Note: for non-commercial purposes only

Evidence that early growth influences adiposity at age 9-13 years and is mediated by epigenetic regulation of gene expression

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hnrc molecules to populations

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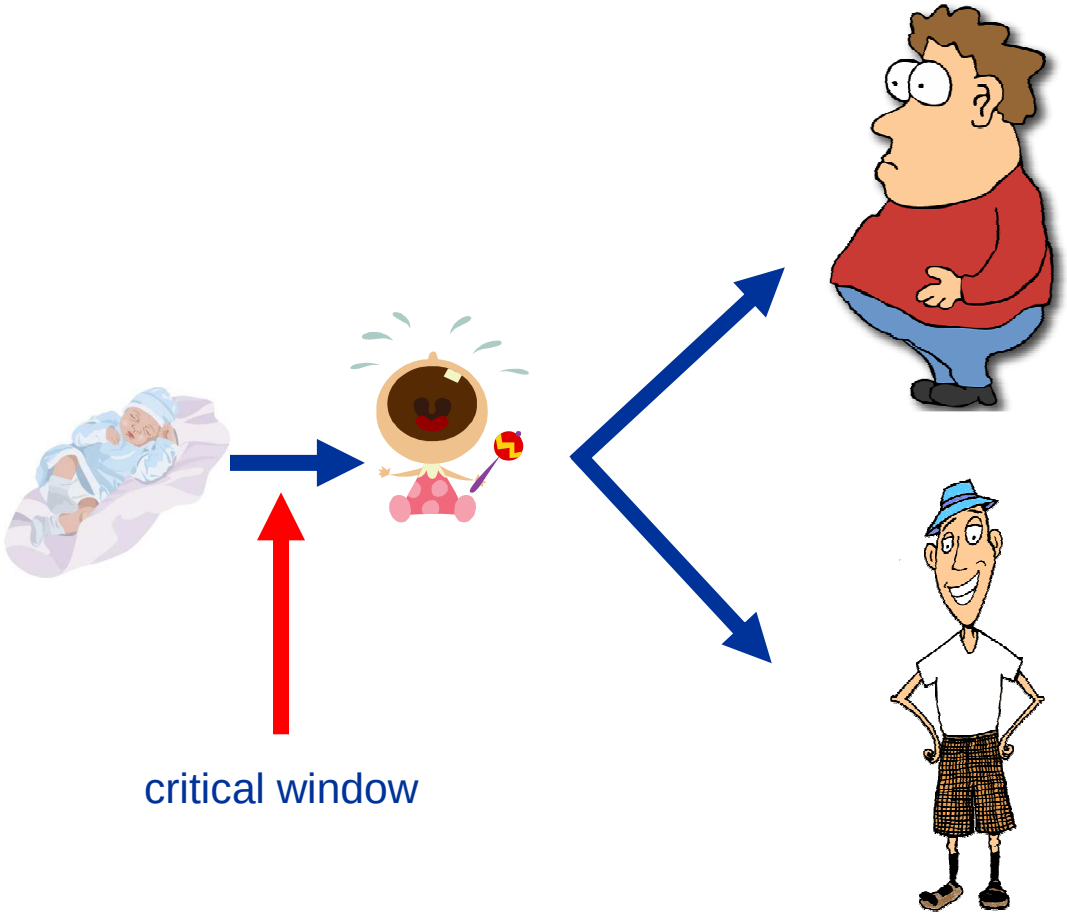
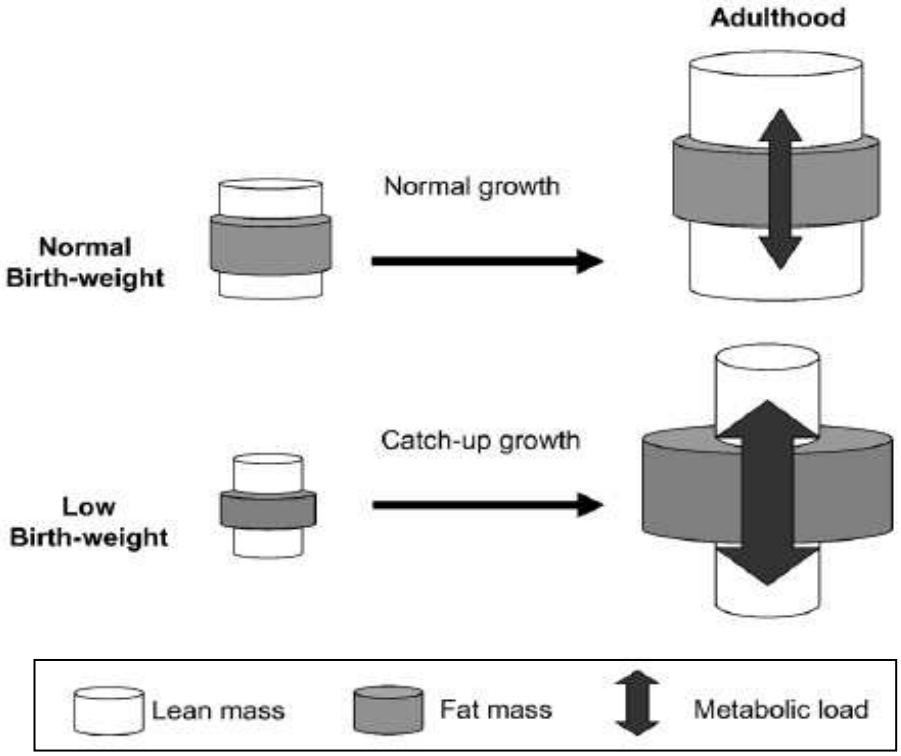
Nutrition and preterm infants



