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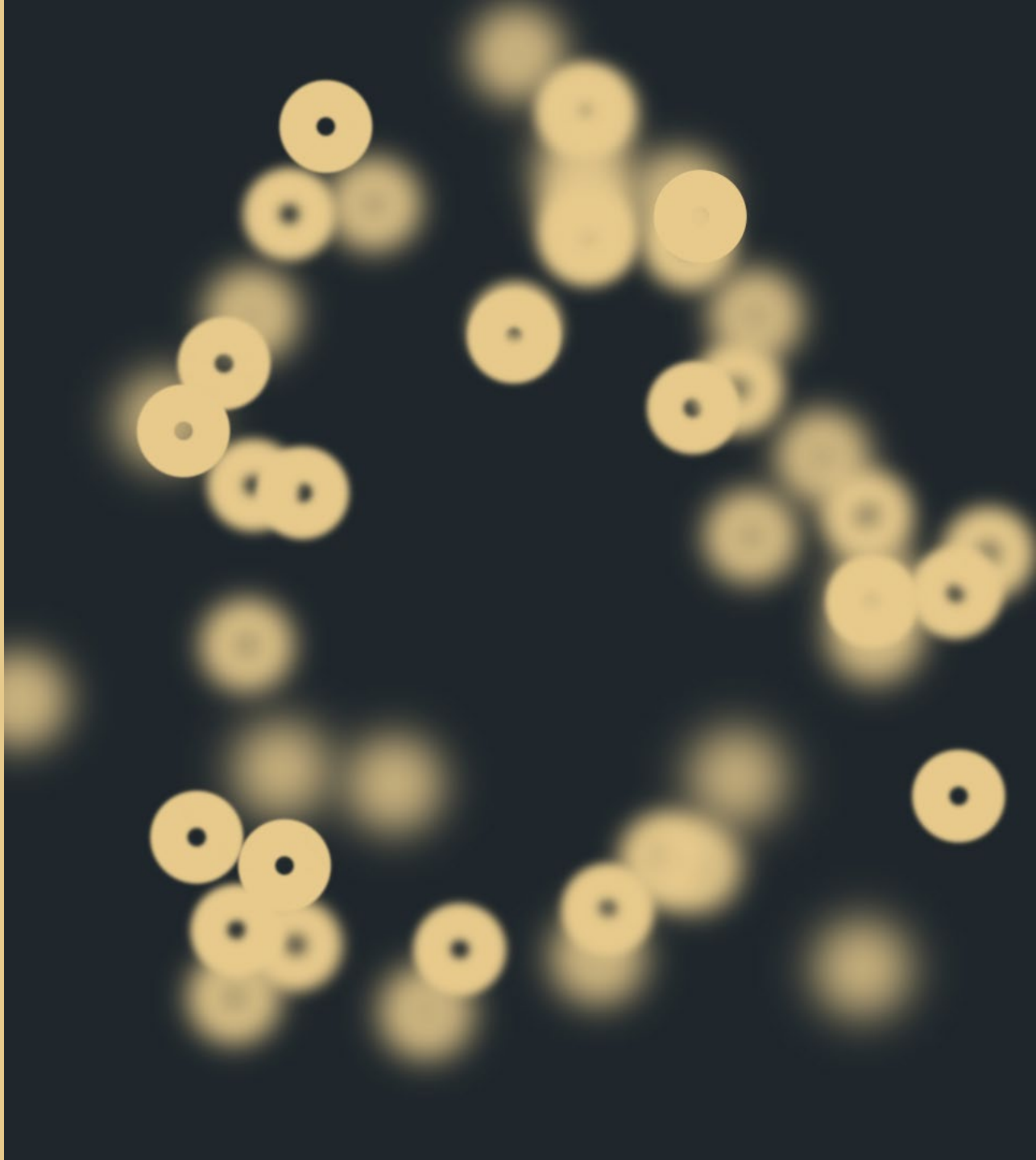
EHA-SWG Scientific Meeting on Recent Advances in the Pathogenesis and Treatment of Secondary Acute Myeloid Leukemias

