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Trends in Cancer

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Forum

Puzzling phenomenon: adult-onset cancer predisposition and pediatric cancer

Michaela Kuhlen [1,*], Thomas G. Hofmann[2], and Monika M. Golas [3]

Pathogenic variants (PVs) in DNA repair–linked adult-onset cancer predisposition genes, including double heterozygosity, are increasingly identified in pediatric patients with cancer. Their role in childhood cancer, however, remains poorly understood. Integrating comprehensive tumor analysis is integral for understanding the contribution of such PVs in cancer development and personalized cancer care.

Adult-onset cancer predisposition genes and pediatric cancer

The availability of next-generation sequencing (NGS) has fostered detection of (likely) pathogenic variants (PVs) in adult-onset cancer predisposition genes (aoCPGs) in pediatric patients with cancer. In children and adolescents, ~3% of cancers harbor an aoCPG PV, and ~80% of these are confirmed as germline in origin [1]. PVs are observed in aoCPGs related to hereditary breast and/or ovarian cancer (HBOC), such as *BRCA1*, *BRCA2*, *PALB2*, and *ATM*, as well as the Lynch syndrome (LS)-associated mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*, among others. These genes often play crucial roles in DNA damage response (DDR) and DNA repair (Figure 1A).

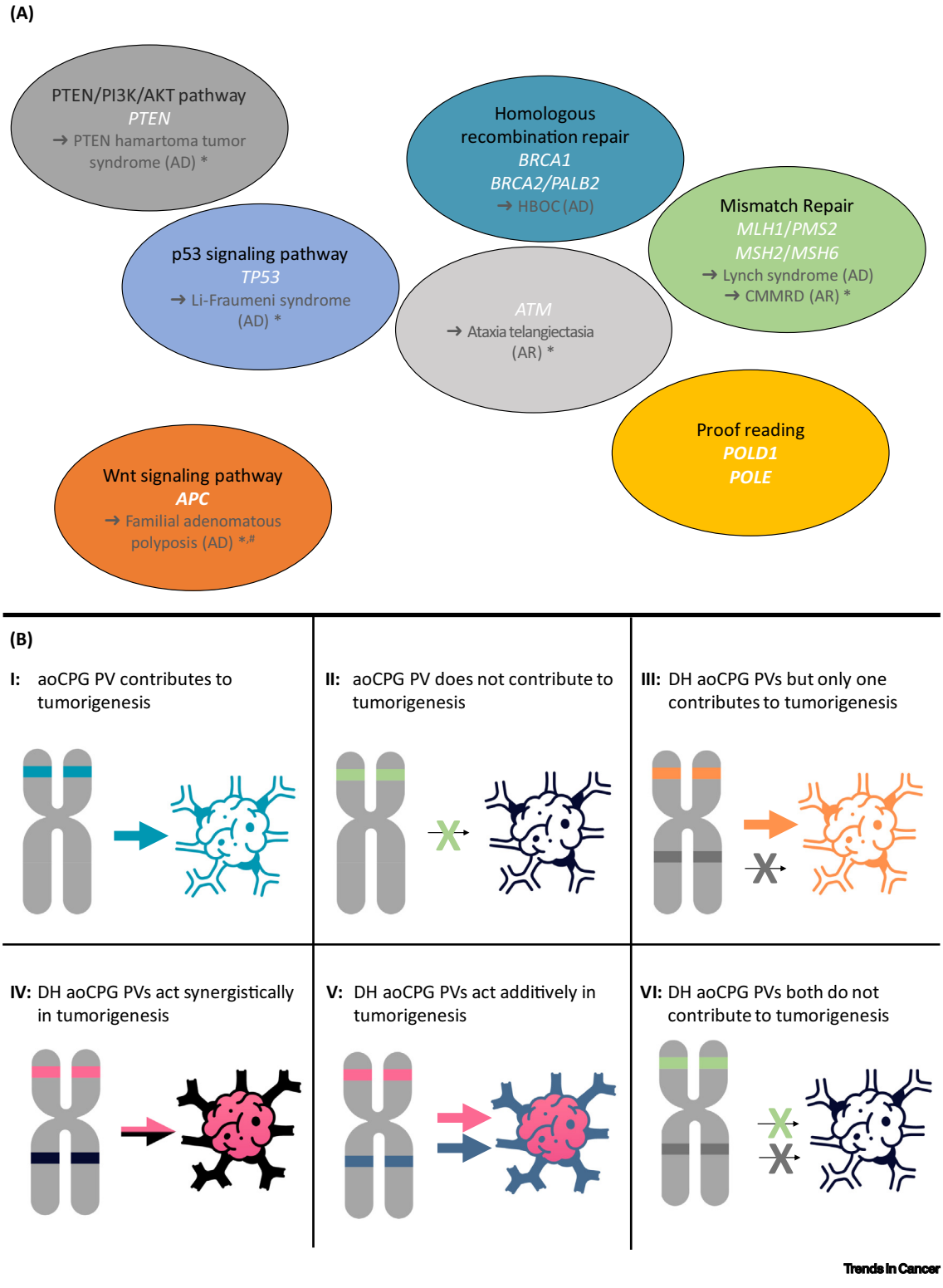
Specific aoCPG PVs are well known to cause pediatric cancer, depending on genotype/phenotype correlations and the presence of mono- or biallelic PVs. For example, in Li-Fraumeni syndrome (LFS), the age of first cancer is younger and the cancer risk greater in patients carrying *TP53* dominant-negative missense variants. Monoallelic and biallelic MMR gene PVs cause adult-onset LS and childhood-onset constitutional mismatch repair deficiency, respectively. However, in some patients, the aoCPG genotype does not have a known association with pediatric cancer, and therefore its contribution to tumorigenesis is uncertain. This forum explores the consequences of recent advancements aimed at understanding the impact of PVs in aoCPGs on childhood cancer, with a focus on aoCPGs linked to DDR and DNA repair.