Catch up growth



Wells, *Early Human Development* (2007) **83**:743-748

- Beneficial for neurodevelopment
- Associated with adverse metabolic consequences in adulthood

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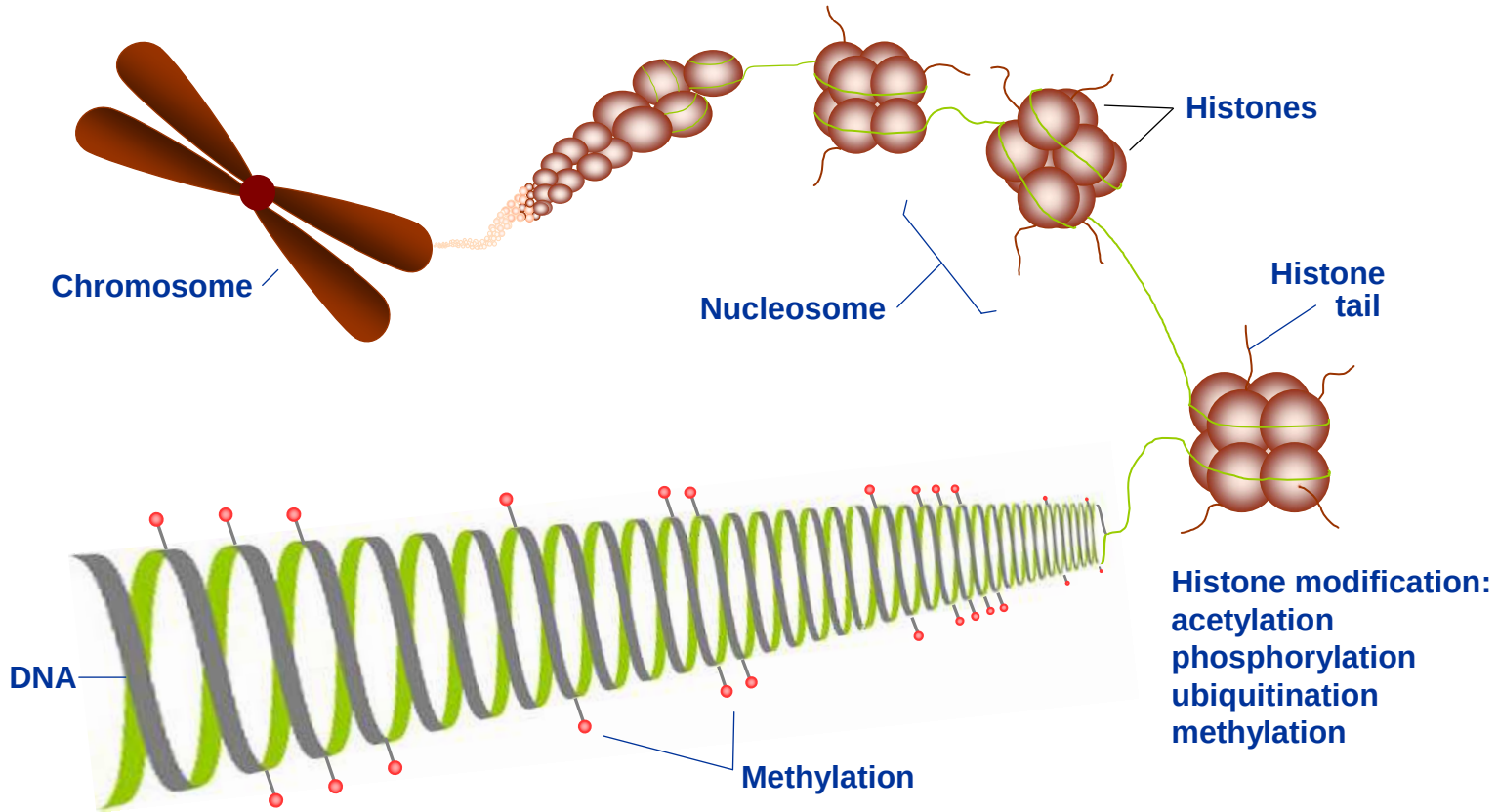
Mechanisms of programming

Epigenetics?