Berlin, Germany
April 25-26, 2025



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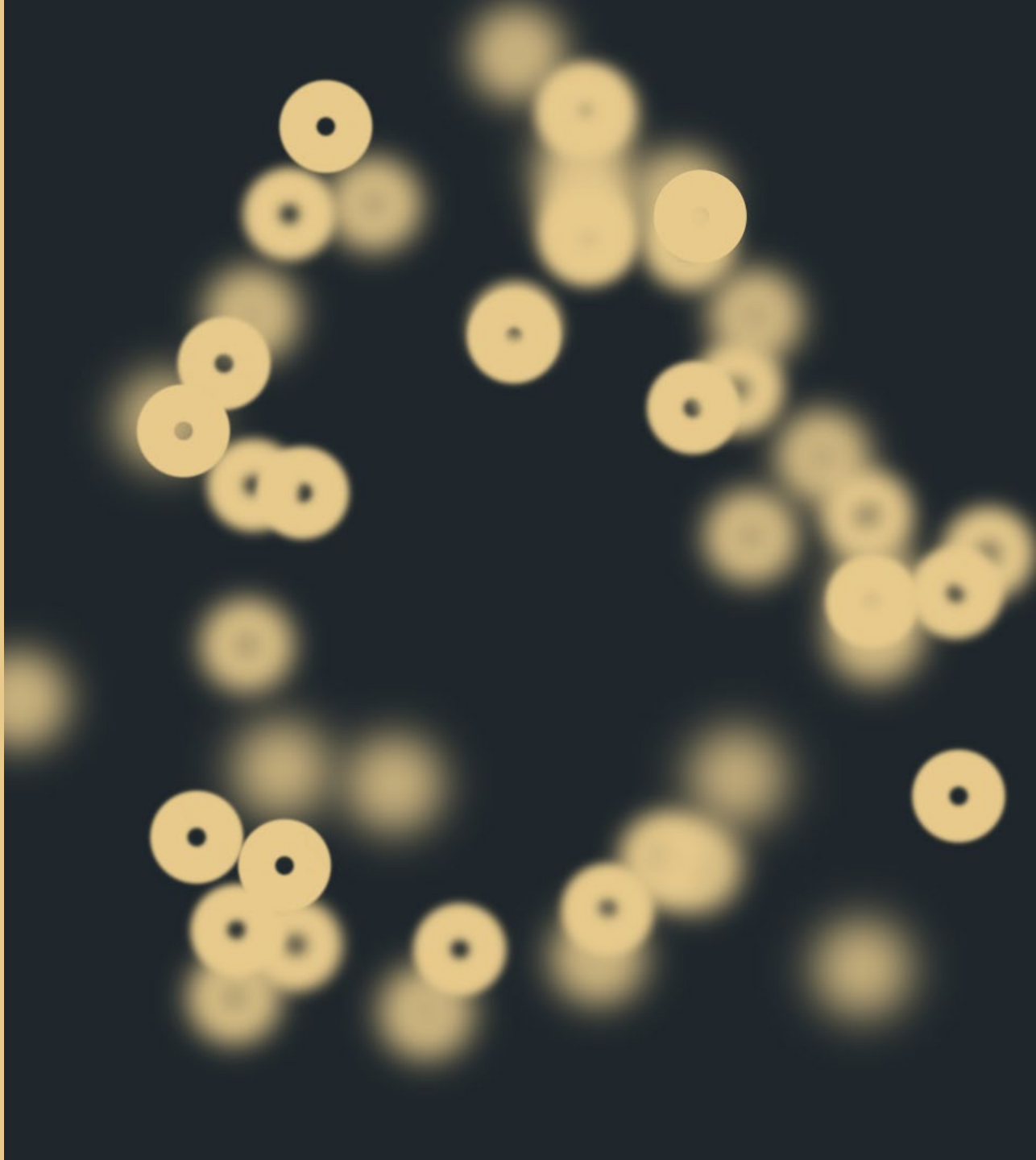
三軍總醫院 Tri-Service General Hospital

Analysis of Germline Variants in Taiwanese Pediatric AML Patients

Focus on Secondary AML and Family Cancer History

April/26/2025, Der-Shiun Wang MD



Pediatric AML: Advances, Gaps, and Biological Distinctions

Recent advances in molecular profiling have redefined AML classification and unveiled therapeutic vulnerabilities. *(J Hematol Oncol. 2023;16:29)*

Research progress in pediatric AML—particularly in novel agents and clinical trials—lags behind adult AML, primarily due to the significantly lower case numbers in children; some investigators even propose that pediatric and adult AML represent entirely distinct diseases. *(Front Oncol. 2025;15:1466818; Meshinchi S, Fred Hutchinson Cancer Research Center)*

Aim

This study aims to investigate the impact of germline variants previously associated with adult AML in a pediatric AML cohort using whole-exome sequencing (WES) data in Taiwan.


新疆維吾爾
自治區
甘肅
寧夏回族
自治區
青海
中國
西藏
陝西
山西
河北
北京
遼寧
北韓
南韓
日本海
(東海)
日本
東京
大阪
黃海
山東
河南
江蘇
上海
東海
湖北
安徽
四川
重慶
浙江
貴州
湖南
江西
福建
臺北
台灣
廣東
深圳市
廣西壯族
自治區
雲南
尼泊爾
不丹
孟加拉
印度
緬甸
河內
Hà Nội
寮國
泰國
越南
柬埔寨
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南海
West
Philippine Sea
呂宋
Luzon
馬尼拉
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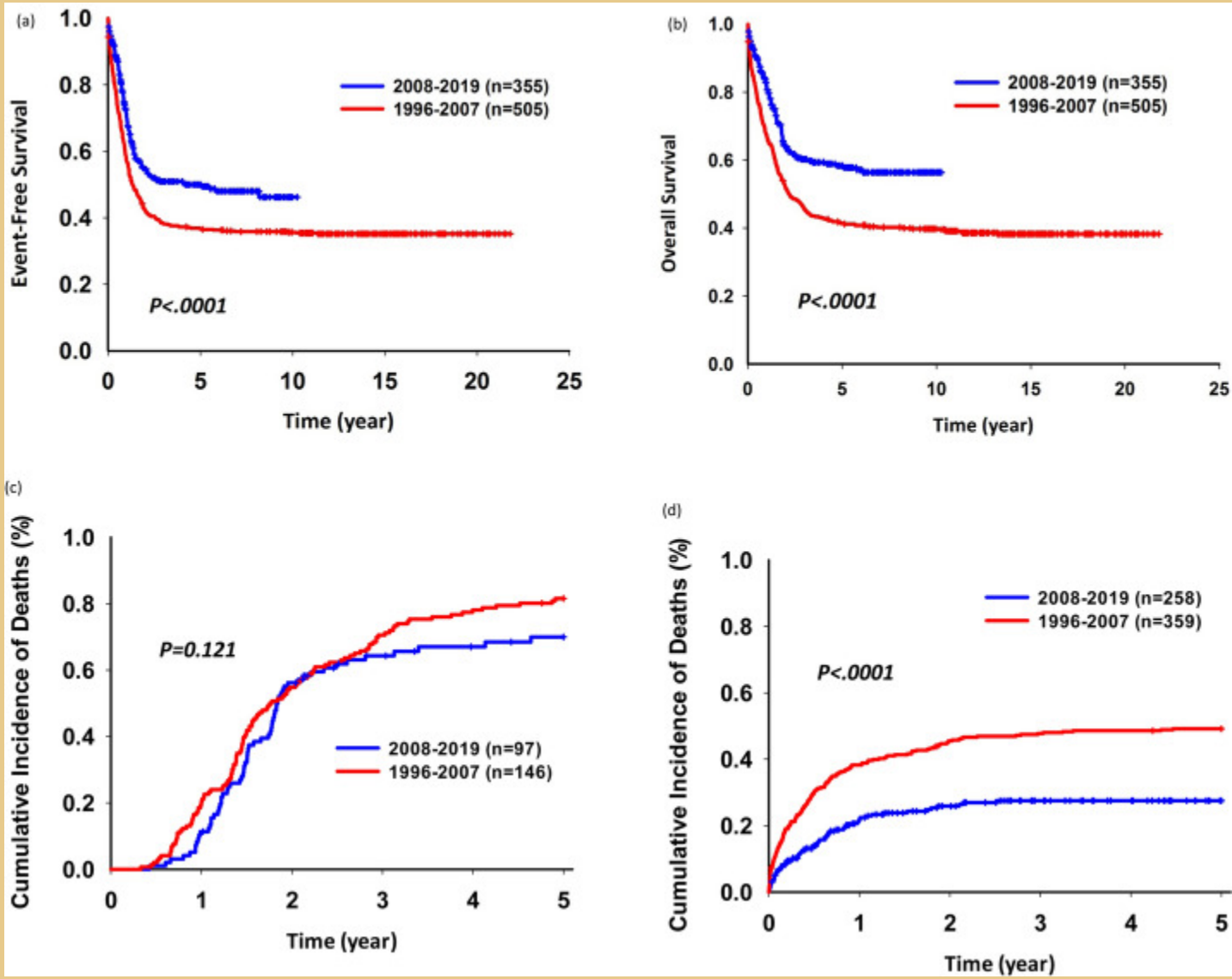
中華民國兒童癌症基金會
Childhood Cancer Foundation