Causal role of aoCPGs in childhood cancer

Integral to the interpretation of genomic data is the recognition that germline PVs in CPGs can either contribute to cancer development or be coincidental (Figure 1B). To delineate this distinction, comprehensive analyses of the individual tumor, complemented by germline sequencing, is required to assess the impact of germline PVs on the tumor. Key findings arise from (i) revealing a second hit through somatic mutation, loss of heterozygosity (LOH), or epigenetic silencing causing biallelic inactivation of the gene with the germline PV; (ii) conducting tumor analyses for homologous recombination repair deficiency (HRD), microsatellite instability (MSI), and tumor mutational burden; and (iii) analyzing the somatic mutation pattern, often categorized into Alexandrov mutational signatures [2], among other approaches. Such comprehensive analyses are increasingly employed in the study of pediatric cancer.

The following are examples where tumor molecular analyses have been used to confirm or refute the association of an aoCPG germline PV with pediatric cancer. In a male carrier of an HBOC-associated *PALB2* PV with metachronous acute lymphoblastic leukemia and Ewing sarcoma, tumor analyses found no evidence of *PALB2*-dependent tumorigenesis (Figure 1B,II) [3]. In contrast, an association was observed in pediatric medulloblastoma between germline *BRCA2* and *PALB2* PVs and Alexandrov mutational signature 3, among others (Figure 1B,IV) [1]. This signature is indicative of HRD, implying a contribution of HBOC-associated PVs to the somatic mutation landscape. Mutational signature 3 was also identified in one tumor each (primitive neuroectodermal tumor, embryonal rhabdomyosarcoma) with monoallelic and biallelic *ATM* variants, whereas an osteosarcoma with monoallelic *BRCA2* inactivation did not show a signature attributed to HRD (Figure 1B,II) [1].

Similarly, ependymoma tissue analyses did not support LS-associated tumor development in a female carrier of a *PMS2* PV (Figure 1B,II) [4]. In a male adolescent with germline *MSH6* PV, however, NGS revealed an ultrahypermutated glioblastoma consistent with mutational signature 14 (Figure 1B,I) [5]. This signature was attributed to somatic inactivation of the second *MSH6* allele, followed by a somatic *POLE* mutation. In a female patient with osteosarcoma with another *PMS2* PV, tumor analysis demonstrated features consistent with LS-related tumorigenesis, including hypermutation, alternative telomere lengthening, loss of PMS2 expression, and MSI (Figure 1B,I) [4]. The presence of a somatic chromosome 7 loss (including the *PMS2* locus), coupled with MMR-associated signature 26, indicated a second hit mechanism in a myelodysplastic syndrome observed in a child with a germline *PMS2* PV (Figure 1B,I) [1]. Note that these cancer entities expand beyond the core LS and HBOC cancer spectrum, suggesting a potentially broader tumor profile than previously recognized.



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Digenic and oligogenic PV combinations in cancer

A limited number of individuals in the pediatric population have been documented with multiple germline PVs linked to DNA repair processes (Table 1). A carrier status for PVs in two genes is referred to as 'double heterozygosity' (DH) or more generally as 'multiple heterozygosity' or 'multilocus inherited neoplasia allele syndrome' [6].

