Folate and childhood ALL

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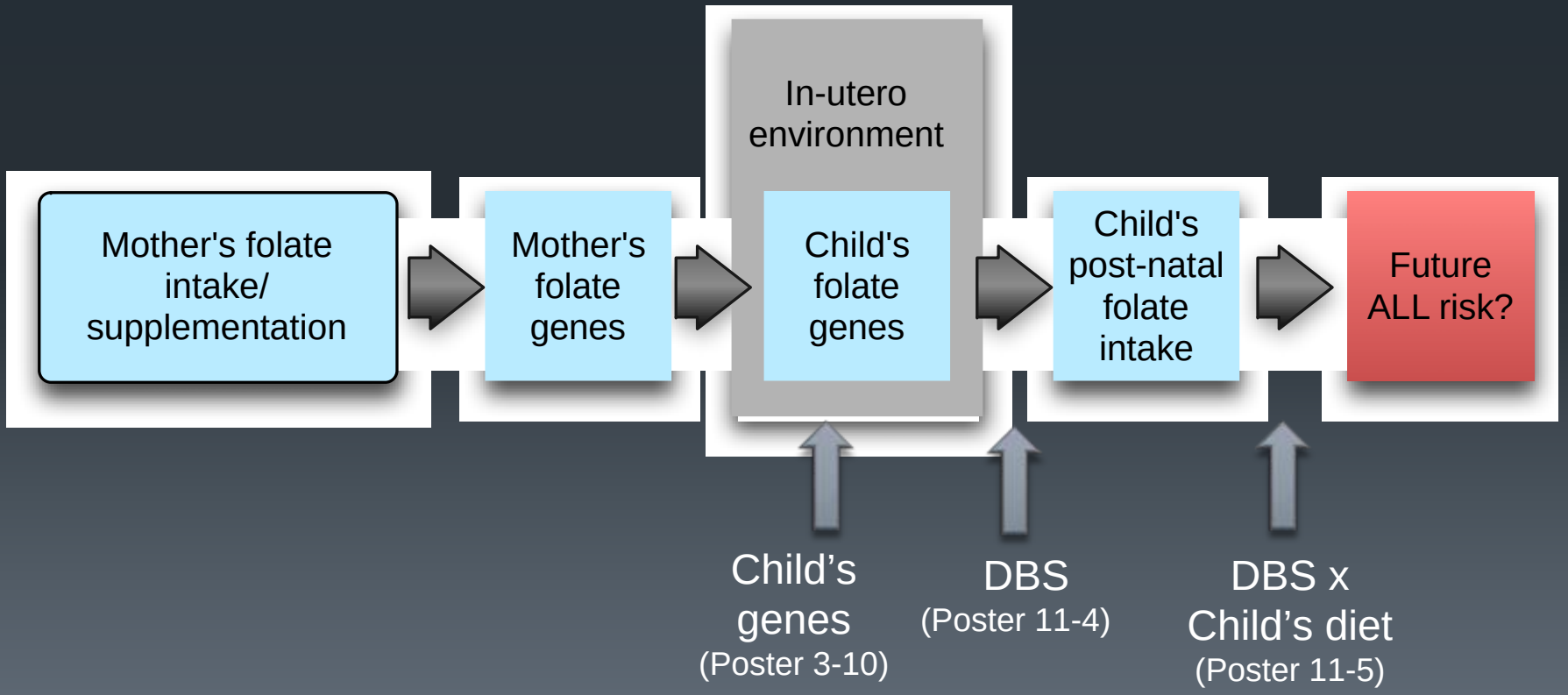
Background

- Childhood ALL: biologically heterogeneous disease characterized by chromosomal breakage and abnormalities.
- Folate deficiency has been associated with chromosomal breakage and abnormalities, and is a potential causal agent in childhood ALL
- Epidemiologic studies of maternal folate intake during pregnancy (diet and supplements) have been mixed; recent meta-analysis indicates little to no effect of folate supplementation [a]
- A child's exposure to folate prior to diagnosis is modulated by several factors….