Sci Rep. 2021

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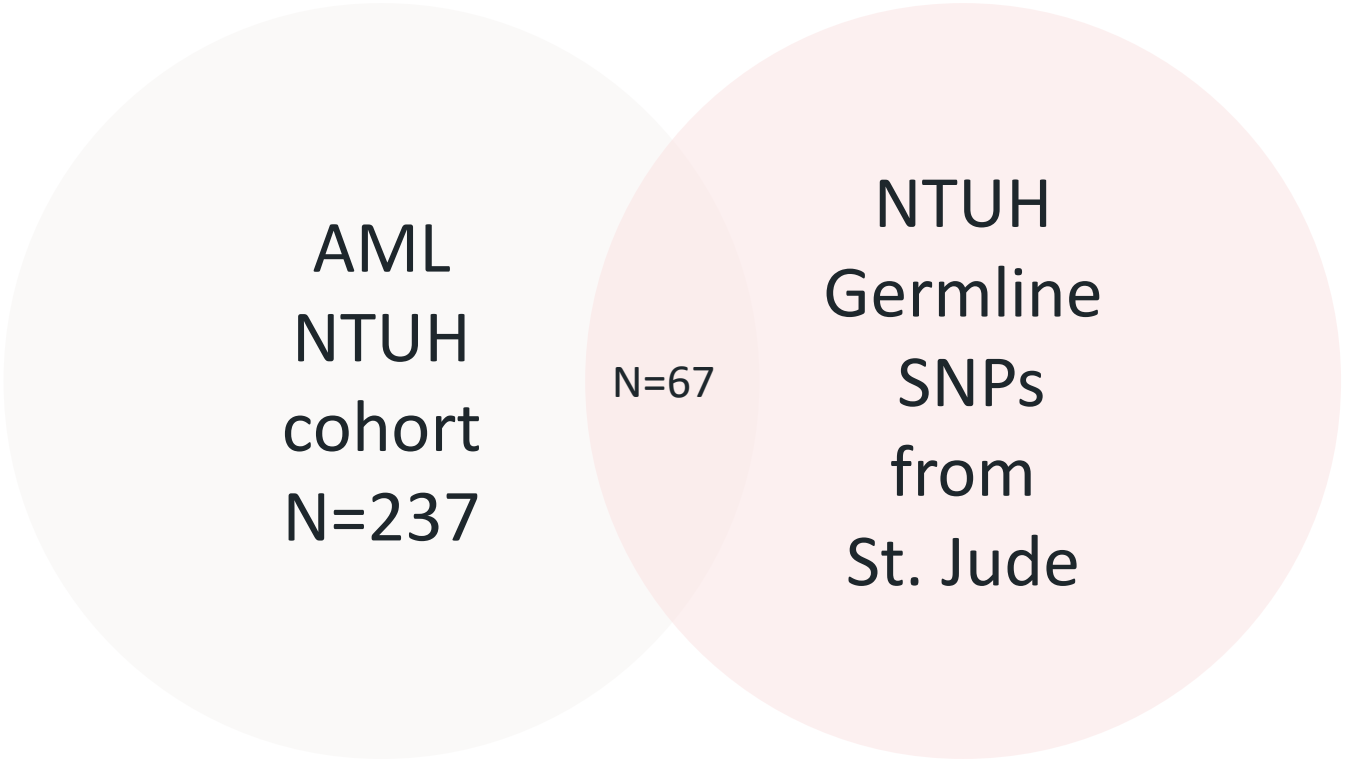
Patient enrollment



