LETTER TO THE EDITOR

A first-born twin has a higher risk of acute leukemia in a population-based assessment of cancer in twins in California, and a lower than anticipated rate of twin concordance

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Table S1: Standardized incidence ratios (SIRs) of risk of any cancer development in siblings of twins with cancer for the same pediatric or adolescent/young adult (AYA) cancer by ICCC-3 subgroup (top panel) and for any pediatric/AYA cancer type (bottom panel). Results are displayed by broad cancer group diagnosed in the proband, and SIRs are based on risk of any cancer type in the proband. The SIR was obtained by dividing the observed number of siblings with cancer by the expected number of cancers among siblings, with expected values generated as the total years at risk are multiplied by the corresponding age group (5-year intervals) and sex-specific incidence rate of cancer, calculated individually and summed. Years at risk are individually determined by subtracting the age at the start of risk (the year of cancer diagnosis in the proband) from the age at the end of risk (the end year of follow up or the year when the sibling received a cancer diagnosis). Age group and sex-specific incidence rates of cancer were obtained from SEER*Stat version 8.4.3, utilizing California data from SEER 17 Registries, and 95% confidence intervals (CIs) were computed assuming a Poisson distribution.

SIR for development of the same cancer type				
Category	**Probands**	**Observed**	**Expected**	**SIR (95% CI)**
Leukemias	254	2	0.13	15.6 (1.9 - 56.4)
Lymphomas	134	1	0.06	16.3 (0.4 - 90.7)
CNS Neoplasms	233	1	0.06	17.2 (0.4 - 95.6)
Neuroblastoma	54	1	0.004	249.9 (6.3 - 1392.4)
Retinoblastoma	17	2	0.0006	3166.0 (383.4 - 11436.9)
Renal Tumors	39	0		
Hepatic Tumors	33	0		
Malignant bone tumors	54	0		
Soft Tissue Sarcomas	91	1	0.02	62.4 (1.6 - 347.9)
Germ Cell Tumors	95	3	0.04	66.7 (13.8 - 195)
Epithelial Neoplasms	214	2	0.37	5.4 (0.7 - 19.7)
Other Neoplasms	7	0		
SIR for development of the any cancer type				
Category	**Probands**	**Observed**	**Expected**	**SIR (95% CI)**
All Cancer	1213	15	3.47	4.3 (2.4 - 7.1)
Broad groups				
Leukemias	254	2	0.69	2.9 (0.4, 10.5)
Lymphomas	134	1	0.41	2.5 (0.1, 13.7)
CNS Neoplasms	233	1	0.62	1.6 (0.0, 9.0)
Neuroblastoma	54	1	0.14	7.2 (0.2, 40.0)
Retinoblastoma	17	2	0.07	29.2 (3.5, 105.4)
Renal Tumors	39	0		
Hepatic Tumors	33	0		
Malignant bone tumors	54	1	0.16	6.4 (0.2, 35.4)
Soft Tissue Sarcomas	91	2	0.29	6.8 (0.8, 24.6)
Germ Cell Tumors	95	4	0.26	15.5 (4.2, 39.7)
Epithelial Neoplasms	214	2	0.67	3.0 (0.4, 10.8)
Other Neoplasms	12	0		

Table S2: Top 20 significant differentially methylated probes at birth identified from birth plurality order linear regression analysis in 41 ALL-discordant twin pairs. Positions referenced to Hg19. Std. Error = Standard error. FDR = False discovery rate. Chr. = Chromosome.

