 133, 139, 142, 270) (Table 1).

Many studies have found the presence of DICER1 germline mutations in sporadic RMS patients for whom DICER syndrome has been ruled out (52, 142). WES and WGS on 1,120 patients with pediatric cancers identified germline pathogenic variants in 3/43 RMS patients in TP53 and BRCA2 (2). In a cohort of 66 patients with sarcoma, one patient with ARMS showed a protein-truncating variant (in ERCC4) co-occurring with predicted pathogenic mutations (in ATM, FANCI, and MSH6), suggesting a possible collective impact of these genetic variants on DNA repair and genomic instability, therefore conferring susceptibility to tumorigenesis (133).

EWING SARCOMA

Ewing sarcoma (EWS) is the second most frequent primary skeletal tumor that mainly affects bone and can also arise in soft tissue. It occurs in children, adolescents, and young adult (Figure 2). It is highly aggressive, with a survival of 70–80% for patients with standard-risk and localized disease and 30% for those with metastasis at diagnosis (20–25% of those resistant to intensive therapy) (271). EWS is characterized by low somatic mutation rate (272–274), mainly including fusions between EWSR1 and members of the ETS gene family, usually EWSR1-FLI1, that play a key role in its pathogenesis. The chimeric protein EWSR1-FLI1 leads to the production of an oncogenic transcription factor that binds GGAA motifs (174, 271, 275, 276).

Familial Ewing Sarcoma

To date, no susceptibility genes to familial forms of EWS have been reported, and only case reports about siblings and cousins affected by this tumor have been documented (277, 278). On the basis of these isolated clinical cases, the presence of other cancer types among familial members of EWS patients (279, 280) suggests an important contribution of genetic susceptibility factors in this tumor. Nowadays, EWS is not considered part of predisposition syndromes because of its rare occurrence among these (281).

Sporadic Ewing Sarcoma

WES, WGS, and GWAS studies have led to the identification of uncommon (Table 1) and common (Table 3) germline variants associated with the risk of developing EWS. Despite the rarity and the paucity of information about familial cases, most of the known genetic scenario on this tumor concerns the sporadic form.

Uncommon, Moderate-Penetrance Variants

Two WGS and WES studies on EWS revealed an over-representation of uncommon pathogenic and likely pathogenic variants in DNA repair and cancer-predisposing syndrome genes (2, 130). Studies on small cohorts of patients identified other uncommon germline variants in BRCA2 (146) and in PTPRD (140).

Common, Low-Penetrance Variants

In 2012, the first GWAS on EWS found 3 susceptibility loci at 1p36.22, 10q21, and 15q15, identifying a strong association of EWS risk with rs9430161 (25 kb upstream of TARDBP) and rs224278 (5 kb upstream of EGR2), and a modest association with rs4924410 (at 15q15) (172). The second GWAS detected a tagging variant strongly associated with EWS at 15q15.1 (rs2412476 near BMF) and new risk loci at 6p25.1, 20p11.22, and 20p11.23 (152). Expression quantitative locus (eQTL) analyses identified candidate genes at 6p25.1 (RREB1) and 20p11.23 (KIZ) (152). Independent studies showed that a different number of germline GGAA repeats in polymorphic enhancer-like GGAA microsatellites impacts the binding between these regulatory elements and EWS cancer driver mutations (EWSR1-FLI1), affecting downstream genes expression (174, 178, 282).

These studies further suggest that cooperation between regulatory germline variants and somatic mutations can drive oncogenesis and create a major source of inter-tumor heterogeneity, determining clinical outcome and drug response through modulation of a druggable key downstream player.

Constitutional Chromosomal Abnormalities

Only one study reports the presence of germline CNV associated with EWS, describing a 14-year-old male with EWS carrying an intragenic deletion in PTPRD (283). Notably, germline and somatic variants in PTPRD have been already identified in a limited number of EWS patients (140).

CONCLUSIONS

For a long time, the prevalence of childhood cancer attributed to genetic predisposition was generally considered very low. However, to date, WGS, WES, and GWAS studies performed on pediatric cancers have made it possible to highlight a strong contribution of germline variants to tumorigenesis, helping us to better understand the etiology underlying pediatric tumors. Indeed, an important body of work allows us to highlight that...
the prevalence of hereditable risk variants in pediatric solid cancers ranges between 6% and 18% (Figure 3). These variants generally affect the functions of genes belonging to biological processes linked to tumorigenesis, such as cell-cycle control, apoptosis, DNA repair, and transcriptional regulatory programs. The enrichment of genetic alterations in these pathways is often due to a bias because, since germline variant analysis is a highly challenging task in general, the vast majority of studies are based on a "candidate-gene" approach, which means they focus on specific subsets of genes already known to play a key role in cancer predisposition and tumorigenesis. For this reason, it may be useful exploiting a genome-wide scale approach, e.g., exome-wide association studies, to investigate the presence of genetic alterations predisposing to cancer also in genes involved in pathways others than the ones above mentioned. This approach may contribute in a meaningful way to the current knowledge of the mechanisms underlying solid pediatric tumors onset.