Cohort Overview

- Total AML patients: 237
- Institution: NTUH
- Period: 1997–2019

Selected for Study

- 67 pediatric AML patients
- Complete AML treatment
- Clinical & genetic data available

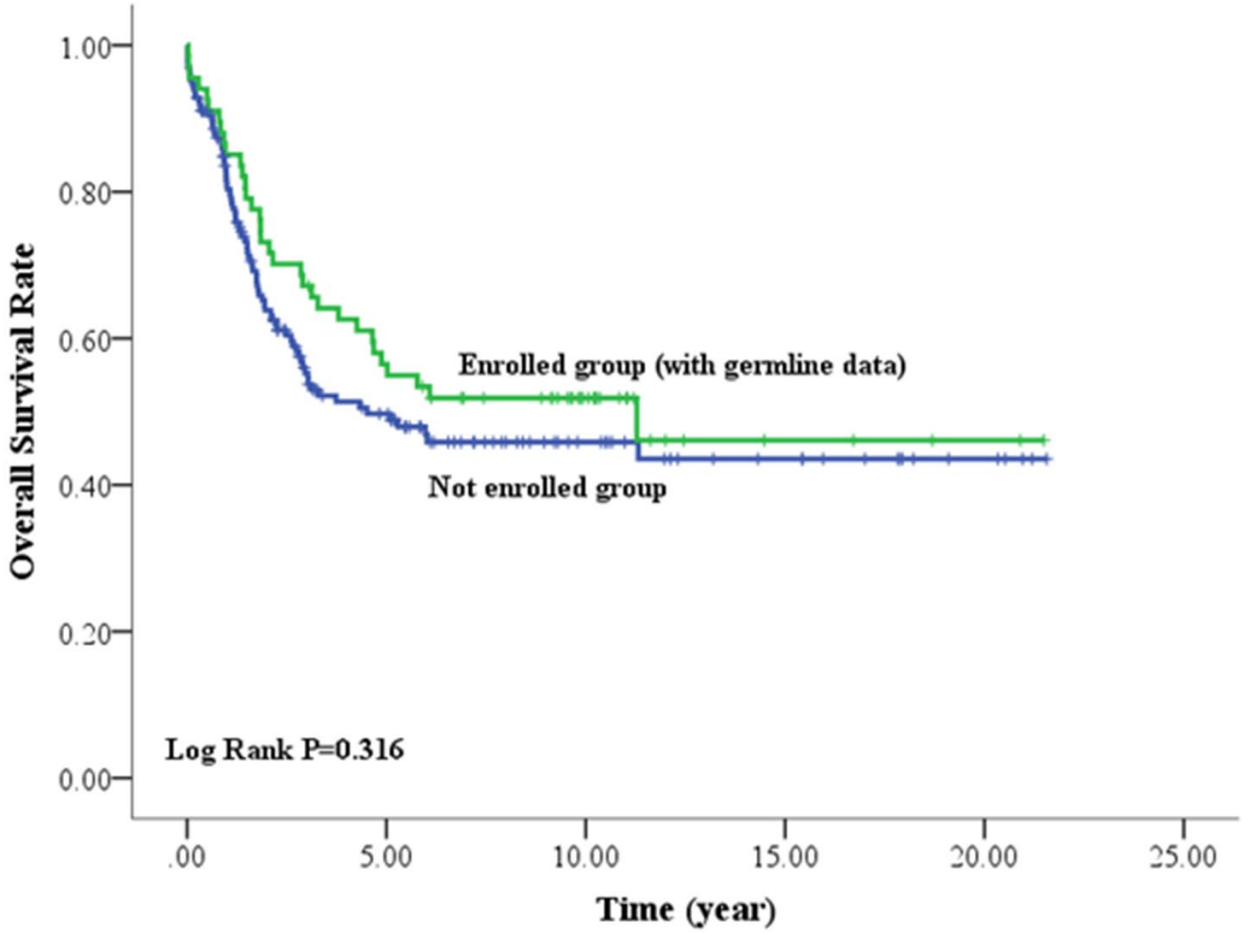
LDH was higher in study group
Follow-up time was longer in study group

No significant difference between Sex, Diagnosis age, whether IVF or not, whether Down Syndrome or not, on of twin, family cancer history, de novo or secondary AML and documented sepsis and overall survival rate.

supplement Table 1 Basline charcters between enrolled and not enrolled

	Total		Enrolled		Exculed		P value
	N	%	N	%	N	%	
	237	100.00	67	28.27	170	71.73	
Sex							0.912
Male	134	56.54	37	55.22	97	57.06	
Female	103	43.46	30	44.78	73	42.94	
Diagnosis age (Mean+/-SD)	9.23 ± 5.75		8.09 ± 5.46		9.69 ± 5.82		0.054
IVF							0.611
Yes	3	1.27	2	2.99	1	0.59	
Not	183	77.22	65	97.01	118	99.16	
Down Syndrome							1.000
Yes	10	4.22	4	5.97	6	3.53	
Not	176	74.26	63	94.03	113	94.96	
One of Twin							0.950
Yes	4	1.69	2	2.99	2	1.18	
Not	182	76.79	65	97.01	117	98.32	
Family cancer history							0.751
Yes	37	15.61	12	17.91	25	14.71	
Not	149	62.87	55	82.09	94	78.99	
Secondary AML							0.176
Yes	12	5.06	7	10.45	5	2.94	
Not	174	73.42	60	89.55	114	95.80	
LDH	1465.9 ± 1584.9		1953.15 ± 2041.8		1273.6 ± 1322.59		0.0193*
Documented Sepsis							0.051
Yes	95	40.08	34	50.75	61	35.88	
Never	142	59.92	33	49.25	109	64.12	
Follow-up time (years)	5.29 ± 5.35		6.72 ± 5.52		4.72 ± 5.31		0.0093*
overal survival rate	51.50%		50.70%		51.80%		0.316