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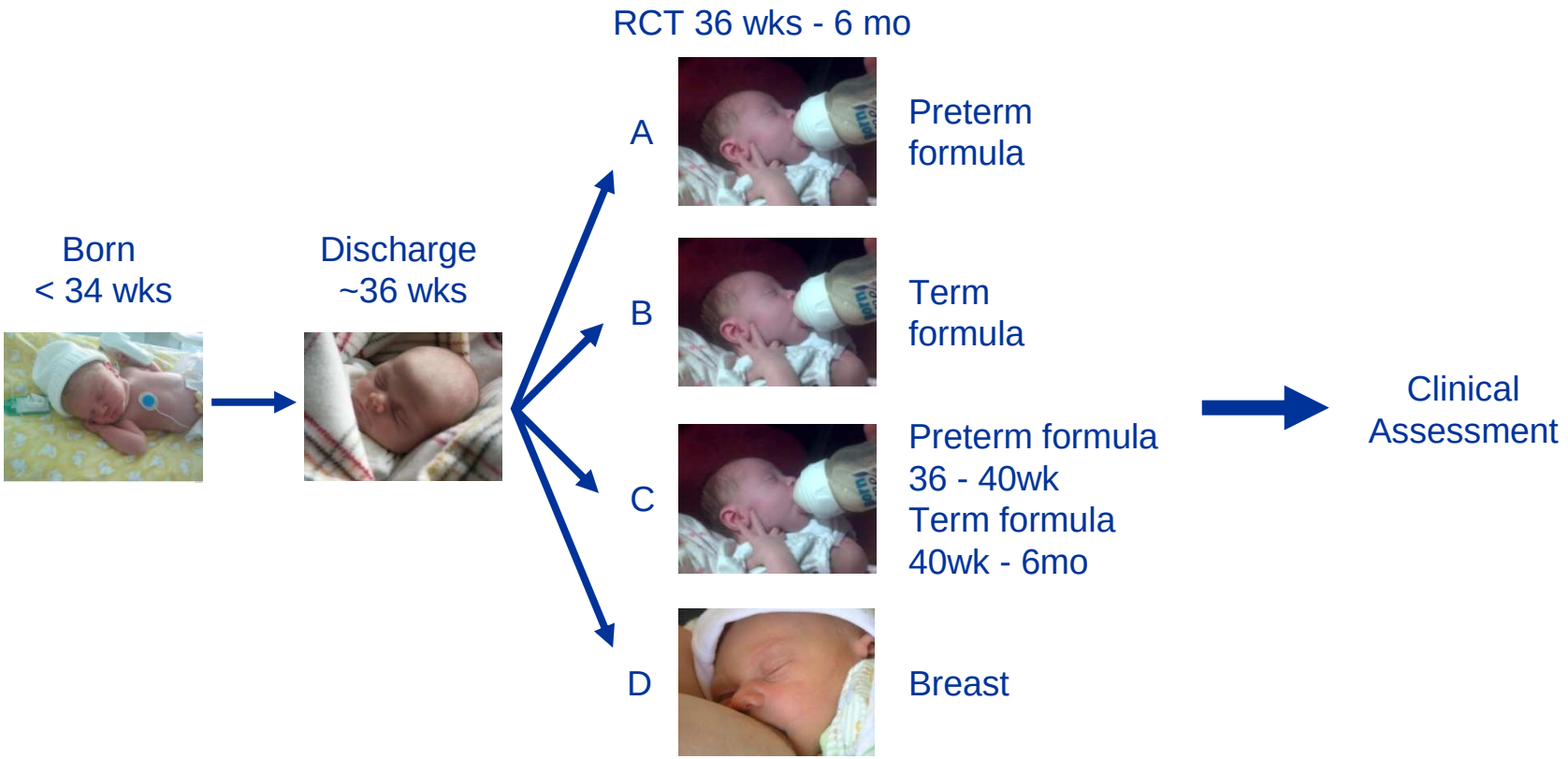
Hypothesis

- Early environmental exposures are “memorised” by the cell by epigenetic markings of the genome
- These epigenetic modifications produce a stable alteration in the expression of specific genes
- Aberrant epigenetic marking and subsequent altered expression of genes results in changes to body composition and metabolic health in childhood

