

# Congenital Abnormalities and Acute Leukemia among Children with Down Syndrome: A Children's Oncology Group Study

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## Abstract

Children with Down syndrome, due to their heightened risk of leukemia and increased prevalence of congenital abnormalities, comprise a valuable population in which to study etiology. A Children's Oncology Group study investigated the causes of childhood leukemia in children with Down syndrome diagnosed at ages 0 to 19 years during the period 1997-2002. Telephone interviews were completed with mothers of 158 cases [ $n = 97$  acute lymphoblastic leukemia (ALL) and  $n = 61$  acute myeloid leukemia (AML)] and 173 controls. Odds ratios (OR) and 95% confidence intervals (95% CI) were computed via unconditional logistic

regression to evaluate the association between congenital abnormalities and acute leukemia overall, and ALL and AML analyzed separately. The results do not provide evidence for an association among the index children (OR<sub>Combined</sub>, 0.74; 95% CI, 0.45-1.23; OR<sub>ALL</sub>, 0.67; 95% CI, 0.38-1.20; OR<sub>AML</sub>, 1.03; 95% CI, 0.49-2.16) or their siblings (OR<sub>Combined</sub>, 1.23; 95% CI, 0.71-2.13; OR<sub>ALL</sub>, 1.12; 95% CI, 0.60-2.09; OR<sub>AML</sub>, 1.60; 95% CI, 0.66-3.86), suggesting congenital malformations do not confer additional risk of leukemia beyond the risk attributable to trisomy 21 in this population. (Cancer Epidemiol Biomarkers Prev 2008;17(10):2572-7)

## Introduction

Children with Down syndrome comprise a unique and valuable population for etiologic studies of acute leukemia because they have a 10- to 20-fold increased risk for the disease (1). Congenital abnormalities are also highly prevalent in this population (2). The most common birth defects observed in children with Down syndrome include abnormalities of the cardiovascular (56-57%; refs. 2, 3), digestive (5-11%; refs. 2, 3), and genitourinary (11%; ref. 3) systems; the prevalence of several rarer abnormalities is also greater in these children (3). The association between malformations and childhood cancer has been previously studied (4-14), as malformations serve as markers of genetic alteration. The objective of this study was to examine whether congenital abnormalities in the index children with Down syndrome or their siblings are associated with subsequent development of acute leukemia.

## Materials and Methods

The methods of participant ascertainment, enrollment, and data collection for this Children's Oncology Group

(COG) study are described briefly below; these have been described in greater detail elsewhere (15, 16). Cases were eligible if they had a prior Down syndrome diagnosis, were diagnosed with acute leukemia between ages 0 to 19 y at a participating COG institution in the United States or Canada from January 1997 to October 2002, had a telephone in their residence, and had a biological mother who spoke English and consented to participate. Deceased cases meeting these criteria were eligible for participation.

Following the telephone interview, mothers of cases were asked to provide the name and contact information of their child's primary care practitioner at the time of diagnosis. Controls were then randomly selected from rosters of children with Down syndrome provided by the primary care practitioners of the cases. They were eligible if they had a prior diagnosis of Down syndrome but no cancer diagnosis, had a telephone in the residence, and a biological mother who spoke English and consented to an interview. Controls were frequency-matched to cases on age in the following groupings: 0, 1-3, 4-6, 7-10, 11-14, and 15-18 y. All Down syndrome and leukemia diagnoses were confirmed by central review.

Maternal report of congenital abnormalities was used in this analysis. Mothers of cases ( $n = 158$ ) and controls ( $n = 173$ ) were asked via telephone interview if the index children were born with unusually small head or microcephaly; cleft lip or palate; spina bifida or other spinal defect; unequal sized limbs or hemihypertrophy; heart defect; defect of the pancreas or digestive tract; kidney, bladder, or sex organ abnormalities; hernia; deafness or

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**Table 1. Baseline characteristics of 158 acute leukemia cases and 173 controls**