No significant difference of overall survival rate between study group and not enrolled group



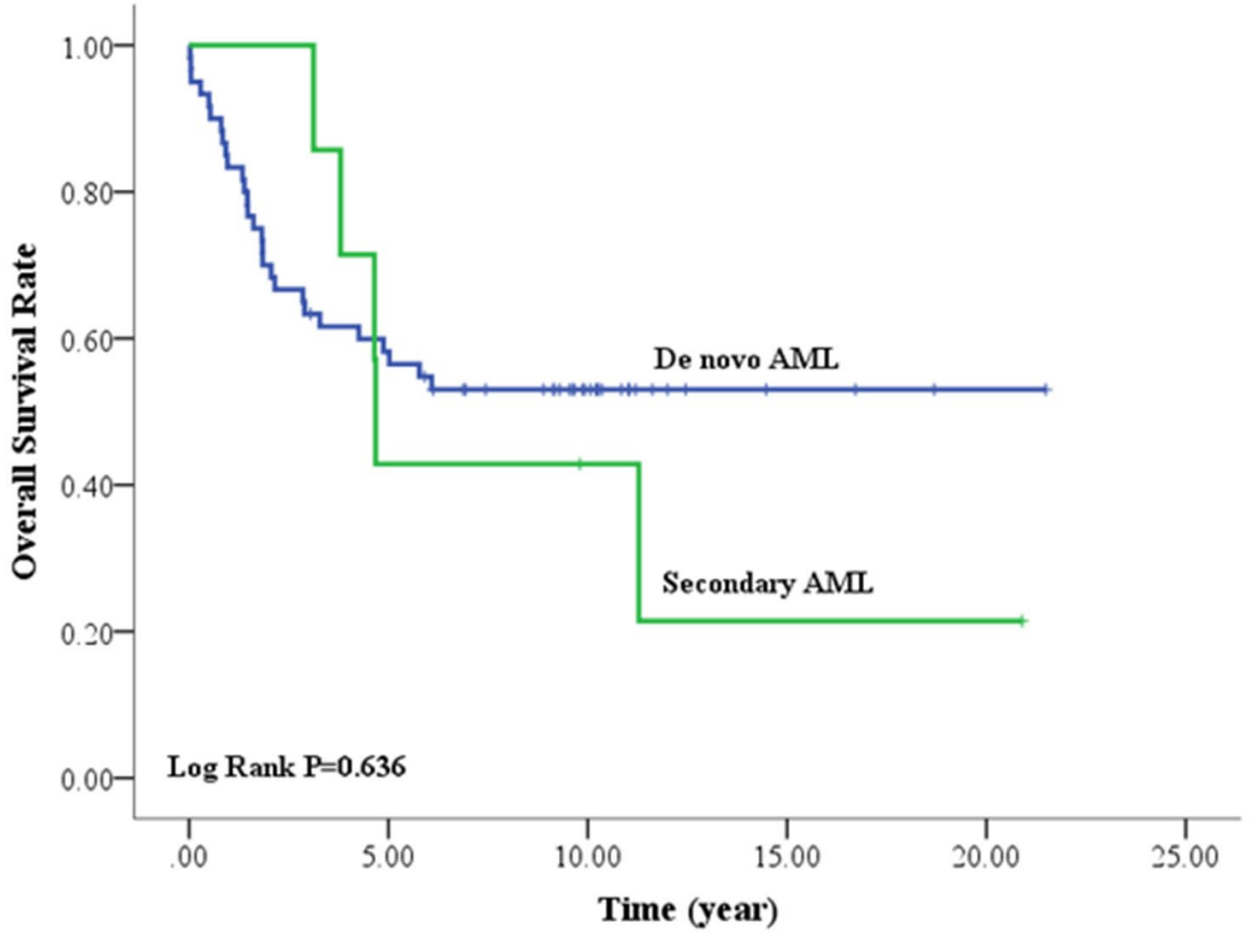
Higher **LDH** in De novo AML than secondary AML

No significant difference between Sex, Diagnosis age, whether IVF or not, whether Down Syndrome or not, on of twin, family cancer history documented sepsis, follow-up time and overall survival rate.

Table 1. Baseline charaters of NTUH Pediatric AML cohort with germline study

	Total		De novo AML		Secondary AML		P value
	N	%	N	%	N	%	
	67	100.00	60	89.55	7	10.45	
Sex							0.610
Male	37	55.22	32	53.33	5	71.43	
Female	30	44.78	28	46.67	2	28.57	
Diagnosis age (Mean+/-SD)	7.85 ± 5.54		8.00 ± 5.62		6.58 ± 5.00		0.501
IVF							0.495
Yes	2	2.99	1	1.67	1	14.29	
Not	65	97.01	59	98.33	6	85.71	
Down Syndrome							1.000
Yes	4	5.97	4	6.67	0	0.00	
Not	63	94.03	56	93.33	7	100.00	
One of Twin							0.495
Yes	2	2.99	1	1.67	1	14.29	
Not	65	97.01	59	98.33	6	85.71	
Family cancer history							0.798
Yes	12	17.91	10	16.67	2	28.57	
Not	55	82.09	50	83.33	5	71.43	
LDH	1953.2 ± 2041.84		2129.4 ± 2108.99		619.00 ± 311.63		1.060E-05
Documented Sepsis							0.967
Yes	34	50.75	31	51.67	3	42.86	
Never	33	49.25	29	48.33	4	57.14	
Follow-up time	6.72 ± 5.22		6.53 ± 5.11		8.32 ± 6.37		0.498
overal survival rate	50.70%		53.30%		28.60%		0.636

No significant difference of **overall survival rate** between de novo AML and secondary AML in study group



Diagnosis age in patient with family cancer history in order than those without family cancer history.