Newcastle Preterm Birth Growth Study



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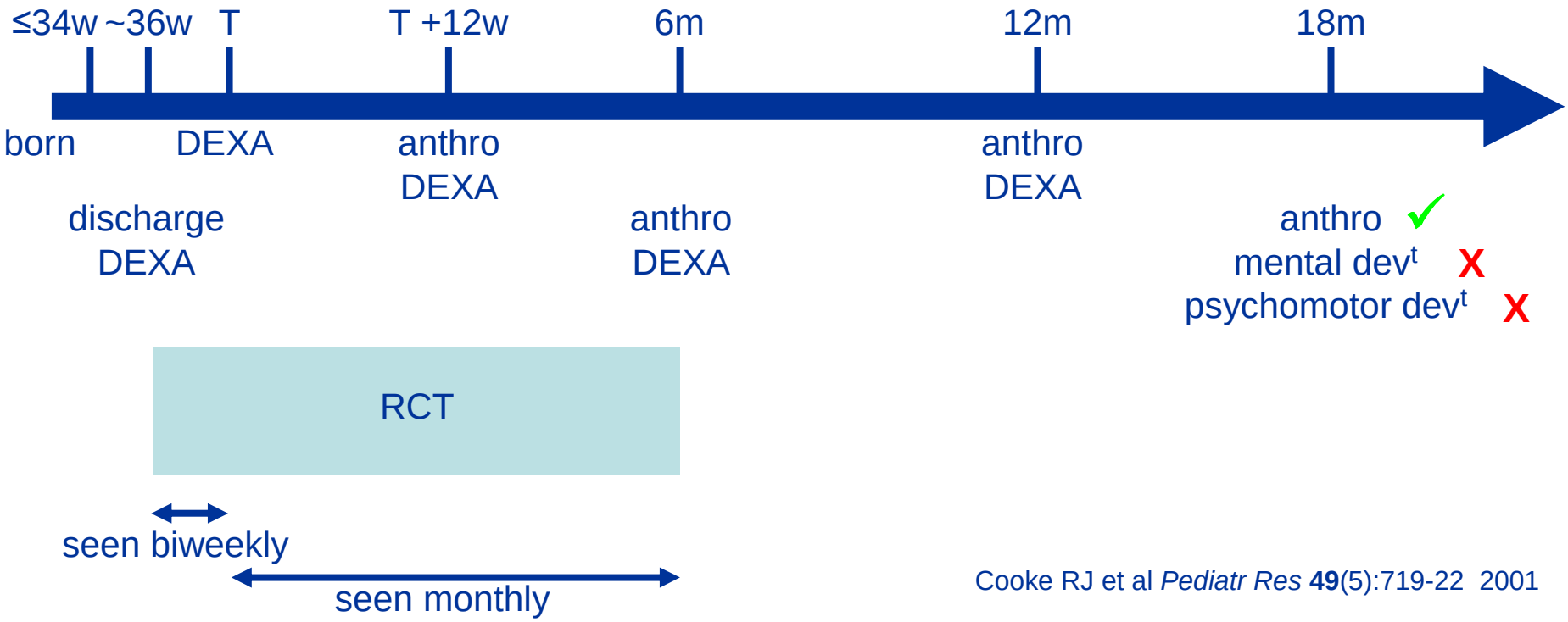
Newcastle Preterm Birth Growth Study