DH in children with cancer thus introduces an additional layer of complexity to the assessment of the PVs' role in cancer development. Due to synergistic effects, DH in high/moderate penetrance autosomal-dominant genes within the same pathway may potentially lead to a more severe phenotype, with earlier cancer development or a broader cancer spectrum (Figure 1B,IV). Multiple PVs could also have an additive effect, with each PV independently promoting cancer, regardless of the respective other PV (Figure 1B,V). Conversely, if the DH involves two autosomal-recessive CPGs, the effect of DH may be negligible, even in the presence of PVs within genes of the same pathway (Figure 1B,VI). Variations of these effects may arise in patients with combinations of high/moderate penetrance PVs in genes of related but not identical pathways or with one PV in a high/moderate penetrance autosomal-dominant CPG and another PV in an autosomal-recessive CPG. Moreover, as for the single PVs, one or both PVs may represent mere coincidence, unrelated to the cancer in a given child (Figure 1B,III).

In the studies listed in Table 1, mechanistic data are available. Some DH cases, with genes sharing a common pathway, suggest a synergistic effect on cancer development. For example, a young girl with missense PVs in both *TP53* and *PTEN* manifested multiple tumors at an early age, including neuroblastoma, granulosa cell tumor, xanthoastrocytoma, and liposarcoma [7]. PTEN and p53 collaborate in the PI3K/AKT/MDM2 pathway, where PTEN prevents p53 from being degraded by MDM2 [8] (Figure 1A). Additionally, p53 regulates *PTEN* expression [9]. Simultaneous PVs in *PTEN* and *TP53* may thus interact, potentially resulting in a more severe LFS phenotype, as observed in the young patient (Figure 1B,IV). Notably, despite no somatic second hit in *TP53* being detected in the patient's tumor tissues, there was observed LOH in *PTEN* in certain cancer tissues after chemotherapy [7]. The data presented do not exclude the possibility of biallelic *TP53* and *PTEN* inactivation through alternative mechanisms; however, the absence of a second hit also aligns with the notion that the biallelic inactivation, as per Knudsen's two-hit hypothesis, seems incomplete, even for highly penetrant genes such as *TP53* [10].

An accelerated adenomatous polyposis phenotype was observed in a 10-year-old patient with DH in *APC* and *MLH1* [11]. In this patient, adenomas with low-grade dysplasia showed aberrant β-catenin immunohistochemical staining, indicative of biallelic *APC* inactivation, whereas high-grade dysplasia areas exhibited additional MLH1 loss, suggesting a sequential mechanism: biallelic *APC* loss first, followed by biallelic *MLH1* loss. The loss of *APC* and *MLH1* impacts distinct pathways, the *MLH1* PV affecting the mismatch repair system and the *APC* PV being affecting the Wnt signaling pathway. Thus, both PVs promote tumorigenesis by an 'additive effect' (Figure 1B,V). The dual loss has the potential to intensify carcinogenesis by favoring the acquisition of diverse genomic alterations and proliferation, thereby contributing to the severe phenotype observed in the patient.

In contrast, Schamschula *et al.* reported a patient with PVs in *PMS2* and *POLD1* and a severe phenotype including early cancer onset and tumor features supporting a mixed MSI-ultrahypermutator phenotype [12]. The *POLD1* PV and the *PMS2* PV both lead to reduced fidelity of DNA replication through loss of polymerase proofreading and loss of mismatch repair, respectively. This 'synergistic effect' is evident in the ultramutation of the tumor and its mutational signature SBS20 that is specifically caused by concurrent deficiencies of both polymerase delta proofreading and mismatch repair (Figure 1B,IV).

Concluding remarks

Growing molecular evidence indicates that aoCPGs in DDR and DNA repair pathways play a previously underestimated and poorly understood role in childhood cancer. We advocate for individual assessments of each cancer found in pediatric patients to identify aoCPG PVs and assess their impact on cancer development, treatment response, and future cancer risk. Understanding these will have implications for both genetic counseling and clinical management, including personalized treatment, surveillance, and prevention strategies.

Figure 1. Role of DNA repair–linked germline pathogenic variants (PVs) in cancer. (A) (Adult-onset) cancer predisposition genes in various cancer/signaling pathways including DNA damage response and DNA repair, mode of inheritance (AD, autosomal-dominant; AR, autosomal-recessive), and associated cancer predisposition syndromes (*childhood onset, #in childhood primarily associated with hepatoblastoma, medulloblastoma). The Wnt signaling pathway does not interrelate with the other cancer/signaling pathways; the latter are linked among each other. (B) PVs in adult-onset cancer predisposition genes (aoCPGs) and tumorigenesis. (I) aoCPG PV contributes to tumorigenesis. (II) aoCPG PV does not contribute to tumorigenesis; i.e., PV is coincidental. (III) Double heterozygous (DH) aoCPG PVs, but only one contributes to tumorigenesis. (IV) DH aoCPG PVs act synergistically in tumorigenesis. (V) DH aoCPG PVs act additively in tumorigenesis. (VI) Both DH aoCPG PVs do not contribute to tumorigenesis.

