

Role of Infection on the etiology of childhood acute lymphoblastic leukemia

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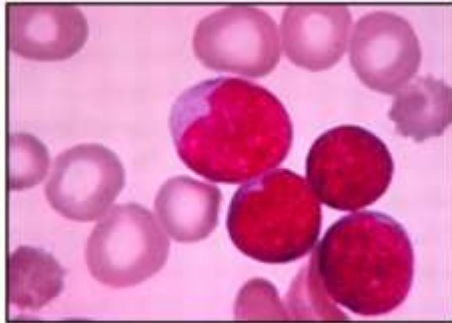
Natural History of Disease: timing of events

Archived Neonatal Blood Spots

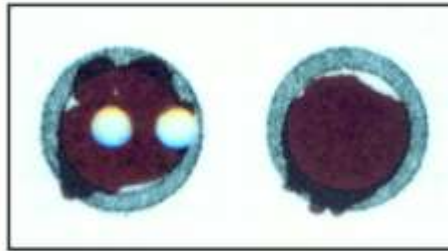


Sample of blood taken immediately after birth (1-3 days)

Leukaemia cells at diagnosis



Guthrie blood spots



DNA



PCR amplification of the fusion gene

Diagnostic DNA

Guthrie DNA

Patient

Control

Patient

Control



Genomic sequence

TEL

AML1

Diagnostic DNA GGCTAAGCGAAAACATTTTCAGCGGACACTTCAGGAAG

Guthrie DNA GGCTAAGCGAAAACATTTTCAGCGGACACTTCAGGAAG

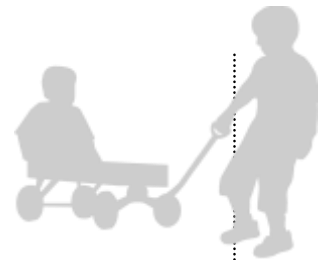
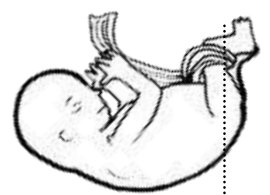


Fusion point between genes
with 4 extra nucleotides added

Greaves,

BMJ 2002;324:283-287

Natural history: Leukemia is a disease with prenatal and postnatal events



TEL-AML1
AML1-ETO
PML-RARA
CBFB-MYH11

FIRST HIT:
TRANSLOCATION

SECOND HIT *del12p* (for *TEL-AML1*) *dx*

E2A-PBX1

(**FIRST HIT?**)

SECOND HIT?
TRANSLOCATION

?

dx

Hyperdiploid

FIRST HIT:
PLOIDY CRISIS

SECOND HIT:RAS/FLT3

dx

MLL

HIT:
TRANSLOCATION *dx*

HIT:
TRANSLOCATION *dx*

Patient 1

Patient 2

Birth

1

2

3

4

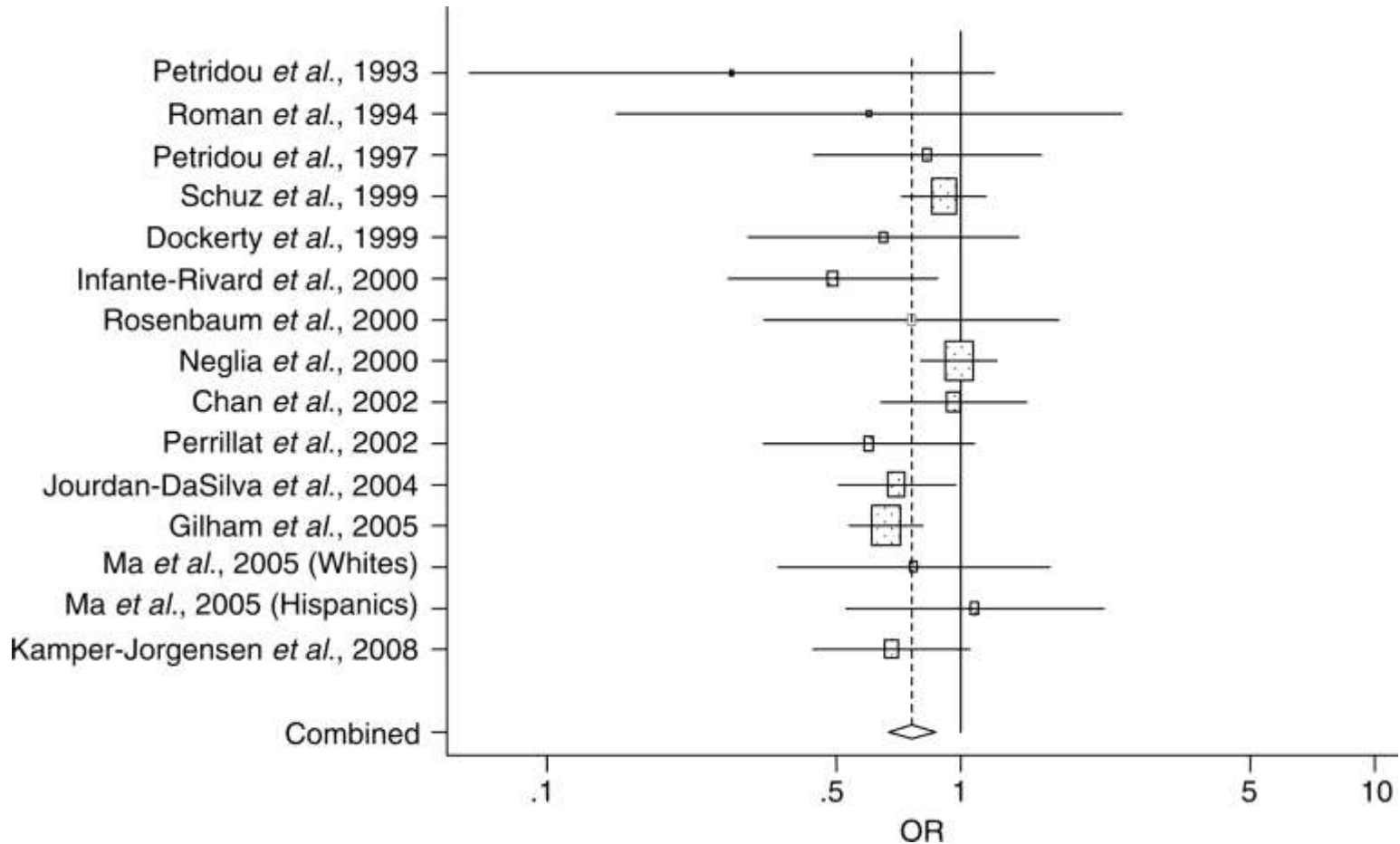
Age (years)