[a] Milne et al, Int J Cancer, 2010

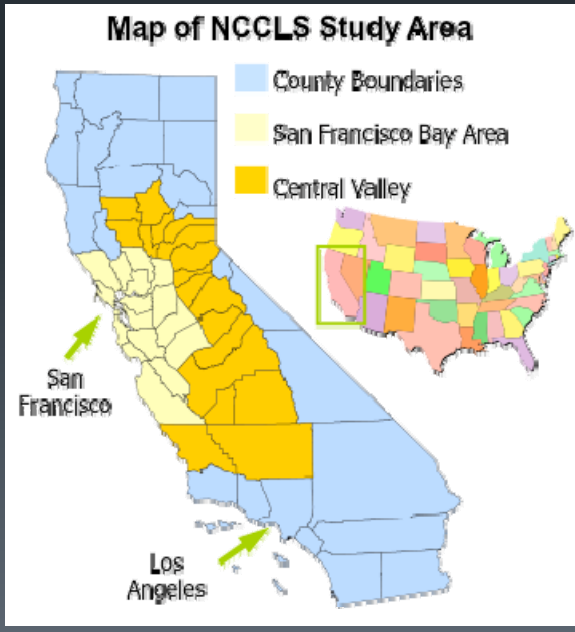
Potential exposure periods for folate



NCCLS

Northern California Childhood Leukemia Study

- Population-based case-control study
- Cases: incident ALL <15 years
- Controls: matched to cases
  - >40% Hispanic
- In-person interviews used to elicit information on maternal pre-pregnancy dietary folate intake and supplement use, as well as child's early diet (prior to age 2)
- Included subjects were those enrolled 1995-2002