Cooke RJ et al *Pediatr Res* **49**(5):719-22 2001

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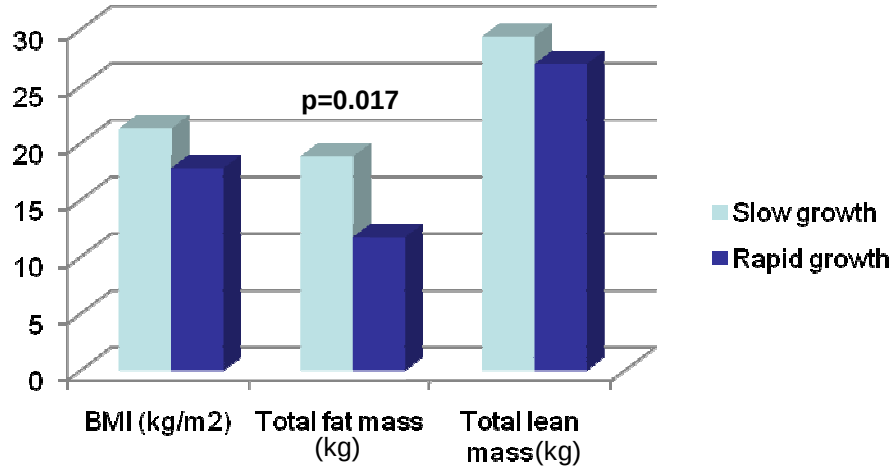
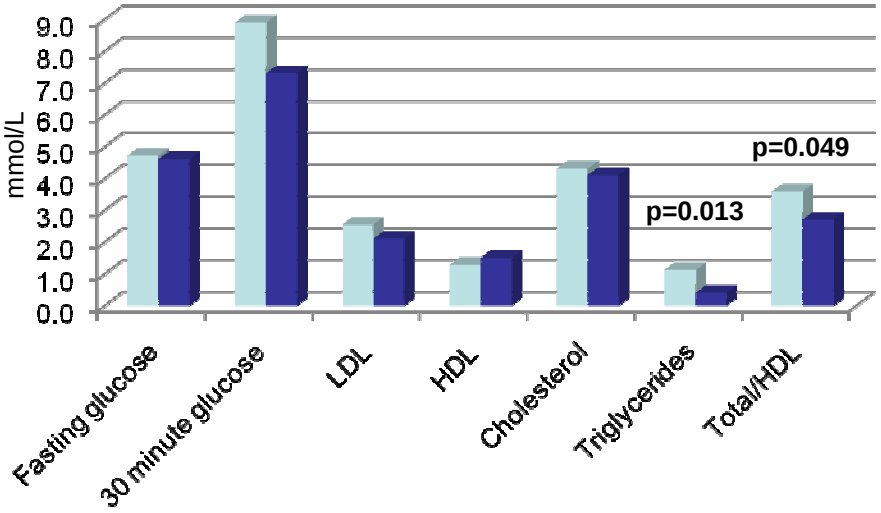
Assessment at mean age 12 years