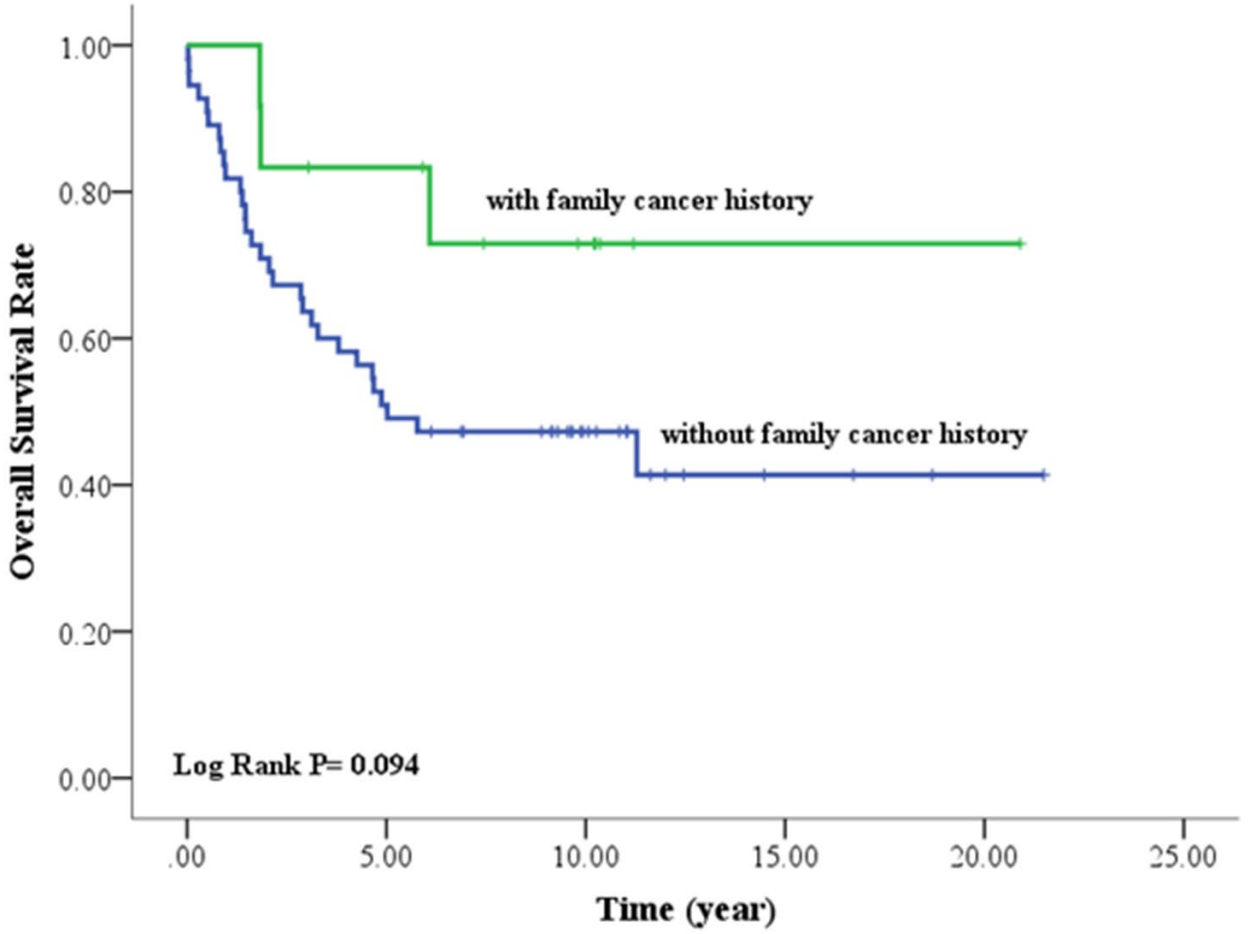
LDH level was lower in patient with family cancer history than those without family cancer history

Sepsis occurred more in patient with family cancer history.

Table 2. Baseline charaters of NTUH Pediatric AML cohort with germline study

	Total		With family cancer history		without family cancer histpry		P value
	N	%	N	%	N	%	
	67		12	17.91	55	82.09	
Sex							0.935
Male	37	55.22	6	50.00	31	56.36	
Female	30	44.78	6	50.00	24	43.64	
Diagnosis age (Mean+/-SD)	7.85 ± 5.54		11.07 ± 4.09		7.15 ± 5.60		0.011
IVF							
Yes	2	2.99	0	0.00	2	3.64	
Not	65	97.01	12	100.00	53	96.36	
Down Syndrome							1.000
Yes	4	5.97	0	0.00	4	7.27	
Not	63	94.03	12	100.00	51	92.73	
One of Twin							0.771
Yes	2	2.99	0	0.00	2	3.64	
Not	65	97.01	12	100.00	53	96.36	
Secondary AML							0.798
Yes	7	10.45	2	16.67	5	9.09	
Not	60	89.55	10	83.33	50	90.91	
LDH	1953.2 ± 2041.84		1253.9 ± 991.9		2128 ± 2201.6		0.048
Documented Sepsis							0.005
Yes	34	50.75	11	91.67	23	41.82	
Never	33	49.25	1	8.33	32	58.18	
Follow-up	6.72 ± 5.22		8.24 ± 5.25		6.39 ± 5.21		0.285
overal survival rate	50.70%		75%		45.50%		0.094