	Controls		Combined cases		ALL		AML	
	n (%)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	
Reference age (y)*								
<2	77 (45%)	63 (40%)		13 (13%)		50 (82%)		
2-5	51 (29%)	66 (42%)		55 (57%)		11 (18%)		
≥6	45 (26%)	29 (18%)		29 (30%)		0 (0%)		
Gender								
Male	90 (52%)	85 (54%)	1.00	57 (59%)	1.00	28 (46%)	1.00	
Female	83 (48%)	73 (46%)	0.93 (0.60-1.43)	40 (41%)	0.76 (0.46-1.26)	33 (54%)	1.28 (0.71-2.29)	
Number of siblings								
0	23 (13%)	24 (15%)	1.00	12 (12%)	1.00	12 (20%)	1.00	
1	67 (39%)	56 (35%)	0.80 (0.41-1.57)	30 (31%)	0.86 (0.38-1.95)	26 (43%)	0.74 (0.32-1.71)	
≥2	82 (48%)	78 (49%)	0.91 (0.48-1.75)	55 (57%)	1.29 (0.59-2.80)	23 (38%)	0.54 (0.23-1.24)	
Household income								
≤\$30,000	57 (33%)	57 (37%)	1.00	37 (39%)	1.00	20 (33%)	1.00	
\$30,001-\$50,000	41 (24%)	43 (28%)	1.05 (0.60-1.84)	22 (23%)	0.83 (0.43-1.60)	21 (35%)	1.46 (0.70-3.04)	
>\$50,000	74 (43%)	56 (36%)	0.76 (0.46-1.25)	37 (39%)	0.77 (0.44-1.36)	19 (32%)	0.73 (0.36-1.50)	
Maternal age at index child's birth (y)								
<35	120 (70%)	95 (60%)	1.00	63 (65%)	1.00	32 (52%)	1.00	
≥35	52 (30%)	63 (40%)	1.53 (0.97-2.41)	34 (35%)	1.25 (0.73-2.11)	29 (48%)	2.09 (1.15-3.81)	
Maternal education								
≤High school graduate	41 (24%)	62 (39%)	1.00	40 (41%)	1.00	22 (36%)	1.00	
Some post-high school	57 (33%)	45 (28%)	0.52 (0.30-0.91)	27 (28%)	0.49 (0.26-0.91)	18 (30%)	0.59 (0.28-1.23)	
College graduate	74 (43%)	51 (32%)	0.46 (0.27-0.78)	30 (31%)	0.42 (0.23-0.76)	21 (34%)	0.53 (0.26-1.08)	
Maternal ethnicity								
White	152 (88%)	126 (80%)	1.00	79 (81%)	1.00	47 (77%)	1.00	
Non-white	20 (12%)	32 (20%)	1.93 (1.05-3.54)	18 (19%)	1.73 (0.87-3.46)	14 (23%)	2.26 (1.06-4.83)	
Maternal X-ray exposure during pregnancy								
No	168 (97%)	150 (96%)	1.00	89 (93%)	1.00	61 (100%)		
Yes	5 (3%)	7 (4%)	1.57 (0.49-5.04)	7 (7%)	2.64 (0.82-8.57)	0 (0%)		
Maternal periconceptional vitamin use								
No	63 (36%)	76 (48%)	1.00	52 (54%)	1.00	24 (39%)	1.00	
Yes	110 (64%)	82 (52%)	0.62 (0.40-0.96)	45 (46%)	0.50 (0.30-0.82)	37 (61%)	0.88 (0.48-1.61)	

\*Reference age, the frequency matching factor, was not evaluated with respect to odds of leukemia.

hearing impairment; blindness or vision problems; other chromosomal abnormalities (e.g., Turner's syndrome, Klinefelter's syndrome, trisomy 18, trisomy 13); large or multiple birthmarks; or any other birth defects. Mothers with >1 live birth were also asked if any of their other children had Down syndrome, developmental delays, or the abnormalities listed above at birth ( $n_{\text{cases}} = 133$ ,  $n_{\text{controls}} = 149$ ).

