Epigenetic biomarkers at the origins of childhood cancers since the time of birth

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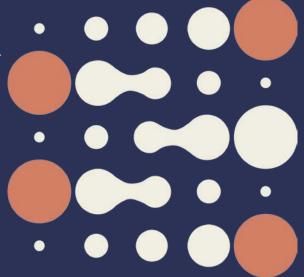
* Equal contribution as first authors + Equal contribution as last authors

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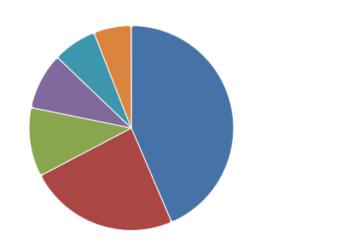
Introduction

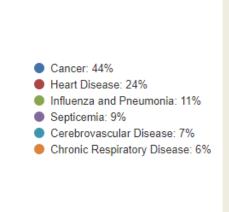
Causes not well understood

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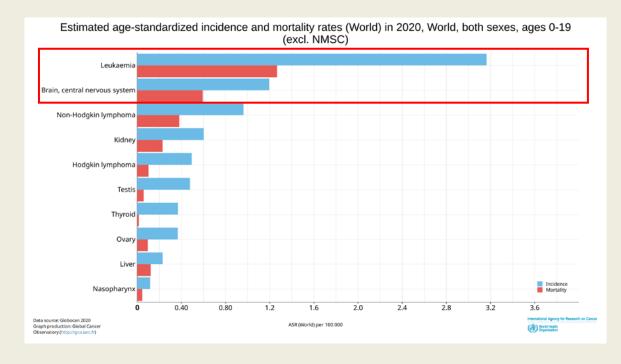
Cancer is the **number one** cause of death by disease in children

Number of U.S. Childhood Deaths by Disease Per Year Ages 1-19 Total = 3,249





https://curesearch.org/childhood-cancer-deaths-per-year. Accessed on Jan 15, 2024



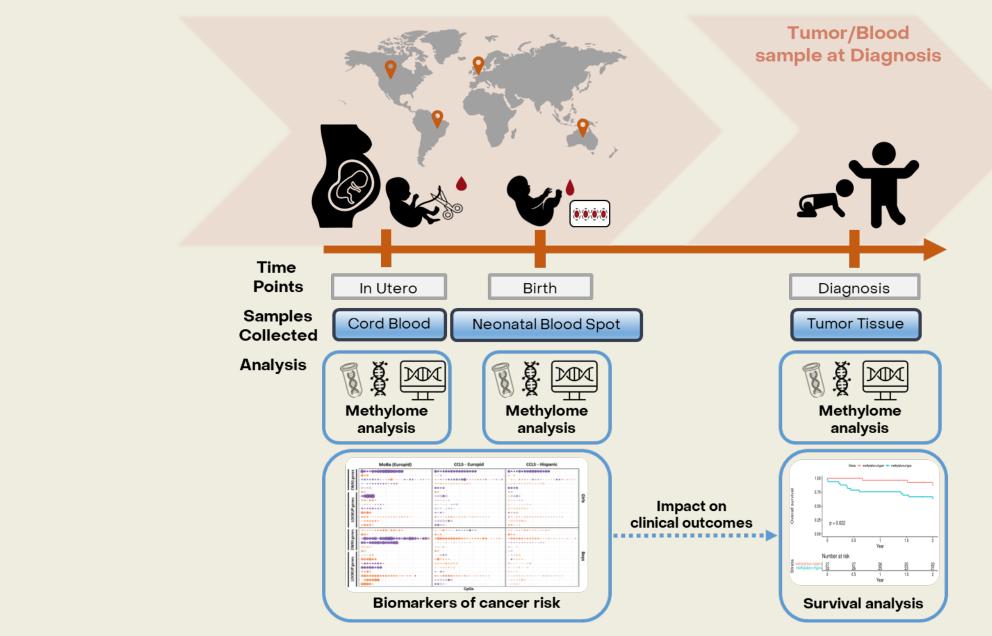
Introduction

- Epigenetics has a driver role that dictates what the different cells of the embryo will become and are heritable so can have long-lasting consequences if deregulated.
- Epigenetic alterations likely play a **pivotal role** in the **development of pediatric cancer**, especially considering the possibility that its origins may trace back to the in utero period.
- Unlike genetic, epigenetics changes are **potentially reversible**, hence, offering interesting targets for prevention.