Do infections affect risk of childhood leukemia?

- Normal course of childhood infections, vaccinations are *protective*
 - *Hygiene hypothesis, “Greaves hypothesis”*

Exposure to infections *decreases* childhood leukemia risk

Day care Attendance & Childhood ALL



Combined OR = 0.77; 95% CI = 0.66-0.88

But.... Doctor-diagnosed infections *increase* risk

Table 2 The association between childhood ALL and infections diagnosed during different time periods, Taiwan, 2000–08

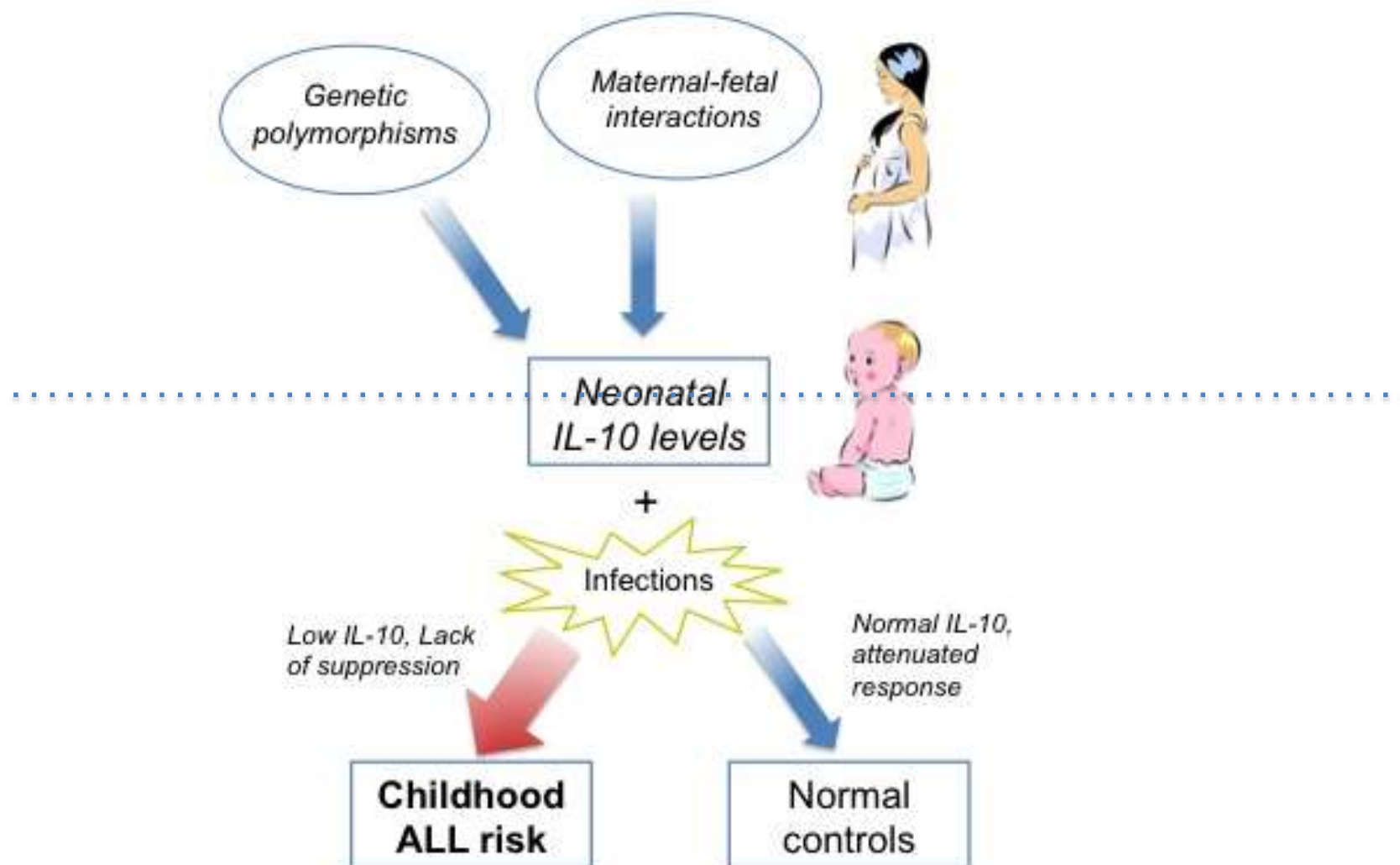
	Before 1 year of age			>1 year before the case's diagnosis		
	Case N = 846 n (%)	Control N = 3374 n (%)	OR (95% CI) ^a	Case ^b N = 762 n (%)	Control ^b N = 3043 n (%)	OR (95% CI) ^a
Medically diagnosed infections						
Any infections^d						
No	305 (36.0)	1429 (42.3)	Referent	33 (4.3)	368 (12.1)	Referent
Yes	510 (60.3)	1831 (54.3)	3.18 (2.17–4.66)	696 (91.4)	2503 (82.2)	3.90 (2.61–5.81)
Possible	31 (3.7)	114 (3.4)	2.67 (1.48–4.79)	33 (4.3)	172 (5.7)	1.83 (1.05–3.17)
Each additional visit ^c			1.014 (1.006–1.022)			1.003 (1.001–1.005)
Number of clinical visits for infection						
0 visits	305 (37.4)	1429 (43.8)	Referent	33 (4.5)	368 (12.8)	Referent
1–5 visits	109 (13.4)	441 (13.6)	2.77 (1.81–4.26)	63 (8.6)	350 (12.2)	2.26 (1.38–3.69)
6–10 visits	101 (12.4)	369 (11.3)	3.27 (2.10–5.09)	56 (7.7)	191 (6.7)	4.33 (2.58–7.28)