**Statistical Analysis.** Unconditional logistic regression (SAS 9.1, SAS Institute, Inc.) was used to quantify the association between congenital abnormalities and acute leukemia overall, and acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) analyzed separately; odds ratios (OR) and 95% confidence intervals (95% CI) were produced. Reference age, the frequency matching variable, was included in all regression models as a continuous variable. Potential confounders, selected a priori and listed in Table 1, that had different distributions among cases and controls and that changed the natural logarithm of the OR by  $\geq 10\%$  were retained in the final multivariate models, as these variables were not highly correlated ( $p \leq 0.3$ ). The total number of birth defects in the index children and the number of siblings with  $\geq 1$  birth defect were each summed to evaluate dose response, where the sums were represented as ordinal variables in the regression models. One case mother answered less than half of the questions regarding congenital abnormalities and was excluded.

The study was approved by the institutional review boards of the University of Minnesota and participating COG institutions.

## Results

Of the 210 cases identified as eligible, 158 mothers completed interviews (97 ALL, 61 AML; response rate, 75%). Mothers of 215 eligible controls were approached regarding the study and 173 participated (response rate, 80.5%). Cases and controls were generally comparable (Table 1), although they differed somewhat by maternal age at birth, maternal educational attainment, maternal ethnicity, and maternal vitamin use.

Congenital anomalies were reported slightly less often among cases (69% versus 76% in controls) and siblings of controls (26% versus 29% in case siblings; Tables 2 and 3, respectively). The adjusted logistic regression results provide no evidence of an association between any congenital abnormalities in the index children ( $OR_{\text{Combined}}$ , 0.74; 95% CI, 0.45-1.23;  $OR_{\text{ALL}}$ , 0.67; 95% CI, 0.38-1.20;  $OR_{\text{AML}}$ , 1.03; 95% CI, 0.49-2.16; Table 2) or their siblings ( $OR_{\text{Combined}}$ , 1.23; 95% CI, 0.71-2.13;  $OR_{\text{ALL}}$ , 1.12; 95% CI, 0.60-2.09;  $OR_{\text{AML}}$ , 1.60; 95% CI, 0.66-3.86; Table 3) and childhood leukemia, either overall or by leukemia type. No linear trend was found with respect to the number of birth defects in index children or the number of affected siblings, respectively. Further, there were no significant associations observed for the

individual birth defects, either in the index children or among their siblings; these estimates lacked precision due to the limited number of affected subjects. The results of a sensitivity analysis restricting cases to those from the same primary care clinics as the controls ( $n = 67$ ) did not yield appreciably different results (data not shown), partially addressing concerns about bias in control selection. A second sensitivity analysis including only older siblings resulted in ORs similar to those shown in Table 3 (data not shown).

Other congenital defects described by mothers included deformities of the hand or toes (4 cases, 2 controls, 1 control sibling); club foot (2 cases, 1 control sibling); scoliosis (1 case, 1 control, 1 case sibling); eye problems (2 controls, 1 case sibling); hydrocephalus (1 case, 1 case sibling); cerebral palsy/spastic diplegia (1 control, 1 case

sibling); enlarged internal organs (1 case); minor intracranial anomalies (1 case); trouble swallowing (1 control); Hirschsprung's disease (1 control); anomaly of the larynx, trachea, or bronchus (1 control); ankylloglossia (1 case sibling); and no spleen (1 case sibling).

## Discussion

Population-based childhood cancer studies examining nonsyndromic malformations have consistently reported strong associations overall, and among specific malformations and malignancies (4-6). In a recent report involving comprehensive physical examinations, major and minor abnormalities were significantly more common among childhood cancer cases than controls; the