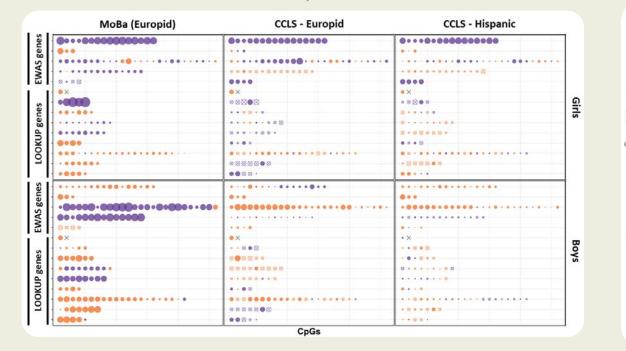
Hypothesis

Methylome changes associated with childhood cancer risk can be identified in blood cells at birth, and these changes can serve as sensitive biomarkers for prevention as well as targeted therapy.

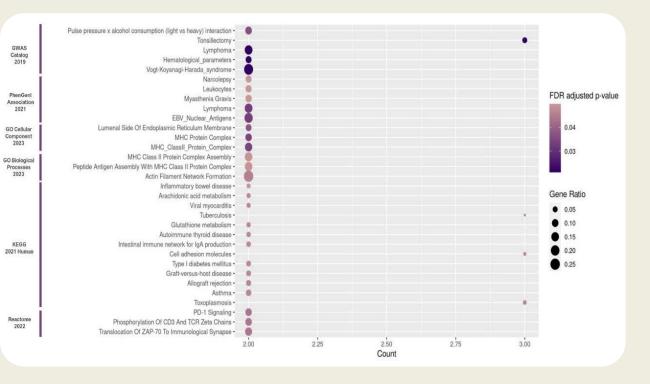
Design



Epigenetic alterations at birth predisposing to childhood pre-B leukemia



Molecular imprint at birth





Epigenetic alterations at birth associated to childhood CNS tumors

	Melbourne		organic cation transmembrane transporter activity (GO:0015101) - • transmembrane receptor protein phosphatase activity (GO:0019198) - •			
	Melbourne	-	oxidoreductase activity, acting on NAD(P)H, oxygen as acceptor (GO:0050664)			
			superoxide-generating NAD(P)H oxidase activity (GO:0016175)			
	00		UDP-glucosyltransferase activity (GO:0035251)			
	0 + 0 + 0 + +		ubiquitin-like protein ligase activity (GO:0061659)-			
	00.00.00		ubiquitin protein ligase activity (GO:0061630)			
	0000		heme binding (GO:0020037)		GO_Molecular_Function_2021	
	0000		non-membrane spanning protein tyrosine phosphatase activity (GO:0004726)			
		-	collagen receptor activity (GO:0038064) -			
	0		proton channel activity (GO:0015252)			
			protein tyrosine phosphatase activity (GO:0004725)			
			choline transmembrane transporter activity (GO:0015220) -			
	0.0	Effect size < 3%	protein kinase binding (GO:0019901)-			Adjusted.P.value
	0 + 0	Hypermeth	protein tyrosine kinase binding (GO:1990782)	•		
	00.0	Hypometh				0.08
		• • • • • • • • • • • • • • • • • • • •	Wholebrain -	•	Human_Gene_Atlas	0.06
	• • •	MethDiff (%)	Babesiosis - 😐			0.04
			Dysentery -			
	•	• 0.1	Aortic valve insufficiency -			0
	*********	• 2.0	Cervix uteri carcinoma in situ - 🔍			Gene ratio
	0.0.	• 4.0	Anogenital venereal wart-			• 0.05
		6.0	Sertoli cell tumor- 🔵			 0.10 0.15
	****	8.0	Spondylolysis - 🔵			0.20
		•	Reticulate acropigmentation of Kitamura - 🔵			•
			Crohn's disease-			
	00000.0		Toxocariasis - 🔵			
		-	Vitreous detachment-		Jensen_DISEASES	
	• • •		Childhood absence epilepsy - 🔵			
	0		Duane retraction syndrome -			
	0 0 + +	-	Supratentorial primitive neuroectodermal tumor			
	00		Reticulosarcoma - 🔵 —			
		-	Neuronal intestinal dysplasia - 🔵 —			
	0.0		Splenic infarction -			
	CpGs		Hypospadias -	•		
			Glycine encephalopathy-	•		
	0		Type 1 diabetes mellitus-	•		
or CpC	Gs considered as	informative of	Oxidative Stress WP408-		WikiPathway_2021_Human	
	on* to assist in int		Ondaile Siless WI 400		inter annay_cocr_manan	

We checked for CpGs the brain methylation* methylation levels of the CpGs identified in blood within the context of the brain.

