Exploring rare germline variants in childhood cancer patients with features suggestive of an underlying genetic predisposition to cancer

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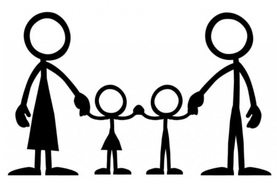
Introduction and Aims: Detection of cancer-predisposing germline variants in childhood cancer patients can influence therapeutic decisions, disease surveillance and cancer risk clarification for family members. We aimed to expand existing knowledge of cancer-predisposing germline variants by sequencing the germline DNA of childhood cancer patients with features indicative of a genetic predisposition to cancer.

Methods:

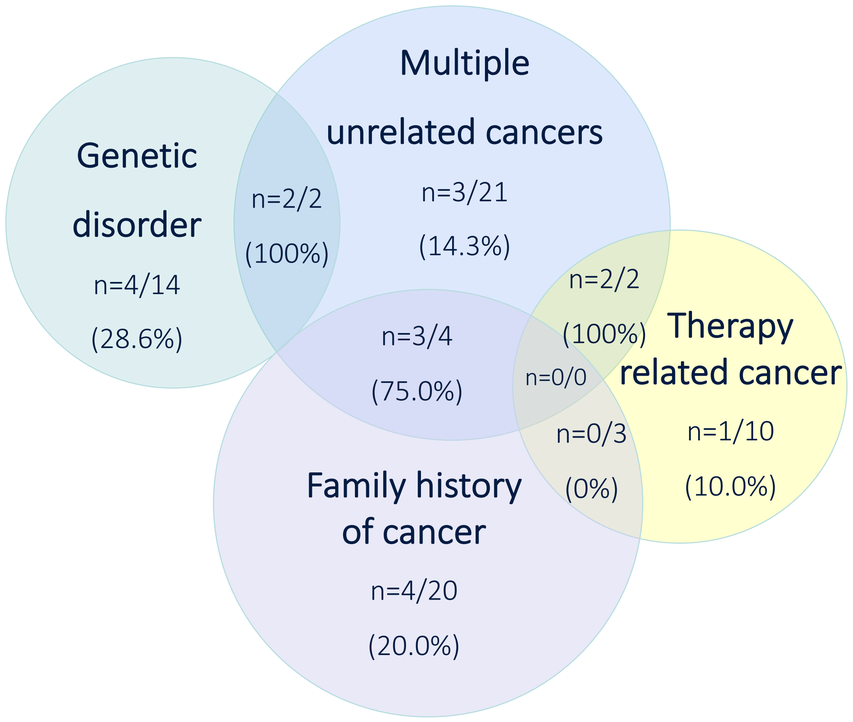


Childhood cancer patients suspected of genetic predisposition.

Exome sequencing germline DNA and pathogenicity interpretation of rare copy number and exonic non-synonymous variants in known cancer predisposition genes, as well as cancer related and DNA repair genes (n=1047). Rare variant burden analysis of cancer predisposition genes in patients compared to healthy aged controls.

Results: Pathogenic or likely pathogenic (P/LP) variants in known cancer predisposition genes were detected in19/76 patients (Figure 1). Patients meeting two inclusion criteria were more likely to carry a P/LP germline variant (Figure 1). Genotype-phenotype associations were discordant in 11/19 (58%) patients, with 10/11 patients variants detected in adult onset cancer predisposition genes (Table 1). Of the 14 patients with a first cancer diagnosis of lymphoma, 7 (50%) were found to carry a P/LP variant (Figure 2). A rare variant burden analysis found significant enrichment of P/LP variants in autosomal dominant cancer predisposition genes (n=31) in the patients compared to healthy aged controls (Figure 3). Selected discordant and candidate cancer-predisposing germline variants were considered for further analyses (Figure 4).

19/76 (25%) childhood cancer patients carried P/LP germline variants in cancer predisposition genes



7/11 (63.6%) childhood cancer patients meeting two inclusion criteria carried P/LP variants

**p=0.0039 (Fishers exact test, n=76)

Figure 1: Venn diagram of the number of childhood cancer patients with each circle representing the inclusion criteria. The percentage indicates the proportion of patients with P/LP variants detected in known cancer predisposition genes (n=13).

Table 1: Cancer predisposition genes (n=13) with P/LP germline variants detected, listed according to genotype phenotype association

Concordant (8/19 patients)	Discordant (11/19 patients)
ELP1	***ATM***
ITK (bi-allelic)	***CHEK2***
MSH2 (bi-allelic)	***BRCA1***
MSH6(bi-allelic)	***EPCAM***
PMS2(bi-allelic)	***PMS2***
RB1	*SBDS*
TP53	
TRIM37(bi-allelic)	

In bold are the genes with pathogenic heterozygous germline variants, typically associated with adult onset cancers.