- Anthropometry
- Whole body DEXA
- Bio-electrical impedance
- Leptin, insulin, adiponectin
- Blood pressure
- Fasting glucose, 30 min glucose
- Triglycerides, cholesterol, lipids
- Blood samples for DNA and RNA
- Saliva samples





Catch up growth:
difference in z score for weight between term and term plus 12 weeks

slow growth	-0.7
rapid growth	0.7

p <0.0001

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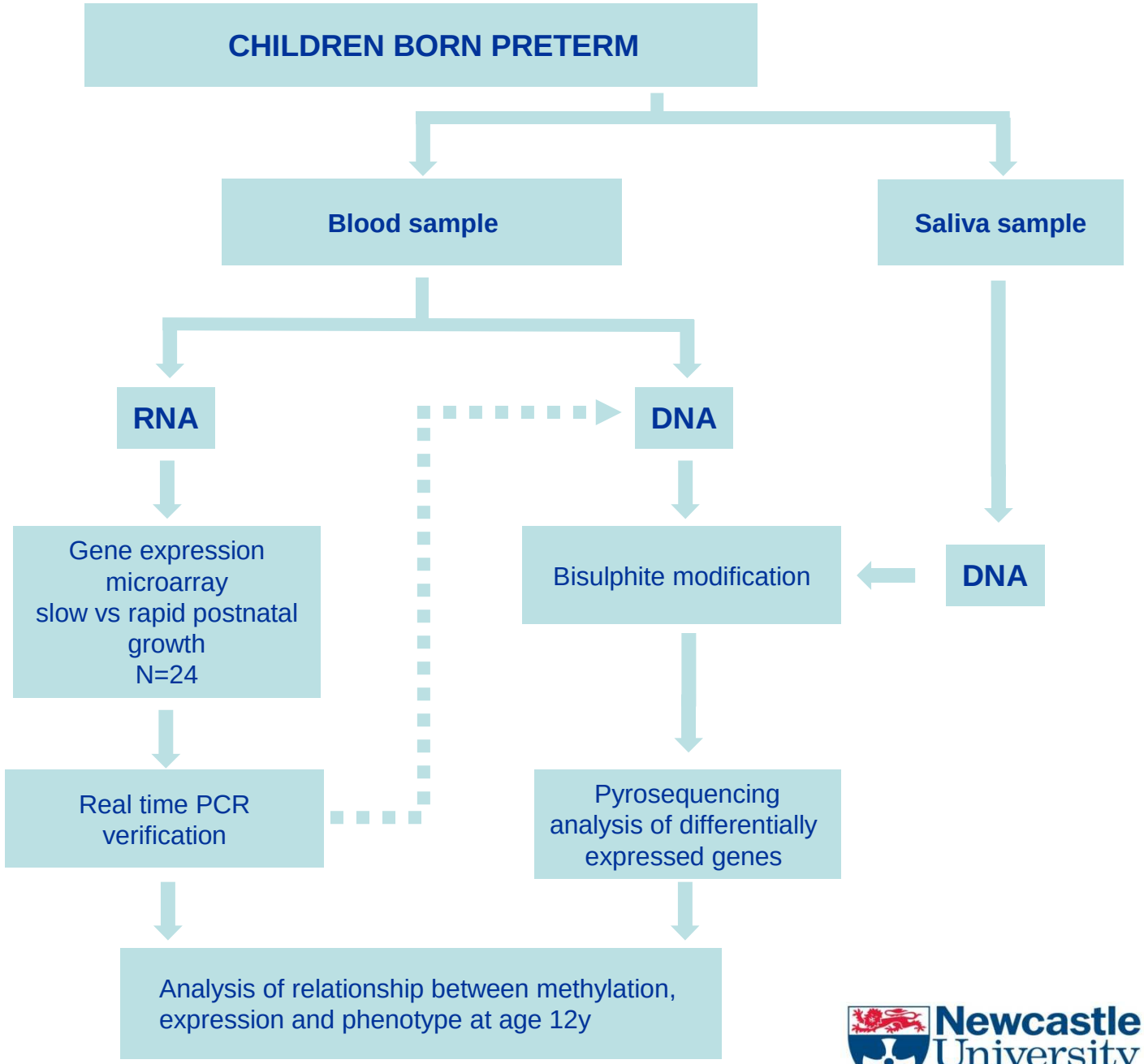