**Table 2. Association between congenital abnormalities and acute leukemia among children with Down syndrome**

	Controls		Combined cases		ALL		AML	
	<i>n</i> (%)	<i>n</i> (%)	OR* (95% CI)	<i>n</i> (%)	OR* (95% CI)	<i>n</i> (%)	OR* (95% CI)	
<b>At least one abnormality</b>								
No	41 (24%)	48 (31%)	1.00	31 (32%)	1.00	17 (28%)	1.00	
Yes	132 (76%)	109 (69%)	0.74 (0.45-1.23)	66 (68%)	0.67 (0.38-1.20)	43 (72%)	1.03 (0.49-2.16)	
<b>Number of abnormalities</b>								
0	41 (24%)	48 (31%)	1.00	31 (32%)	1.00	17 (28%)	1.00	
1	74 (43%)	56 (36%)	0.66 (0.38-1.16)	34 (35%)	0.60 (0.31-1.14)	22 (37%)	0.92 (0.40-2.12)	
≥2	58 (34%)	53 (34%)	0.84 (0.47-1.51)	32 (33%)	0.78 (0.40-1.53)	21 (35%)	1.15 (0.50-2.67)	
			$P_{\text{trend}} = 0.55$		$P_{\text{trend}} = 0.38$		$P_{\text{trend}} = 0.63$	
<b>Microcephaly</b>								
No	165 (95%)	151 (96%)	1.00	93 (96%)	1.00	58 (97%)	1.00	
Yes	8 (5%)	6 (4%)	0.73 (0.24-2.22)	4 (4%)	0.99 (0.28-3.50)	2 (3%)	0.50 (0.09-2.70)	
<b>Cleft lip or palate</b>								
No	171 (99%)	156 (99%)	1.00	97 (100%)	1.00	59 (98%)	1.00	
Yes	2 (1%)	1 (1%)	0.60 (0.05-6.86)	0 (0%)		1 (2%)	13.00 (0.65-262.16)	
<b>Spina bifida/other spinal defect</b>								
No	172 (99%)	157 (100%)	1.00	97 (100%)	1.00	60 (100%)	1.00	
Yes	1 (1%)	0 (0%)		0 (0%)		0 (0%)		
<b>Hemihypertrophy</b>								
No	172 (99%)	156 (99%)	1.00	96 (99%)	1.00	60 (100%)	1.00	
Yes	1 (1%)	1 (1%)	1.37 (0.08-22.53)	1 (1%)	1.78 (0.11-30.11)	0 (0%)		
<b>Heart defect</b>								
No	74 (43%)	69 (44%)	1.00	47 (48%)	1.00	22 (37%)	1.00	
Yes	99 (57%)	88 (56%)	0.97 (0.62-1.53)	50 (52%)	0.83 (0.49-1.40)	38 (63%)	1.43 (0.73-2.81)	
<b>Pancreas/digestive tract defect</b>								
No	155 (90%)	145 (92%)	1.00	89 (92%)	1.00	56 (93%)	1.00	
Yes	18 (10%)	12 (8%)	0.82 (0.37-1.79)	8 (8%)	0.86 (0.35-2.11)	4 (7%)	0.73 (0.22-2.44)	
<b>Kidney/bladder/sex organ defect</b>								
No	158 (91%)	147 (94%)	1.00	93 (96%)	1.00	54 (90%)	1.00	
Yes	15 (9%)	10 (6%)	0.73 (0.31-1.72)	4 (4%)	0.45 (0.14-1.45)	6 (10%)	1.37 (0.44-4.28)	
<b>Hernia</b>								
No	149 (86%)	130 (83%)	1.00	79 (81%)	1.00	51 (85%)	1.00	
Yes	24 (14%)	27 (17%)	1.37 (0.74-2.54)	18 (19%)	1.56 (0.78-3.11)	9 (15%)	1.25 (0.50-3.13)	
<b>Deafness/hearing impairment</b>								
No	159 (92%)	148 (94%)	1.00	93 (96%)	1.00	55 (92%)	1.00	
Yes	14 (8%)	9 (6%)	0.61 (0.25-1.50)	4 (4%)	0.44 (0.13-1.43)	5 (8%)	0.88 (0.28-2.80)	
<b>Blindness/vision problems</b>								
No	151 (87%)	142 (90%)	1.00	86 (89%)	1.00	56 (93%)	1.00	
Yes	22 (13%)	15 (10%)	0.78 (0.38-1.63)	11 (11%)	0.83 (0.36-1.88)	4 (7%)	0.73 (0.21-2.56)	
<b>Other chromosomal abnormalities</b>								
No	171 (99%)	156 (99%)	1.00	96 (99%)	1.00	60 (100%)	1.00	
Yes	2 (1%)	1 (1%)	0.57 (0.05-6.66)	1 (1%)	1.19 (0.10-14.27)	0 (0%)		
<b>Large/multiple birthmarks</b>								
No	171 (99%)	150 (96%)	1.00	93 (96%)	1.00	57 (95%)	1.00	
Yes	2 (1%)	7 (4%)	2.60 (0.51-13.35)	4 (4%)	2.29 (0.38-13.93)	3 (5%)	4.39 (0.48-39.84)	