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Association with prognosis

re-B leuke	emia	Overall Hazar	Surviva d ratio			
risk.group	SR (N=190)	reference				
	Infant (N=3)	6.0e+01 (1.5e+01 - 2.4e+02)		н	₽	<0.001 *
	IR (N=253)	4.9e-01 (2.5e-01 - 9.7e-01)				0.04 *
	HR (N=152)	2.6e+00 (1.5e+00 - 4.6e+00)				<0.001 *
sex	female (N=268)	reference		, i		
	male (N=330)	1.2e+00 (7.4e-01 - 1.9e+00)		, in the second se		0.468
age	(N=598)	1.0e+00 (9.9e-01 - 1.1e+00)		. i		0.09
CpG1	(N=598)	3.2e+00 (8.3e-01 - 1.3e+01)		-		0.09
CpG2	(N=598)	1.8e+00 (4.0e-01 - 7.9e+00)		- 		0.454
CpG3	(N=598)	4.5e-01 (5.9e-02 - 3.3e+00)		⊢∎→		0.432
CpG4	(N=598)	1.0e+00 (2.5e-01 - 4.3e+00)		- # -		0.967
CpG5	(N=598)	1.1e+00 (1.2e-01 - 9.4e+00)		- 		0.949
CpG6	(N=598)	1.1e+00 (1.9e-01 - 5.8e+00)		- #		0.943
CpG7	(N=598)	8.2e+00 (1.0e+00 - 6.7e+01)		- -	•	0.049 *
CpG8	(N=598)	1.0e+00 (7.7e-02 - 1.4e+01)		- -		0.983
CpG9	(N=598)	7.5e+00 (6.0e-04 - 9.3e+04)				0.676
CpG10	(N=598)	2.2e-03 (5.0e-08 - 9.8e+01)		-	-	0.263
CpG11	(N=598)	1.2e+00 (1.1e-03 - 1.3e+03)		·		0.959
CpG12	(N=598)	1.0e-03 (1.4e-08 - 7.6e+01)			-	0.229
CpG13	(N=598)	2.9e+03 (1.2e+00 - 7.0e+06)				- 0.044 *
CpG14	(N=598)	6.0e-01 (5.1e-02 - 7.1e+00)				0.685
CpG15	(N=598)	5.4e-01 (5.1e-02 - 5.7e+00)		⊢		0.604
CpG16	(N=598)	6.5e-01 (5.6e-02 - 7.5e+00)				0.729
# Events: 79; Global AIC: 959.08; Concor		,	1e-06 0.	001 1	1000 1e-	-06

CNS tumors		Ove	rall	Surv	ival		:		
methylation	hyper (N=27)	reference							
	hypo (N=33)	5.703 (1.3587 - 23.94)					·	-	- 0.017 *
cancer_type	Glioblastoma (N=7)	reference							
	Low grade glioma (N=6)	a (NOS) 0.059 (0.0061 - 0.58)	·		-				0.015 *
	others (N=9)	0.318 (0.0857 - 1.18)			-	-	÷-		0.086
	Pilocytic astrocyto (N=38)	oma 0.024 (0.0051 - 0.11)		-					<0.001
Sex	F (N=37)	reference							
	M (N=23)	1.464 (0.4723 - 4.54)				ı—			0.509
AgeAtDiag	(N=60)	0.957 (0.8338 - 1.10)							0.535
# Events: 15; Global p-value AIC: 96.09; Concordance Inc			0050.01	0.0	05 0.1	0.5	1	5 10	

Conclusion

- The identification of a methylome signature at birth associated with childhood cancer development may change the paradigm of tumorigenesis by uncovering molecular precursors of childhood cancer and its early origins.
- Epigenome alterations evident before diagnosis could be interesting actionable targets for risk assessment and prognosis.

Acknowledgements

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- INCa PEDIAHR (PI: A. Ghantous; Co-I: Z. Herceg)

Key take-home messages

Our work presents an innovative approach for the discovery of a new generation of biomarkers for pediatric cancer development that can be applied to future preventive and therapeutic strategies.