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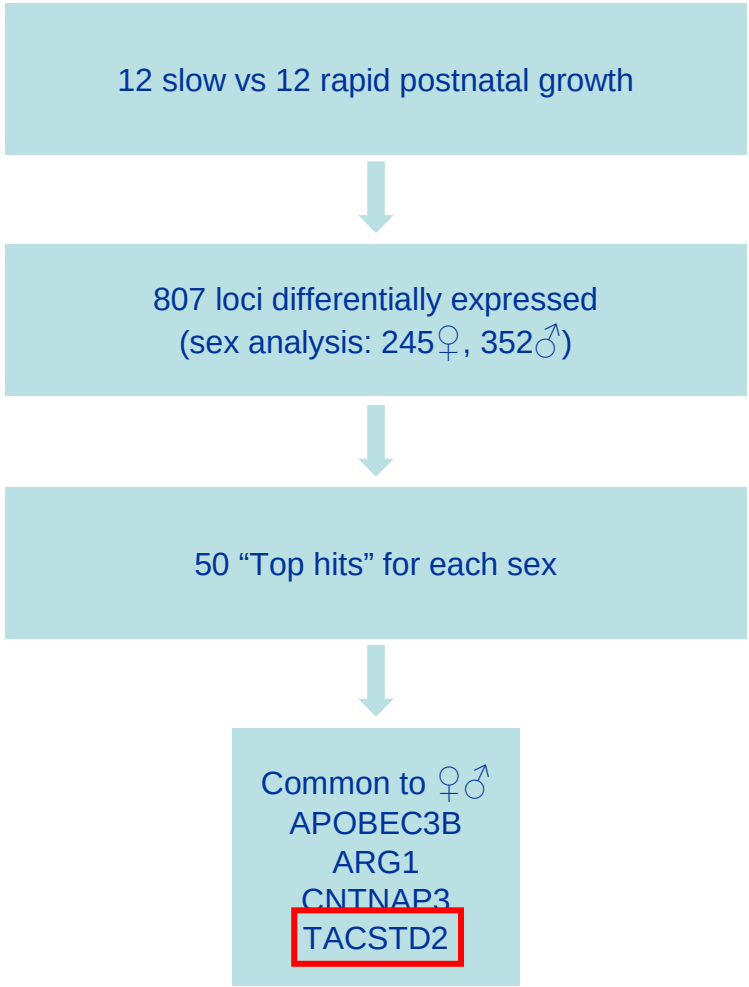
Gene expression microarray