\*Adjusted for child's reference age (continuous), maternal age (<35 versus ≥ 35 y), maternal race (white versus non-white), and maternal education (≤high school versus some post-high school versus college graduate).

†Total count of birth defects within an individual (range, 0 ≤ number of birth defects ≤12).

‡For example, Turner's syndrome, Klinefelter's syndrome, trisomy 18, trisomy 13.

**Table 3. Association between congenital abnormalities among siblings and acute leukemia among children with Down syndrome**

	Controls		Combined cases		ALL		AML	
	n (%)	n (%)	OR* (95% CI)	n (%)	OR* (95% CI)	n (%)	OR* (95% CI)	
At least one sibling with an abnormality <sup>†</sup>								
No	110 (74%)	94 (71%)	1.00	60 (71%)	1.00	34 (71%)	1.00	
Yes	39 (26%)	39 (29%)	1.23 (0.71-2.13)	25 (29%)	1.12 (0.60-2.09)	14 (29%)	1.60 (0.66-3.86)	
Number of siblings with abnormalities <sup>‡</sup>								
0	110 (74%)	94 (71%)	1.00	60 (71%)	1.00	34 (71%)	1.00	
1	32 (21%)	36 (27%)	1.36 (0.76-2.42)	22 (26%)	1.23 (0.64-2.38)	14 (29%)	1.94 (0.78-4.80)	
≥2	7 (5%)	3 (2%)	0.53 (0.12-2.36)	3 (4%)	0.61 (0.14-2.74)	0 (0%)		
			<i>P</i> <sub>trend</sub> = 0.91		<i>P</i> <sub>trend</sub> = 0.88		<i>P</i> <sub>trend</sub> = —	
Down syndrome								
No	148 (99%)	132 (99%)	1.00	85 (100%)		47 (98%)	1.00	
Yes	1 (1%)	1 (1%)	0.52 (0.03-10.47)	0 (0%)		1 (2%)	0.64 (0.03-12.70)	
Microcephaly								
No	149 (100%)	131 (99%)		84 (99%)		47 (98%)		
Yes	0 (0%)	2 (1%)		1 (1%)		1 (2%)		
Cleft lip or palate								
No	148 (99%)	132 (99%)	1.00	84 (99%)	1.00	48 (100%)		
Yes	1 (1%)	1 (1%)	0.85 (0.05-14.31)	1 (1%)	1.48 (0.09-24.80)	0 (0%)		
Spina bifida/other spinal defect								
No	149 (100%)	131 (99%)		84 (99%)		47 (98%)		
Yes	0 (0%)	2 (1%)		1 (1%)		1 (2%)		
Hemihypertrophy								
No	148 (99%)	132 (99%)	1.00	84 (99%)	1.00	48 (100%)		
Yes	1 (1%)	1 (1%)	1.09 (0.06-18.49)	1 (1%)	1.54 (0.08-28.37)	0 (0%)		
Heart defect								
No	139 (93%)	125 (94%)	1.00	81 (95%)	1.00	44 (92%)	1.00	
Yes	10 (7%)	8 (6%)	0.78 (0.28-2.18)	4 (5%)	0.57 (0.16-2.02)	4 (8%)	1.29 (0.30-5.52)	
Pancreas/digestive tract defect								
No	149 (100%)	132 (99%)		85 (100%)		47 (98%)		
Yes	0 (0%)	1 (1%)		0 (0%)		1 (2%)		
Kidney/bladder/sex organ defect								
No	146 (98%)	129 (97%)	1.00	83 (98%)	1.00	46 (96%)	1.00	
Yes	3 (2%)	4 (3%)	1.86 (0.39-8.87)	2 (2%)	1.41 (0.22-9.00)	2 (4%)	1.90 (0.22-16.31)	
Hernia								
No	142 (95%)	125 (94%)	1.00	80 (94%)	1.00	45 (94%)	1.00	
Yes	7 (5%)	8 (6%)	1.44 (0.49-4.20)	5 (6%)	1.30 (0.38-4.48)	3 (6%)	1.96 (0.31-12.52)	
Deafness/hearing impairment								
No	149 (100%)	132 (99%)		84 (99%)		48 (100%)		
Yes	0 (0%)	1 (1%)		1 (1%)		0 (0%)		
Blindness/vision problems								
No	148 (99%)	131 (99%)	1.00	83 (98%)	1.00	48 (100%)		
Yes	1 (1%)	2 (1%)	3.09 (0.25-38.28)	2 (2%)	2.92 (0.22-38.57)	0 (0%)		
Other chromosomal abnormalities								
No	149 (100%)	133 (100%)		85 (100%)		48 (100%)		
Yes	0 (0%)	0 (0%)		0 (0%)		0 (0%)		
Developmental delays								
No	145 (97%)	127 (95%)	1.00	79 (93%)	1.00	48 (100%)		
Yes	4 (3%)	6 (5%)	1.61 (0.42-6.22)	6 (7%)	2.21 (0.56-8.62)	0 (0%)		
Large/multiple birthmarks								
No	131 (88%)	120 (90%)	1.00	77 (91%)	1.00	43 (90%)	1.00	
Yes	18 (12%)	13 (10%)	0.82 (0.37-1.83)	8 (9%)	0.78 (0.30-2.01)	5 (10%)	1.02 (0.31-3.36)	