A very recent study reports a high number of germline variants in new candidate susceptibility genes, highlighting that some of them carry druggable alterations (3). It should be emphasized that the presence of germline variants in target therapeutic genes could improve current approaches of personalized therapy, making them more efficient and less toxic to patients. Furthermore, a more in-depth investigation of the germline component underlying tumor development should also be performed on pediatric solid tumors for which there is not yet a broad knowledge of germline landscape (e.g., thyroid carcinoma, melanoma) (284–289).

Our literature review reveals that the presence of specific germline mutations is often associated with increased frequency of somatically acquired cancer-specific abnormalities (such as aberrations, rearrangements). The interplay between somatic and germline mutations may be at the basis of high interindividual tumor heterogeneity (290). For example, the cooperation between regulatory germline variants and somatic mutations underlines the importance of regulatory regions to stratify patients into risk groups to predict the clinical outcome and therapeutic approaches (290). In NB, inherited deleterious variants in genes that code for proteins involved in chromosomal segregation, centrosome segregation, DNA repair, and spindle apparatus machinery are thought to be the cause of chromosome instability at somatic levels (199). A similar germline–somatic interaction has been proposed for MB; indeed, germline TP53 mutations are often found in combination with tumors characterized by catastrophic DNA chromothripsis. Determining if germline risk alleles predispose to genomic instability in

![Figure 3](image-url)
pediatric cancers is an important research objective for biologists and geneticists. Another interesting research field is related to the impact of risk alleles on genomic regions that regulate mutated cancer driver genes. The mechanisms underlying this type of interaction between germline–somatic variation have been elegantly elucidated in the EWS (174, 178, 282), and it is reasonable to think that it is common to other pediatric tumors as well. No relevant study has investigated the possible interplay between germline variations and epigenetic somatic events. For instance, there is an urgent need to find possible associations between germline risk alleles and DNA methylation of tumor. Studies integrating information on germline, somatic, and epigenomic variations using gene expression data as the intermediate phenotype may unravel the biological mechanisms underlying oncogenic interactions and cooperation of these different types of genomic variations.

The low number of recurrent somatic mutations in some pediatric cancers, compared to adult ones (135), does not explain the clinical heterogeneity and the resulting need for personalized therapies in tumors. Confirming a germline contribution to the clinical heterogeneity, some studies have highlighted that specific pathogenic variants are much more common in specific tumor histotypes (137, 147) and these associations could be used for the management and stratification of patients. Thereby, implementing screening tests with the introduction of germline detection would bring clinical benefits. In addition, screening for germline and somatic components of the tumor could lead to the identification of new prognostic markers to monitor cancer and predict clinical outcome. Finally, the use of these information in screening tests is important in the context of genetic counseling, to monitor and supervise family members of patients.

It is also important to note that many genetic syndromes such as Beckwith–Wiedemann, Costello, Fanconi anemia, Gorlin, Noonan syndrome, Li-Fraumeni, and others (Table 2) are both characterized by genetic and/or allelic heterogeneity and associated with the risk to develop different types of pediatric cancers. Therefore, NGS-based cancer gene panel tests should be performed in children with a genetic syndrome to ensure the patient a more precise diagnosis and to be able to assess the risk of developing a cancer disease. A clinical management that includes a cancer genetic test not only is useful to indicate a modification of the surveillance that also integrates periodic and cancer specific diagnostic tests, but over time it will increase our knowledge of genetic risk variants and thus will give a clearer picture of cancer risk in children affected by genetic syndrome. This surely can have a positive impact on improving patient care and survival.

**AUTHOR CONTRIBUTIONS**

MC and AI contributed to the design, reviewing, and editing of this manuscript. AM, SC, TM, and MT contributed to the design, writing, and editing of this manuscript. All authors have read and agreed to the published version of the manuscript.

**FUNDING**

This research was funded by Associazione Italiana per la Ricerca sul Cancro (Grant no. 19255 to MC and Grant no. 20757 to AI), Fondazione Italiana per la Lotta al Neuroblastoma (to MC), Associazione Oncologia Pediatrica e Neuroblastoma (to MC), and Regione Campania SATIN grant 2018–2020 (to MC).

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27.低价提取的基因

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Capasso et al. Genetics of Pediatric Cancers

October 2020 | Volume 10 | Article 590033

Frontiers in Oncology | www.frontiersin.org

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**Conflict of Interest:** All authors were employed by the company CEINGE Biotecnologie Avanzate.