>10 visits	300 (36.8)	1021 (31.3)	3.63 (2.40–5.48)	577 (79.2)	1962 (68.3)	4.78 (3.08–7.39)

Cytokines at birth - are children's immune systems "tuned" differently?

	Control (N=116)	Acute lymphoblastic leukemia (N=116)	OR (95% CI) [†]	P-value
Tertiles				
IL4				
Tertile (pg/ml)				
<0.11	38 (33.0 %)	51 (44.4 %)	Referent	
0.11-0.179	38 (33.0 %)	46 (40.0 %)	2.00 (0.88-4.52)	0.10
≥0.18	39 (34.0 %)	18 (15.6 %)	2.01 (0.57-7.12)	0.28
IL6				
Tertile (pg/ml)				
< 0.57	36 (31.0 %)	56 (48.3 %)	Referent	
0.57-0.889	40 (34.5 %)	29 (25.0 %)	0.61 (0.27-1.36)	0.22
≥0.89	40 (34.5 %)	31 (26.7 %)	0.78 (0.31-1.93)	0.58
IL10				
Tertile (pg/ml)				
< 1.08	38 (32.8 %)	83 (72.1 %)	Referent	
1.08-1.69	38 (32.8 %)	21 (18.3 %)	0.16 (0.07-0.39)	<0.0001
≥1.69	40 (34.4 %)	11 (9.6 %)	0.04 (0.01-0.18)	<0.0001
IL12				
Tertile (pg/ml)				
< 1.5	38 (32.8 %)	34 (29.3 %)	Referent	
1.5-3.69	38 (32.8 %)	44 (37.9 %)	1.84 (0.86-3.94)	0.12
≥3.7	40 (34.4 %)	38 (32.8 %)	1.78 (0.80-3.96)	0.16
IL13				
Tertile (pg/ml)				
< 0.85	37 (31.9 %)	60 (51.7 %)	Referent	
0.85-1.139	39 (33.6 %)	33 (28.5 %)	0.98 (0.43-2.22)	0.96
≥ 1.14	40 (34.5 %)	23 (19.8 %)	2.10 (0.63-7.03)	0.23

IL-10 at birth profoundly decreased in children who contract leukemia - Chang... Wiemels CEBP 2011

Causes and consequences of IL-10 levels at birth



Two hit hypothesis and role of infections in leukemogenesis