CpG	Estimate	Std. Error	P-Value	FDR	Chr.	Position	UCSC_RefGene_Name
cg26335251	-45.606557	5.89765682	1.41E-07	0.02548192	chr17	75539921	NA
cg10817023	-21.832225	2.89403871	2.08E-07	0.02548192	chr5	133853517	NA
cg19442702	-22.309636	2.95434736	2.05E-07	0.02548192	chr5	398425	AHRR
cg01321488	-21.106998	2.74806767	1.57E-07	0.02548192	chr9	127380298	NR6A1;NR6A1;NR6A1
cg09738193	-21.973898	2.94816072	2.51E-07	0.02548192	chr16	67926317	PSKH1
cg26618645	-34.533609	4.63063711	2.49E-07	0.02548192	chr16	30780332	RNF40
cg01813254	-27.728941	3.49704088	9.49E-08	0.02548192	chr11	9036548	NA
cg19262334	-29.220747	3.9599124	2.93E-07	0.02602671	chr18	74631861	ZNF236
cg05573381	-30.678108	4.23816372	3.94E-07	0.02796016	chr5	1653258	NA
cg05052194	-29.266438	4.03893695	3.88E-07	0.02796016	chr1	2160249	SKI
cg18690833	-34.167392	4.87896345	6.49E-07	0.02949527	chr20	13972022	SEL1L2
cg10329345	-22.583062	3.18165365	5.30E-07	0.02949527	chr1	45083079	RNF220
cg09407429	-22.558022	3.21493351	6.30E-07	0.02949527	chr3	4534383	ITPR1;ITPR1;ITPR1
cg25528260	-38.485094	5.50421806	6.65E-07	0.02949527	chr7	72777727	NA
cg07876051	-38.942799	5.53220661	6.01E-07	0.02949527	chr10	3159145	PFKP
cg07805959	-18.607996	2.62367993	5.37E-07	0.02949527	chr17	2595004	KIAA0664
cg27120649	-31.710823	4.59687307	8.12E-07	0.03393192	chr7	94286261	SGCE;PEG10;SGCE;PEG10;SGCE
cg07607077	-19.43779	3.30165743	7.63E-06	0.03408781	chr7	919584	C7orf20
cg04376617	32.6600413	5.25666516	3.66E-06	0.03408781	chr18	43685360	ATP5A1;HAUS1;HAUS1
cg12285834	-31.06016	4.7980595	2.05E-06	0.03408781	chr3	72345017	NA

Table S3: Top 20 significant differentially methylated regions at birth identified from Comb P analysis of birth plurality order linear regression analysis in 41 ALL-discordant twin pairs. Positions referenced to Hg19. Min. P-value = Minimum P-value of CpGs within region. Sidak P-value = Adjusted P-value for multiple comparisons across the epigenome.

Chromosome	Start	End	Min. P-value	#Probes	P-value	Sidak P-value	Gene
chr16	89349945	89352007	0.007374	10	1.30E-10	4.46E-08	*ANKRD11*
chr16	89437341	89439497	0.009317	12	1.46E-09	4.81E-07	*ANKRD11*
chr5	169658215	169659950	0.001232	16	1.20E-09	4.92E-07	NA
chr19	48674931	48676053	0.001771	6	1.62E-09	1.02E-06	*ZSWIM9*
chr2	168724333	168726607	0.01452	9	6.68E-09	2.09E-06	*B3GALT1*
chr17	77951408	77952463	0.002708	7	3.60E-09	2.43E-06	*TBC1D16*
chr13	113718453	113719440	2.67E-04	5	3.57E-09	2.57E-06	*MCF2L*
chr1	68516272	68517691	4.44E-04	15	7.42E-09	3.71E-06	*DIRAS3*
chr2	228497892	228499386	0.004894	6	8.25E-09	3.92E-06	*C2orf83*
chr17	74303724	74304023	9.65E-05	8	1.84E-09	4.38E-06	*QRICH2*
chr12	131271323	131272183	0.001841	3	7.46E-09	6.16E-06	NA
chr5	170883661	170884806	0.01135	6	9.94E-09	6.17E-06	*FGF18*
chr19	46917727	46918365	0.005363	3	6.03E-09	6.71E-06	NA
chr6	87804765	87806133	0.001279	8	1.37E-08	7.11E-06	*CGA*
chr15	69221572	69223018	0.007071	8	1.58E-08	7.78E-06	*MIR548H4*
chr1	192917420	192918151	0.002707	4	8.35E-09	8.11E-06	NA
chr17	17124521	17124969	1.55E-04	6	6.23E-09	9.87E-06	*PLD6; FLCN*
chr12	101752716	101754080	0.002954	5	2.17E-08	1.13E-05	*UTP20*
chr11	118501494	118502454	0.002753	6	1.90E-08	1.40E-05	*PHLDB1*
chr2	106959205	106959878	8.18E-04	7	1.35E-08	1.42E-05	NA