Germline mutational landscape in pediatric cancers and disease relevance: Insights from a Canadian Experience

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BACKGROUND AND AIMS

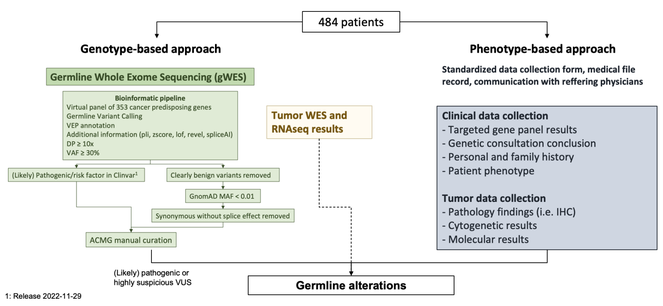
- Wide **variability** in the reported **rate of cancer predisposition syndromes (CPS)** accross pediatric cancer predisposition studies: 3.8-18% (1-3)
- Factors influencing CPS rate:
  - **Cohort** heterogeneity
  - Variability in **genes** included in panels
  - Definition of positive **germline findings**
  - Consideration of clinical diagnoses w/o molecular defects

Study objectives:

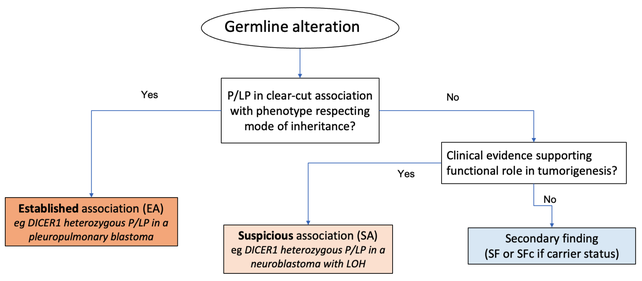
- Characterize the germline mutational landscape of **children** with **cancer** in **Quebec**
- Assess the clinical relevance of these findings by integrating **clinical** and **molecular** data.

METHODS

Combined genotype and phenotype-based approach of 484 pediatric cancer patients in Quebec



Categorization of germlines alterations in 3 levels of causality according to phenotype and transmission mode



RESULTS

This multicenter study includes an equal distribution of hematologic and solid cancers, with 17 patients diagnosed with multiple cancers.

Original cohort		
Triceps	183	37,81
Signature	304	62,81
	median	**range**
Follow-up duration (years)	3,96	2-10,5
Age at inclusion diagnosis (years)	7,8	0-18,9
Sexe	**patients (n)**	**(%)**
Male	280	57,85
Female	204	42,15
Multiple cancers		
All	**17**	**3,51**
Prior	11	2,27
Subsequent malignant neoplasm (SMN	5	1,03
Synchronous	1	0,21

Diagnosis (at inclusion)		
Hematologic malignancy	**240**	**49,59**
ALL	167	34,50
AML	51	10,54
NHL	13	2,69
Myeloproliferative neoplasm	5	1,03
HL	4	0,83
Solid tumor	**244**	**50,41**
Bone	62	12,81
STS	51	10,54
Neuroblastoma	45	9,3
Renal tumor	30	6,2
Other	17	3,51
Liver	11	2,27
Non GCT ovarian tumors	8	1,65
Rhabdoid	8	1,65
Head&Neck	7	1,45
NET	5	1,03

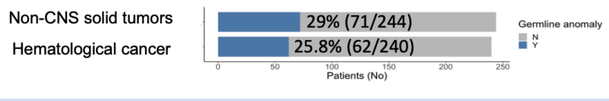
153 germline anomalies were identified in 133 patients (27%)

ACMG STANDARDS AND GUIDELINES

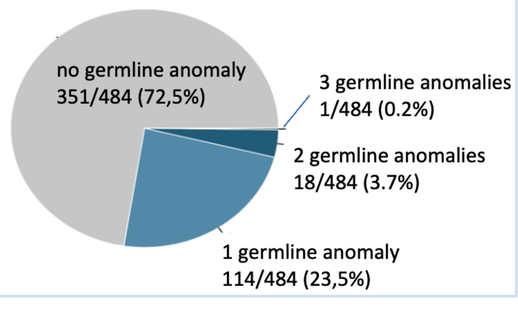
Type of germline finding	n	%
P/LP	150	98,04
VUS suspicious	3	1,96
Total	153	100

+ 1 clinical diagnosis of Beckwith-Wiedemann based on clinical score (*Brioude et al, 2018*)