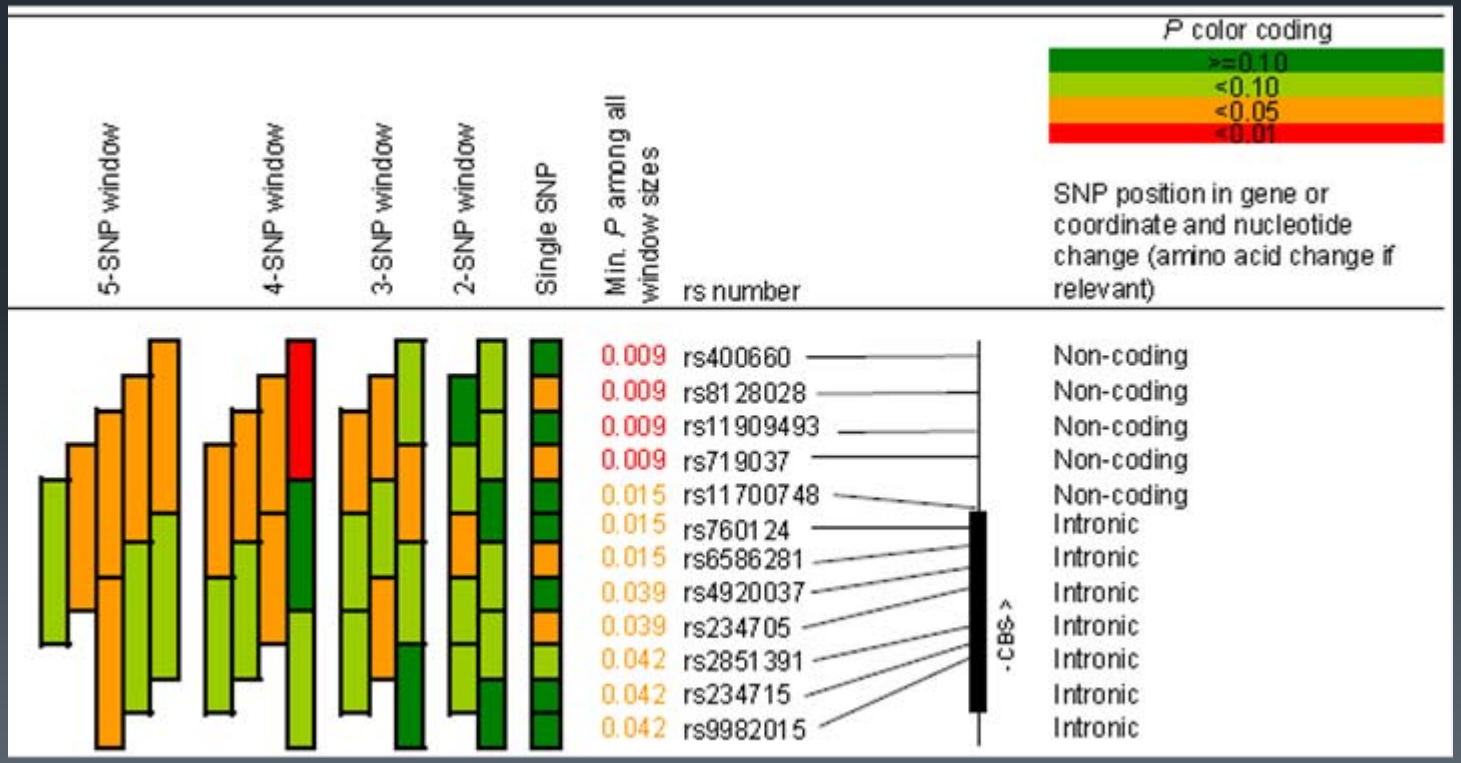


Child's Folate Metabolism genes

- Candidate gene approach: 72 htSNPs in 10 genes
  - Illumina Goldengate
- Haplotype sliding window analysis
- Sample size: 377 cases, 448 controls