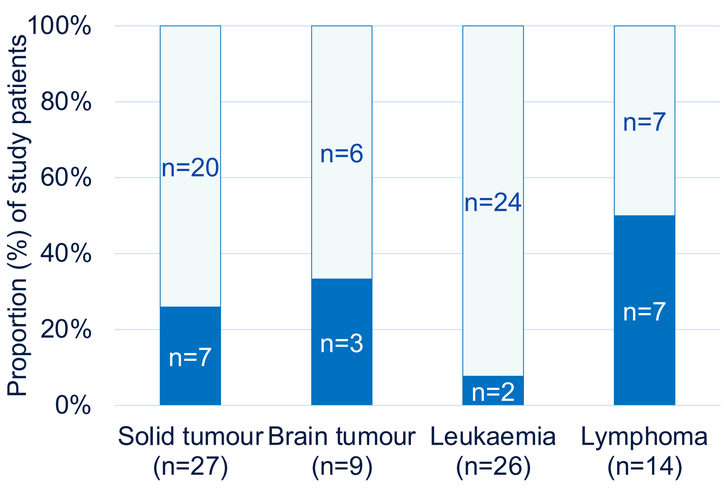


Figure 2: Proportion of patients with P/LP germline variants (dark blue) according to first cancer diagnosis

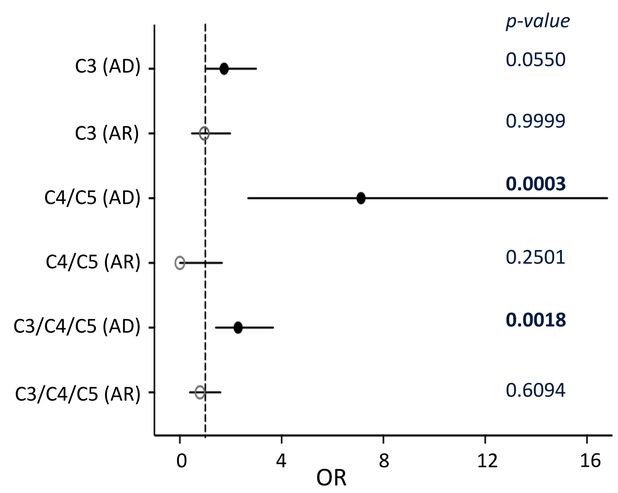


Figure 3: Rare variant burden analysis of 31 autosomal dominant (AD) and 27 autosomal recessive (AR) cancer predisposition genes comparing patients (n=63) to healthy aged controls (n=1107). Variants predicted deleterious (C3), P/LP (C4/C5). Fisher's exact test, OR = odds ratio

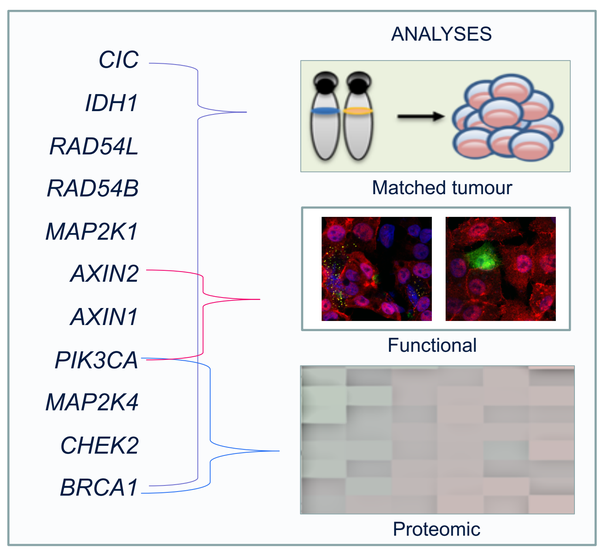


Figure 4: Genes with germline variants detected in childhood cancer patients prioritised for further analyses.

Conclusions: Selecting childhood cancer patients for germline genomic analysis, with features suggestive of genetic predisposition, detected likely cancer-predisposing variants in known cancer predisposition genes in 19/76 (25%). Rare variants in 31 autosomal dominant cancer predisposition genes were significantly enriched compared to a healthy aged population. Selection of childhood cancer patients, particularly those with two suspicious features, would facilitate integration of germline testing in the paediatric oncology clinic. However, more research is required into heterozygous P/LP variants in adult onset cancer predisposition genes detected in the germline of childhood cancer patients. Continuing investigations of candidate cancer-predisposing germline variants is crucial in determining the mechanisms underpinning tumour development in children, potentially leading to earlier detection and uncovering therapeutic targets.

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