No significant difference of overall survival rate between AML patients with and without family history in study group



Selected SNPs in this study

blood advances

LETTER ▸ Blood Adv. 2022 Sep 27;7(6):1040–1044. doi: 10.1182/bloodadvances.2022007988

Germline SNPs previously implicated as prognostic biomarkers do not associate with outcomes in intensively treated AML

Aarif M N Batcha [1,2], Nele Buckup [3], Stefanos A Bamopoulos [3,4], Vindi Jurinovic [1,3], Maja Rothenberg-Thurley [3], Hanna Gittinger [3], Bianka Ksienzyk [3], Annika Dufour [3], Stephanie Schneider [3,5], Mika Kontro [6,7,8], Joseph Saad [7], Caroline A Heckmann [7], Cristina Sauerland [9], Dennis Görlich [9], Wolfgang E Berdel [10], Bernhard J Wörmann [11], Utz Krug [12], Jan Braess [13], Ulrich Mansmann [1,2,14,15], Wolfgang Hiddemann [3,14,15], Karsten Spiekermann [3,14,15], Klaus H Metzeler [16,*], Tobias Herold [3,14,15,*,*]

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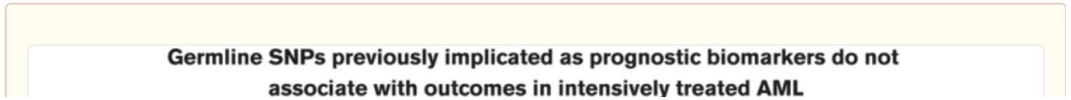
PMCID: PMC10036512 PMID: 36149944

Visual Abstract



Supplementary Tables and Figures

Supplementary Table 1: List of SNPs analyzed from previous publications

SNPs	N	Information
rs1042919[23], rs1045642[24], rs1048977[25], rs10883841[26], rs10932125[27], rs11231825[28], rs1128503[24], rs1130609[23], rs11554137[29,30], rs12036333[31,32], rs1265138[23], rs129081[33], rs13171482[32], rs1533140[32], rs1561876[23], rs1567581[32], rs1567582[32], rs17202778[34], rs1799983[35], rs1826909[36], rs2070673[36], rs2072671[26,37,38], rs212090[33], rs212091[33], rs2229109[39], rs2302948[36], rs2454206[40,41], rs2515641[36], rs2897047[31,32], rs2898950[23], rs3754446[28], rs4073360[32], rs4148405[28], rs4149056[36], rs4956103[32], rs532545[26], rs602950[37], rs6550825[32], rs6550826[31], rs6811453[36], rs747199[42], rs7729269[31,32], rs9883101[31,32]	43	SNPs published to be associated with either of patient characteristics in previous AML studies
rs1045642[24], rs10883841[26], rs1128503[24], rs11554137[29,30], rs12036333[31,32], rs129081[33], rs2072671[26,37,38], rs212090[33], rs212091[33], rs2897047[31,32], rs532545[26], rs602950[37]	12	SNPs published to be associated with OS or RFS in previous AML studies. We tried to reproduce the results in the specified subgroups as best as we can.

No difference in de novo vs secondary AML

SNP Chi-square Test Results (De novo AML vs 2nd_AML)			
SNP	P value	Chi2	df
rs104564	0.7659	0.533	2
rs104897	0.6737	0.79	2
rs108838	0.2415	1.372	1
rs112318	0.1755	3.48	2
rs112850	0.4998	1.387	2
rs113060	0.7076	0.692	2
rs115541	1	0	1

Chi-Square Test With Bonferroni Correction				
SNP	P value	Chi2	df	Bonferroni-adjusted P value
rs104564	0.7659	0.533	2	1
rs104897	0.6737	0.79	2	1
rs108838	0.2415	1.372	1	1
rs112318	0.1755	3.48	2	1
rs112850	0.4998	1.387	2	1
rs113060	0.7076	0.692	2	1
rs115541	1	0	1	1

SNP Fisher's Exact Test Results (De novo AML vs 2nd_AM	
SNP	P value
rs1045642	
rs1048977	
rs10883841	0.1779
rs11231825	
rs1128503	
rs1130609	
rs11554137	1

Extended Fisher Test (Monte Carlo)	
SNP	P value
rs1045642	0.8011
rs1048977	0.6432
rs10883841	
rs11231825	0.3483
rs1128503	0.3526
rs1130609	0.5471

Dominant Model Fisher Test	
SNP	P value
rs1045642	0.4345
rs1048977	0.6972
rs10883841	0.1779
rs11231825	1
rs1128503	1
rs1130609	0.6945
rs11554137	1

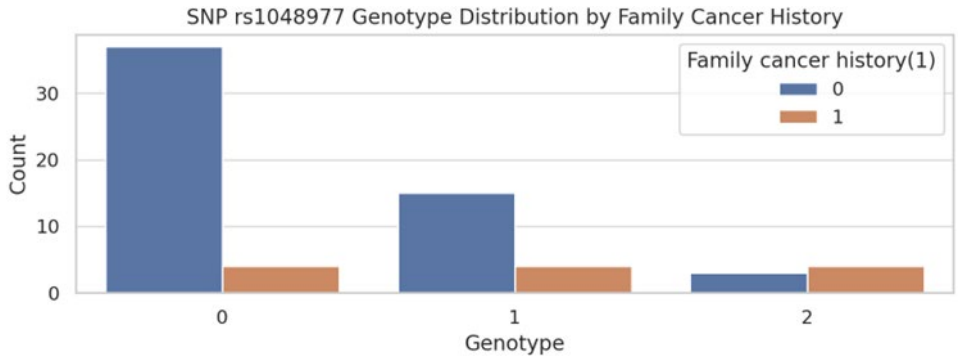
Dominant + Recessive Fisher Test with FDR Correction		
SNP	Method	p-value
rs1048977	Recessive Model Fisher	0.5559
rs11231825	Recessive Model Fisher	0.1995
rs1128503	Recessive Model Fisher	1
rs1130609	Recessive Model Fisher	1

