

Increased neonatal level of arginase 2 in cases of childhood acute lymphoblastic leukemia implicates immunosuppression in the etiology

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Supplementary Table 1: ARG2 levels by case and control status, and within quartiles (protein-corrected)

ARG2	n	median	cases		median	controls		
			mean	range		mean	range	
overall	137	8.0	12.1	0.83-242.3	492	6.9	11.6	1.0-279.7
Q1	21	3.2	3.0	0.83-4.2	123	3.2	3.2	1.0-4.6
Q2	29	5.7	5.7	4.7-6.7	123	5.7	5.7	4.6-6.9
Q3	44	8.5	8.6	6.9-10.7	123	8.5	8.7	6.9-10.9
Q4	43	14.2	24.3	10.9-242.3	123	16.5	28.6	10.9-279.7

Supplementary Table 2: ARG2 levels (protein corrected) by demographic factors

		ARG2 cases (N = 137)			ARG2 controls (N = 492)		
		median	mean	range	median	mean	range
race	White	8.6	10.8	3.2-42.9	7.2	11.1	1.4-192.9
	Hispanic	8.0	10.0	0.8-45.3	7.5	12.6	1.0-279.7
	Other	7.7	21.4	1.1-242.3	5.7	8.4	1.5-61.9
Sex	Female	7.9	9.3	0.8-39.1	6.8	12.0	1.2-279.7
	Male	8.3	14.1	1.5-242.3	7.1	11.2	1.0-222.2
age at collection (hours)	mean (SD)						
birthweight (g)	<2500	10.9	10.2	4.8-14.2	7.3	11.1	3.2-61.9
	2500-2999	7.5	10.9	1.1-45.3	6.9	13.8	2.0-279.7
	3000-3499	9.1	16.3	2.6-242.3	6.8	11.9	1.0-49.6
	3500-3999	7.7	8.2	0.83-22.6	6.7	9.2	1.5-49.6
	4000+	7.3	7.6	4.2-13.5	7.9	13.9	2.1-222.2
gestational age	<37	10.7	32.5	4.8-242.3	6.6	15.7	2.0-279.7
	37-41	7.6	9.9	0.83-68.7	6.8	10.7	1.2-192.9
	42+	9.6	9.3	3.5-13.1	7.1	16.9	1.0-192.9
	Unknown	11.8	11.7	11.2-12.0	9.3	11.8	1.6-30.5
Plurality	No	8.0	12.0	0.83-242.3	6.9	11.6	1.0-279.7
	Yes	9.7	14.1	2.5-39.2	7.1	8.3	1.2-25.3

birth order	1	8.0	10.9	1.1-68.7	7.2	13.7	1.5-279.7
	2	8.0	14.1	0.83-242.3	6.9	9.4	1.8-84.4
	3+	8.4	11.2	1.8-45.4	6.3	11.3	1.0-192.9
C-section	No	7.6	9.2	1.1-42.9	6.8	12.7	1.5-279.7
	Yes	9.6	16.6	0.83-242.3	7.2	8.5	1.0-45.5
Mother's age	<25	9.2	10.2	2.6-22.9	6.7	11.9	1.5-192.9
	25-34	8.0	10.6	0.83-68.7	7.0	11.7	1.0-279.7
	35+	7.5	20.3	2.7-242.3	6.9	10.4	1.5-84.4
Mother's birthplace	US	8.0	9.8	1.5-42.9	6.8	10.2	1.5-192.9
	Other	8.4	15.1	0.83-242.3	6.9	13.1	1.0-279.7
Year of birth	2000	7.1	7.5	3.3-15.5	7.7	11.4	1.7-93.0
	2001	7.2	10.0	0.83-68.7	8.7	19.2	1.5-279.7
	2002	10.5	13.9	5.3-45.4	7.9	13.9	3.3-192.9
	2003	9.7	23.8	4.7-242.3	7.5	9.5	2.6-37.6
	2004	9.1	10.6	1.5-39.1	5.5	9.9	1.0-135.7
	2005	6.3	12.4	3.1-42.9	5.8	12.4	1.5-222.2
	2006	7.6	9.5	3.1-42.9	6.0	8.0	1.7-30.5
	2007	6.1	7.6	2.5-30.6	5.9	7.2	2.2-18.7
	2008	7.7	9.6	3.9-20.3	5.9	7.6	1.8-22.6
	2009				4.7	4.7	2.0-7.3

All values are expressed as ng Arginase-2 per ug protein X 10

Supplementary Table 3: Case-control results for ARG2 levels while exclude participants delivered by c-section, and quartiles cut offs based on all controls (n=84 cases, n=354 controls)

ARG2	Case n (%)	Control n (%)	OR	95% CI	p
1 st quartile	12 (14.3)	84 (23.7)	1		
2 nd quartile	21 (25.0)	95 (26.8)	1.48	0.67-3.31	0.33
3 rd quartile	29 (34.5)	84 (23.7)	2.39	1.10-5.17	0.03
4 th quartile	22 (26.2)	91 (25.7)	1.77	0.82-3.81	0.14
Trend			1.22	0.98-1.52	0.07

Supplementary Table 4: Case-control results for ARG2 levels with all participants adjusted for c-section, and without adjustment (n=137 cases, n=492 controls)

A: with C-section

ARG2	OR	95% CI	p
1 st quartile	1		
2 nd quartile	1.49	0.79-2.80	0.26
3 rd quartile	2.2	1.21-3.99	0.01
4 th quartile	2.28	1.28-4.07	0.01
Trend	1.31	1.10-1.57	<0.01

B: without C-section

OR	95% CI	p
1		
1.42	0.76-2.66	0.28
2.17	1.20-3.92	0.01
2.26	1.27-4.01	0.01
1.32	1.11-1.57	<0.01

Adjusted odds ratios for quartiles of neonatal Arginase 2 associated with childhood acute lymphoblastic leukemia (ALL) (n=137 cases, n=492 controls). Adjusted for sex, race/ethnicity (non-Hispanic white, Hispanic white and other), birth weight (<2500, 2500-2999, 3000-3499, 3500-3999, ≥4000), birth order (first, second, third or higher), plurality (singleton, multiple), delivery mode (A only: vaginal, cesarean delivery), year of birth, age at neonatal blood collection, mother's age at delivery (<25, 25-34, ≥35), and mother's place of birth (United States, other).

Supplementary Table 5: Case control results for ARG2 levels for B-cell ALL only (ICD-O-3:9836, case=100, control=492)

ARG2	Case n (%)	Control n (%)	OR	95% CI	p
1 st quartile	15(15.0)	123(25.0)	1		
2 nd quartile	25(25.0)	123(25.0)	1.82	0.88-3.75	0.11
3 rd quartile	34(34.0)	123(25.0)	2.36	1.18-4.71	0.02
4 th quartile	26(26.0)	123(25.0)	1.91	0.93-3.93	0.08
Trend			1.22	1.00-1.49	0.05

Adjusted odds ratios for quartiles of neonatal Arginase 2 associated with childhood acute lymphoblastic leukemia (ALL) (n=137 cases, n=492 controls). Adjusted for sex, race/ethnicity (non-Hispanic white, Hispanic white and other), birth weight (<2500, 2500-2999, 3000-3499, 3500-3999, ≥4000), birth order (first, second, third or higher), plurality (singleton, multiple), delivery mode (vaginal, cesarean delivery), year of birth, age at neonatal blood collection, mother's age at delivery (<25, 25-34, ≥35), and mother's place of birth (United States, other).