- *CBS*
- *DHFR*
- *FOLH1*
- *MTHFD1*
- *MTHFR*
- *MTR*
- *MTRR*
- *SHMT1*
- *SLC19A1*
- *TYMS*

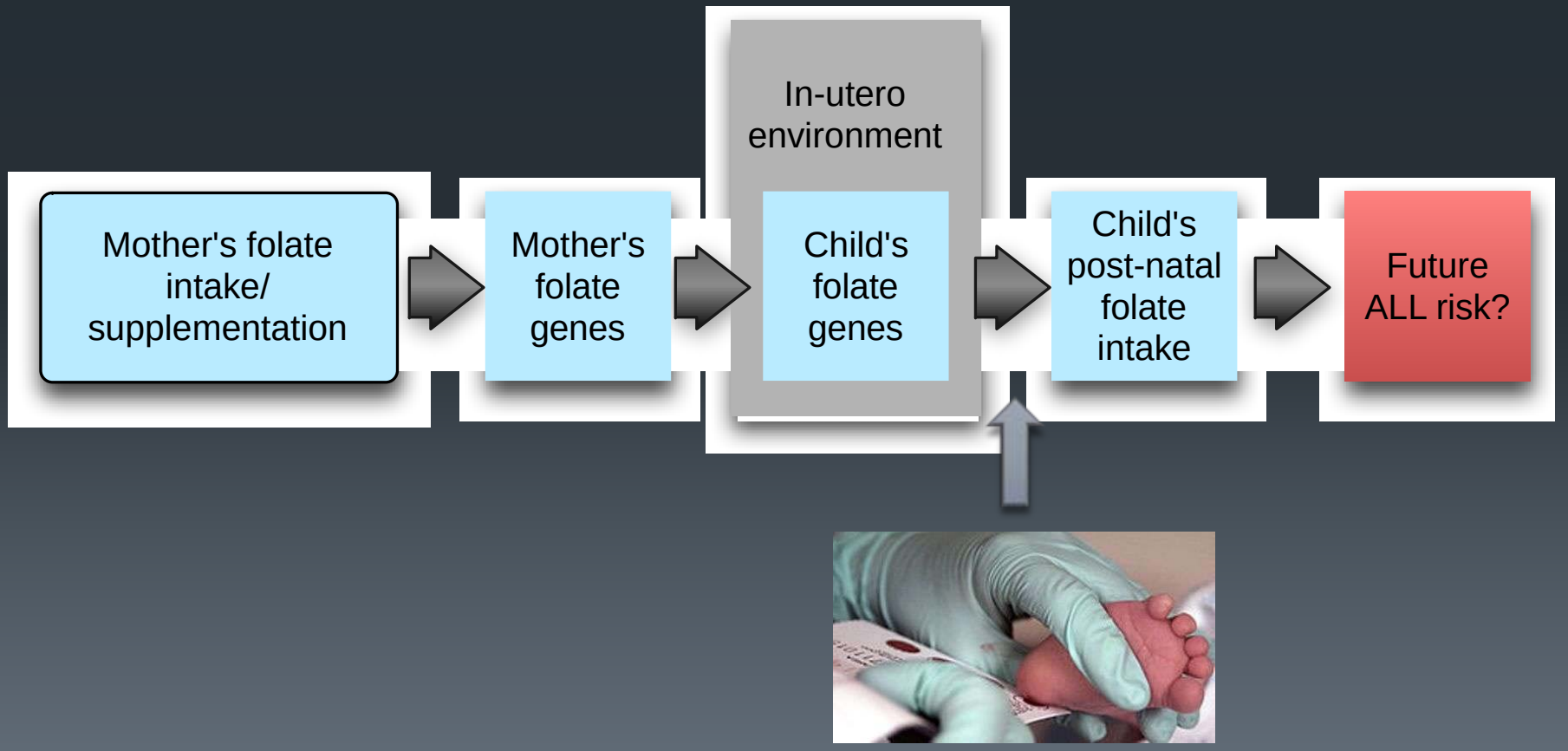
CBS in Hispanics



CBS
Remarks

- Overexpression of *CBS* decreases levels of homocysteine, inducing **functional folate deficiency** (“folate trap”)
- Because homocysteine is at the intersection of the DNA synthesis and repair pathway and the DNA methylation pathway, overexpression of *CBS* may lead to alteration in these functions
- *CBS* is over-expressed in children with trisomy 21
  - Cellular lesions caused by the “folate trap” may relate to leukemia risk in children with Down syndrome.
- Future studies should investigate whether specific CBS alleles are overrepresented in the additional chromosome 21 within hyperdiploid leukemias

Potential exposure periods for folate



Neonatal DBS folate

Study subjects

- Children with available dried blood spot (DBS) collected at birth by the California Department of Public Health (California births only)

Sample size

- 313 ALL cases, 405 controls

Folate (FOL) assays [a]

- Performed on DBS specimens, normalized for Hemoglobin (Hb):

  HbFOL (nmol/g) = FOL_{DBS} (nmol/L) / Hb_{DBS} (g/L)

- 2 replicates per DBS

[a] O'Broin SD and Gunter EW. Am J Clin Nutr 1999;70:359-67

Neonatal folate results for ALL

	N	Mean (SD) *	p
All birth periods			0.941
Case	313	2.82 (1.02)	
Control	405	2.81 (1.02)	

*HbFOL in nmol/g, adjusted for income, race/ethnicity (H, NHW, NHO), sex, and age; back-transformed from log(HbFOL)

- In addition to null effects for total ALL, no associations were observed after stratifying for:
  - Pre-pregnancy supplement use
  - Hispanic ethnicity
  - Major ALL subtypes, including overall B-cell ALL, B-cell hyperdiploid ALL, and B-cell ALL with structural abnormalities (translocations, deletions)

Neonatal folate
Remarks

- Robust assay methodology, large sample size
- Results do not support an association between blood folate levels at birth and risk of childhood ALL
  - Together with inconsistent findings for maternal folate supplementation and dietary intake, these findings suggest that folate exposures before birth may not play a role in risk of childhood ALL
- However, our results do not rule out a role for:
  - Folate exposures after birth, or
  - Modification of birth folate effects by other factors, including child's genetic susceptibility and post-natal exposures

Child's early diet

Previous findings*

- Oranges/Bananas: $OR_{\text{regular vs rare}}$=0.49 (0.26-0.94)
- Orange juice: $OR_{\text{regular vs rare}}$=0.54 (0.31-0.94)
- Other food groups assessed (with no association)
  - Apples/Grapes
  - Beef
  - Hot dogs/Deli meat
  - Other fruit juice
  - Soda
  - Vegetables

*Kwan et al, AJE, 2004

Child's early diet and neonatal folate

- Test for interaction between neonatal folate levels (tertiles) and food group intake (LR test)
- Strongest observed interaction was with Oranges/Bananas
  - Reduced risk main effect largely limited to low folate tertile

Food group		Neonatal folate (tertiles)		
		Low	Med	High
Oranges/Bananas				
	Rare/None	1 (reference)	1 (reference)	1 (reference)
	Occasional	0.53 (0.24-1.16)	1.64 (0.75-3.61)	0.81 (0.39-1.69)
	Regular	0.28 (0.11-0.70)	0.69 (0.28-1.66)	0.84 (0.38-1.90)

Child's early diet and neonatal folate: Remarks

- Absence of interaction effect with "vegetable" food group
  - Variety of vegetables included in this group
- Oranges/bananas are high in folate…
  - Could children with lower folate levels at birth experience a benefit from other sources of folate in early life?
- Biologically intriguing, but still an exploratory analysis → requires confirmation and followup

Future directions

- Predictors of newborn folate levels, incorporating multiple factors discussed here

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