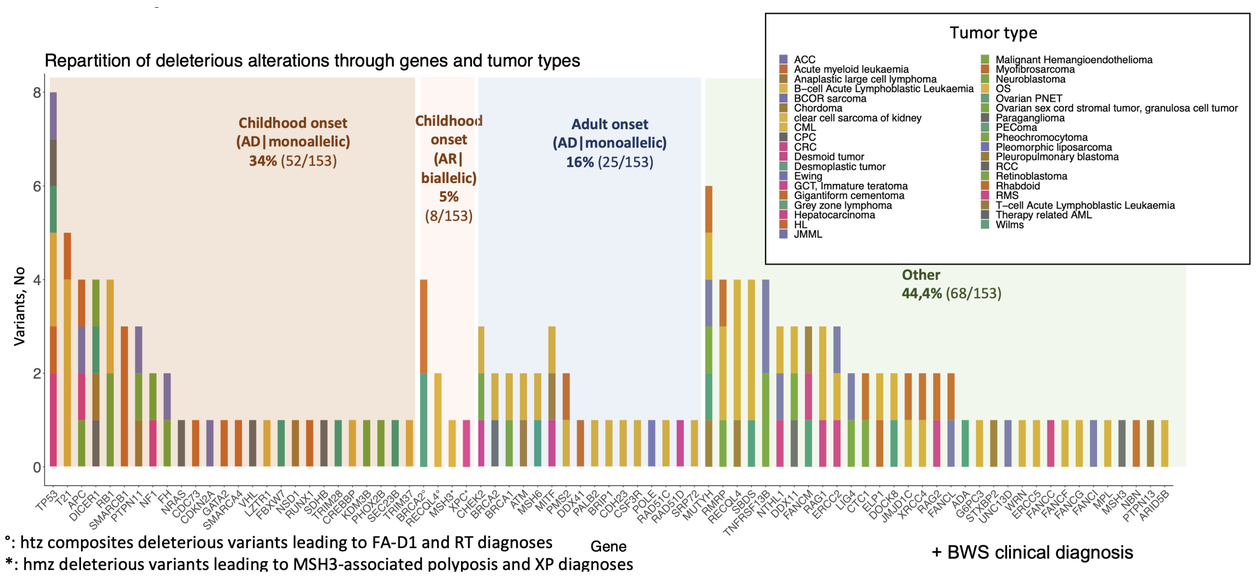
Distribution of variants according to type of cancer



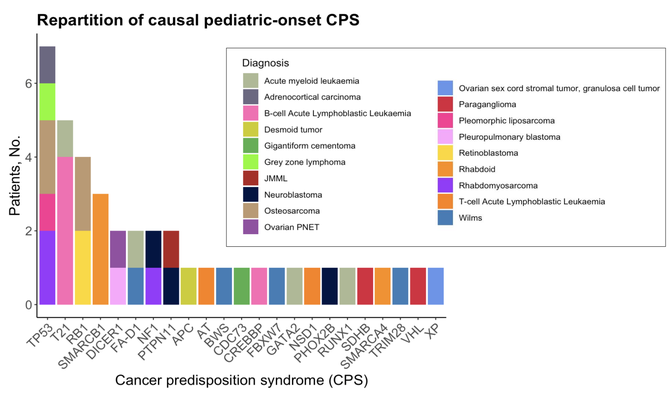
Repartition of germline anomalies across the cohort (n=484)

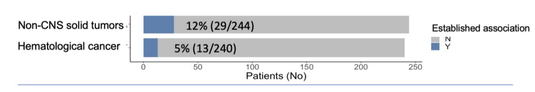


Despite a large panel of 353 genes, **39% (60/153)** of the germline findings were identified in only **30 genes** well associated with **childhood onset cancer**



Among the 484 patients, **42 (8.7%)** had a germline P/LP variant known to be associated with their cancer, classified as **causal pediatric-onset CPS**.





Rate in Triceps (hard to treat) 10% vs Rate in Signature 7.2% (ns)

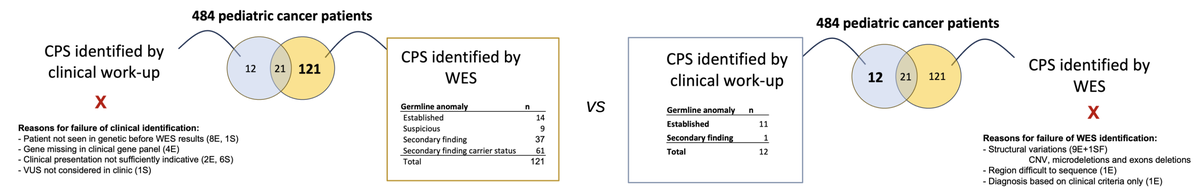
Diagnosis of CPS before cancer: 31% (13/42) based either on
- phenotypic characteristics:
  BWS [n=1], DS [n=5], NF1 [n=1], AT [n=1], XP [n=1], Rubinstein-Taybi [n=1]
- positive family history
  NF1 [n=1], Gardner syndrome [n=1]

Mosaic status: 12% (5/42)
PTPN11 [n=1], SMARCB1 [n=2], T21 [n=1], TP53 [n=1])

Diagnosis based on clinical criteria: 5% (2/42)
AT [n=1], BWS [n=1])

Patient with multiple independant disease-causing CPS: none

Exome sequencing lead to identification of a large number of anomalies with a shorter turnaround time while phenotype-based approach is more efficient, leading to a higher rate of disease-causing anomalies and fewer incidental findings



CONCLUSIONS

- **8.7% (42/484)** of pediatric cancer patients have a **disease-causing CPS** identified
  - **2/3 diagnosed after** cancer development
- WES enables **rapid turnaround**, greater **flexibility in gene panels** and uncovering **new associations**
- Paired somatic and germline exome refines interpretation and enables identification of constitutional **mosaicisms (1%, 5/484)**
- Genotype and phenotype-based approaches are **complementary**

REFERENCES

1) Zhang J, Walsh MF, Wu G et al. N Engl J Med 2015
2) von Stedingk K, Stjernfelt KJ, Kvist A et al. Sci Rep. 2021
3) Newman S, Nakitandwe J, Kesserwan CA et al. Cancer Discov. 2021

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