\*Adjusted for child's reference age (continuous), maternal age (<35 versus ≥ 35 y), maternal race (white versus non-white), and maternal education (≤high school versus some post-high school versus college graduate).

<sup>†</sup>Includes only index children with at least one sibling (*n*<sub>cases</sub> = 133; *n*<sub>controls</sub> = 149).

<sup>‡</sup>Total count of siblings with at least one birth defect (range: 0 ≤ number of siblings ≤ 12).

associations held when recognized genetic syndromes were excluded (7). With respect to leukemia, some studies have observed 1.4- to 5-fold risks for nonchromosomal congenital abnormalities (6, 8, 9), whereas other population-based studies found no evidence of an association (4, 5, 10). One population-based study indicated a 1.5-fold leukemia risk for siblings with any abnormalities and a 2.5-fold risk with respect to heart defects (10); another failed to show an association among siblings (9).

Conceptually, there are at least four potential mechanisms linking congenital abnormalities and acute leukemia formation. Mechanism 1: a genetic or epigenetic alteration occurring early in development results in the development of both congenital anomalies and leukemia (5, 11, 17). An excess of case siblings with birth defects would implicate transmissible germ line mutations, whereas failure to find an association among siblings indicates a sporadic event. Mechanism 2: a common exposure leads to both congenital abnormalities and

leukemia through common or related pathways. This theory assumes childhood leukemia is the result of gene-environment interactions, such that individuals with the necessary genetic hits or polymorphisms are more susceptible to leukemogenesis in the presence of relevant environmental exposures (11, 17). Importantly, only two confirmed human transplacental carcinogens, diethylstilbestrol and irradiation, have been identified thus far (18). A combination of these mechanisms (e.g., initial genetic mutations followed by environmental insults) is also plausible. Mechanisms 3 and 4: a congenital abnormality forms first and initiates leukemogenesis, or the converse (12). Neither a malformation nor leukemia is a sufficient cause, however, as the proportion of leukemia cases who have congenital abnormalities (5) and the proportion of those with congenital abnormalities that develop leukemia (14) are both minor. Both groups include children with Down syndrome, who develop leukemia at a rate of <1% to 3% (2, 19).