Table 1. Children and adolescents with cancer predisposition syndromes carrying two or more pathogenic germline variants in cancer predisposition genes as listed in OMIM, with at least one gene involved in DNA damage response and DNA repair

Refs	Gene	Variant	Protein	Class[a]	Gene	Variant	Protein	Class[a]	Pathomechanistic studies	Associated CPS	Phenotype observed in the patient
Berrino *et al.*, 2022 [13]	***PMS2***	NM_000535.7: c.2174+1G>A	p.?	5	***POLE***	NM_006231.4: c.890C>G	p.Ser297Cys	4	Second hit in *PMS2*; predominant SBS15, followed by SBS6, SBS1, and SBS14; ultramutated tumor with TMB 295–530 mutations/Mb; MSI (7–52% unstable loci)	Lynch syndrome (*PMS2*). Polymerase proofreading-associated polyposis.	Colorectal cancer (bifocal), urothelial carcinoma of the bladder (as young adult)
McGee *et al.*, 2023 [1]	***PMS2***	c.137G>T	p.Ser46Ile	4	*AXIN2*	c.1201-2A>G	p.?	4	PMS2 expression loss in IHC	Lynch syndrome, CMMRD (*PMS2*). Oligodontia-colorectal cancer syndrome (*AXIN2*).	Low-grade glioma (ganglioglioma)
Michaeli *et al.*, 2022 [14]	***PMS2***	NM_000535.7: c.2148dup	p.Val717fs	5	***POLE***	NM_006231.4: c.830A>G	p.Glu277Gly	4	MSS; loss of nuclear PMS2 expression; second hit in *PMS2*; ultramutated tumor with TMB 144–276 mutations/Mb; signatures SBS10a, SBS14, SBS15, and SBS44.	Lynch syndrome (*PMS2*). Polymerase proofreading-associated polyposis.	Medulloblastoma, desmoplastic
Plon *et al.*, 2008 [7]	***TP53***	NM_000546.6: c.844C>T	p.Arg282Trp	5	*PTEN*	NM_000314.8: c.334C>G	p.Leu112Val	4	No somatic mutation in *TP53* or *PTEN* in granulosa cell tumor, xanthoastrocytoma, and liposarcoma; *PTEN* LOH in granulosa cell tumor and liposarcoma (after chemotherapy); no *TP53* LOH	Li-Fraumeni syndrome (*TP53*). PTEN hamartoma tumor syndrome (*PTEN*).	Neuroblastoma, anaplastic juvenile granulosa cell tumor, xanthoastrocytoma, pleomorphic liposarcoma
Schamschula *et al.*, 2022 [12]	***PMS2***	NM_000535.7: c.2007-786_2174+493del (deletion of exon 12)	p.Ser669_Ala725delinsArg	5	***POLD1***	NM_002691.4: c.946G>A	p.(Asp316Asn)	4	MSI, PMS2 expression loss[c], ultramutated TMB 278 mutations/Mb[c]; proportion of short tandem repeat variants, 27%[c]; signature SBS20 and SBS26, each 38%[c]; LOH in *PMS2*[c]	Lynch syndrome (*PMS2*). Polymerase proofreading-associated polyposis.	Colorectal cancer, multiple; urothelial carcinoma of ureter and nephrogenic adenoma of the urinary bladder (as adult)
Scheenstra *et al.*, 2003 [11]	*APC*	NM_000038.6: c.3927_3931del	p.Glu1309fs	5	***MLH1***[b]	NM_000249.4: c.677G>A	p.?	5	Aberrant cytoplasmic and nuclear localization of β-catenin; expression loss of MLH1	Familial adenomatous polyposis (*APC*). Lynch syndrome, CMMRD (*MLH1*).	Adenomatous polyposis, rapidly progressing

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Declaration of interests

The authors have no conflicts of interest to declare.

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Notes to table 1:
Abbreviations: CMMRD, Constitutional mismatch repair deficiency; IHC, immunohistochemistry; TMB, tumor mutational burden.
Bold gene names are genes involved in DNA damage response and DNA repair.
[a]All germline variants were evaluated on the basis of criteria proposed by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) or gene-specific criteria such as ClinGen ENIGMA for *BRCA1/2* (version 1.0.0) and InSiGHT for Lynch syndrome genes (version 2.4). Variants are heterozygous, unless otherwise indicated.
[b]Autosomal recessive.
[c]Analysis performed using tissue of a subsequent cancer.