Dominant Model Fisher Test with Bonferroni			
SNP	Method	p-value	Bonferroni-adjusted P value
rs1045642	Dominant	0.4345	1
rs1048977	Dominant	0.6972	1
rs10883841	Dominant	0.1779	1
rs11231825	Dominant	1	1
rs1128503	Dominant	1	1
rs1130609	Dominant	0.6945	1
rs11554137	Dominant	1	1

Recessive Model Fisher Test With Bonferroni			
SNP	Method	p-value	Bonferroni-adjusted P value
rs1045642	Recessive	1	1
rs1048977	Recessive	0.5559	1
rs10883841	Recessive		1
rs11231825	Recessive	0.1995	1
rs1128503	Recessive	1	1
rs1130609	Recessive	1	1
rs11554137	Recessive		1

Additive Model (Mann–Whitney U Test) with Bonferroni		
SNP	Test	p-value
rs1048977	Mann–Whitney U	0.6781
rs10883841	Mann–Whitney U	0.1086
rs11231825	Mann–Whitney U	0.6474
rs1128503	Mann–Whitney U	1
rs1130609	Mann–Whitney U	0.544
rs11554137	Mann–Whitney U	0.6513

rs1048977 lower in patient without family cancer history group



SNP Test Results (Chi2, Fisher, MWU, T-test)									
SNP	Chi-square p	Fisher p (	Mann?□	T-test p	Chi-squar	Fisher p (	Mann?□	T-test p (	Bonferroni
rs1045642	0.55009161		0.5166	0.3855	1	1	1	1	
rs1048977	0.00951401		0.0104	0.0323	0.0666	1	0.0725	0.2259	
rs10883841	1	1	0.9827	0.9751	1	1	1	1	
rs11231825	0.48540115		0.7152	0.637	1	1	1	1	
rs1128503	0.73924312		0.6538	0.6421	1	1	1	1	
rs1130609	0.29665767		0.7027	0.7952	1	1	1	1	
rs11554137	1	1	0.5235	0.1592	1	1	1	1	

Dominant Model Fisher Test (FDR/Bonferroni)						
SNP	model	P value	FDR-adju	Bonferroni-adjust P value		
rs1045642	Dominant	0.576	1	1		
rs1048977	Dominant	0.048	0.3341	0.3341		
rs10883841	Dominant	1	1	1		
rs11231825	Dominant	1	1	1		
rs1128503	Dominant	1	1	1		
rs1130609	Dominant	0.515	1	1		
rs11554137	Dominant	1	1	1		

Recessive Model Fisher Test (FDR/Bonferroni)						
SNP	model	P value	FDR-adju	Bonferroni-adjust P value		
rs1045642	Recessive	0.755	0.755	1		
rs1048977	Recessive	0.016	0.082	0.082		
rs11231825	Recessive	0.328	0.75	1		
rs1128503	Recessive	0.6	0.75	1		
rs1130609	Recessive	0.576	0.75	1		

Monte Carlo Fisher Approximation (2x3)						
SNP	Test	p-value				
rs1045642	Monte Carlo Fi	0.3543				
rs1048977	Monte Carlo Fi	0.0218				
rs11231825	Monte Carlo Fi	0.5749				
rs1128503	Monte Carlo Fi	0.763				
rs1130609	Monte Carlo Fi	0.192				

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The role of CDA rs1048977 need more investigation

- cytidine deaminase (CDA) converts ara-C to the inactive metabolite uracil arabinoside (ara-U)
- CDA is the key inactivating enzyme in **cytarabine metabolic pathway**, its overexpression is commonly associated with treatment resistance and relapse
- c.435C>T (rs1048977)) were associated with **reduced enzyme activity**
- The association and the role of this SNPs and family cancer history or its inherited role need more investigation.

Summary

- Higher LDH level in De novo pediatric AML than secondary pediatric AML
- Diagnosis age in patient with family cancer history in order than those without family cancer history.
- LDH level was lower in patient with family cancer history than those without family cancer history
- Sepsis occurred more in patient with family cancer history.
- rs1048977 lower in patient without family cancer history group

Acknowledgement

St. Jude Children's Research Hospital
Finding cures. Saving children.
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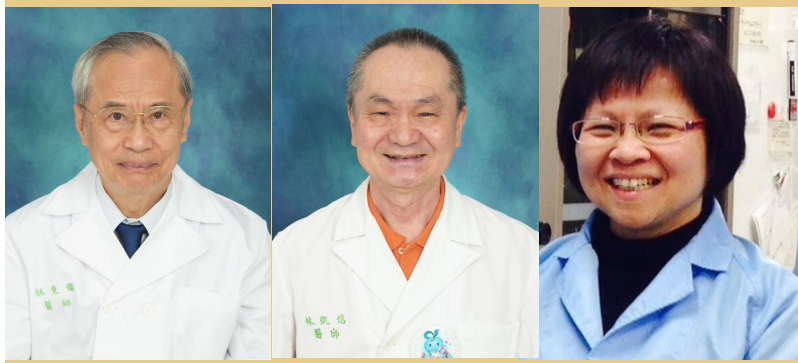

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