To our knowledge, this is the first study to examine the congenital abnormality-leukemia association among children with Down syndrome. We found little evidence of an association, suggesting congenital malformations do not contribute additional risk beyond that attributable to trisomy 21. We speculate trisomy 21 likely leads, through direct or indirect effects, to both acute leukemia and errors in morphology. Children with Down syndrome have a noteworthy increase in risk for leukemia (10- to 20-fold increase; ref. 20), and for acute megakaryoblastic leukemia (AML-M7 or AMKL) in particular (500-fold increase; ref. 21), but have a reduced risk for most solid tumors, including neuroblastoma and Wilms' tumor (reviewed in ref. 19). (Of note, increases in lymphomas, germ cell tumors, and retinoblastoma have also been reported; ref. 19). Thus, the additional copy of chromosome 21 is postulated to be an etiologic feature specific to leukemia. A minority of children with Down syndrome, however, develop leukemia (<1-3%; refs. 2, 19), indicating trisomy 21 is necessary but not sufficient for leukemogenesis. A multistep model for leukemogenesis has been proposed, wherein multiple genetic "hits" are required and trisomy 21 is implicated as an early *in utero* hit (22, 23). Evidence for a trisomy 21-leukemia link is provided by research on *GATA1* mutations, which seem a necessary second step in acute megakaryoblastic leukemia development in individuals with Down syndrome (24). Other chromosome 21q genes involved in the leukemic transformation have been proposed (25). Evidence for trisomy 21 involvement in congenital malformations is suggested by a reported link between increased copies of chromosome 21q genes *DSCR1* and *DYR1A* and common Down syndrome phenotypic characteristics, and cardiac, genitourinary, and gastrointestinal abnormalities (26).

This study features unique strengths. The use of the COG registry in case identification results in a nearly population-based study, because COG institutions treat a large majority of childhood leukemia patients in North America (i.e., 85–100% of cases diagnosed at ages 0 to 14 years and 44%–53% of cases ages 15 to 19 years; refs. 27, 28). We identified 210 eligible cases during the period January 1997–October 2002. The total number of leukemia diagnoses among children with Down syndrome in the United States and Canada during this period

is unknown, because neither the COG registry nor the Surveillance, Epidemiology, and End Results Program (29) collects information on Down syndrome at the time of registration; participating COG institutions were responsible for case identification. The method of control selection ensures that controls should closely represent cases had they not developed leukemia and that any misclassification of abnormalities should theoretically be nondifferential, as case and control mothers would be similarly motivated in their recall of congenital abnormalities.

The results of a validation study examining maternal report of malformations predict a low rate of false positives (specificity, 98%) and the potential for underreporting (sensitivity, 61%; ref. 30). The mothers of children with Down syndrome in the current study, however, may have higher recall than those in the validation study, because Down syndrome is associated with a complement of abnormalities. The prevalence of heart defects and gastrointestinal abnormalities reported among the controls in this study (57% and 10%, respectively) are similar to published rates among children with Down syndrome overall (50–56% and 5–11%, respectively; refs. 2, 3), indicating no systematic underreporting. Conversely, 8% of control and 6% of case mothers reported "deafness/hearing impairment" in our study, whereas published rates of "hearing loss" in children with Down syndrome are 38% to 78% (2, 31), indicating nondifferential underreporting due to differences in question wording or data source (maternal report versus medical records, congenital versus acquired hearing conditions), better surveillance and management of otitis media in our clinic-based study population (31), or simply due to chance.

A key limitation is the sample size, which provides limited power to detect a modest association. A moderate to large association, if present, should be detectable among this highly susceptible population; overall, we had sufficient power to detect an OR of 2.7 in the index children and 2.2 in the sibling analysis. Further, maternal interviews precluded thorough data collection regarding minor anomalies, which may be an important measure (7, 13).

These null results indicate congenital abnormalities do not confer additional risk of leukemia in children with Down syndrome. It will be of interest for others to confirm our findings.

### Disclosure of Potential Conflicts of Interest

The authors report no conflicts of interest regarding this research.

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The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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