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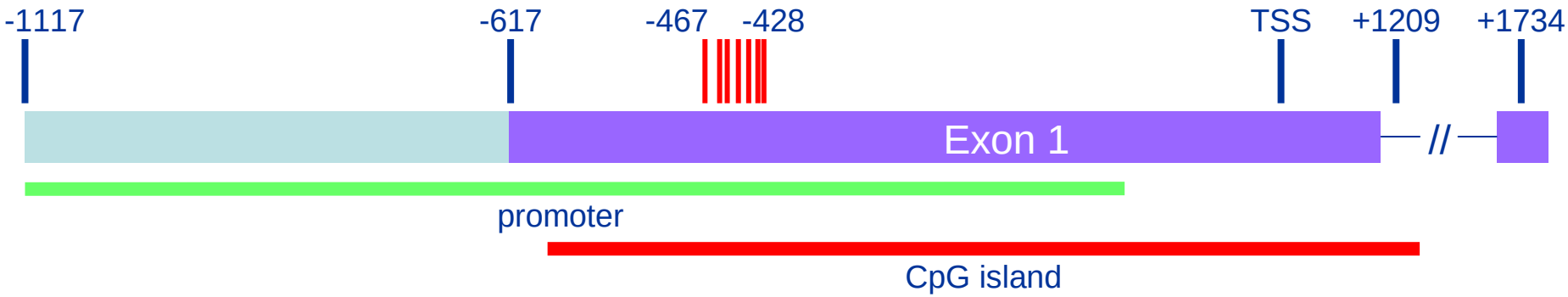
TACSTD2

Tumour associated calcium signal transducer 2



- encodes carcinoma-associated antigen
- family includes type 1 membrane proteins
- transduces an intracellular calcium signal
- acts as cell surface receptor
- autosomal recessive disorder gelatinous drop-like corneal dystrophy

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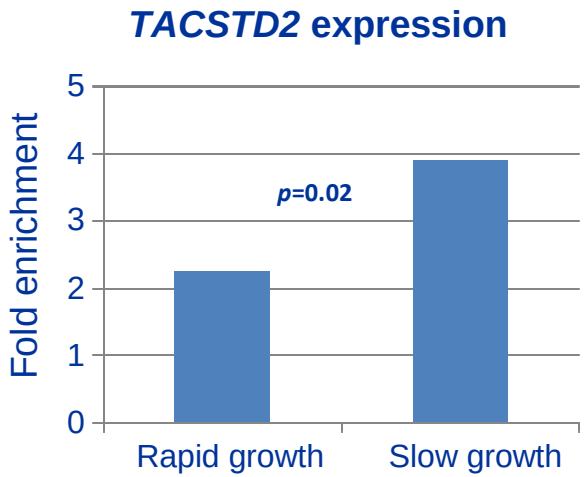
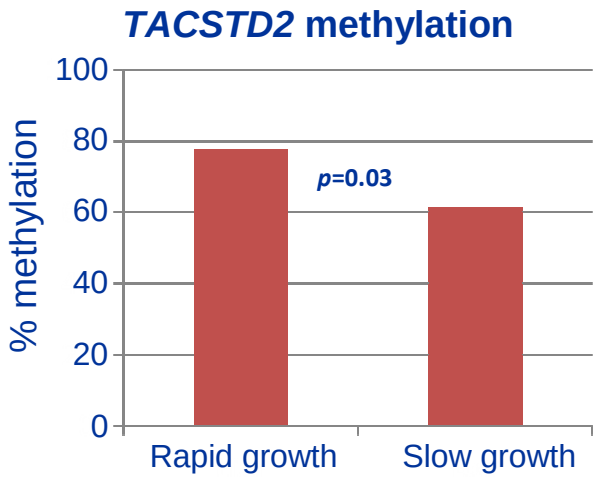
TACSTD2 expression and methylation





expression/methylation correlation coefficient -0.89, p<0.0001

Catch up growth is associated with differential methylation and expression

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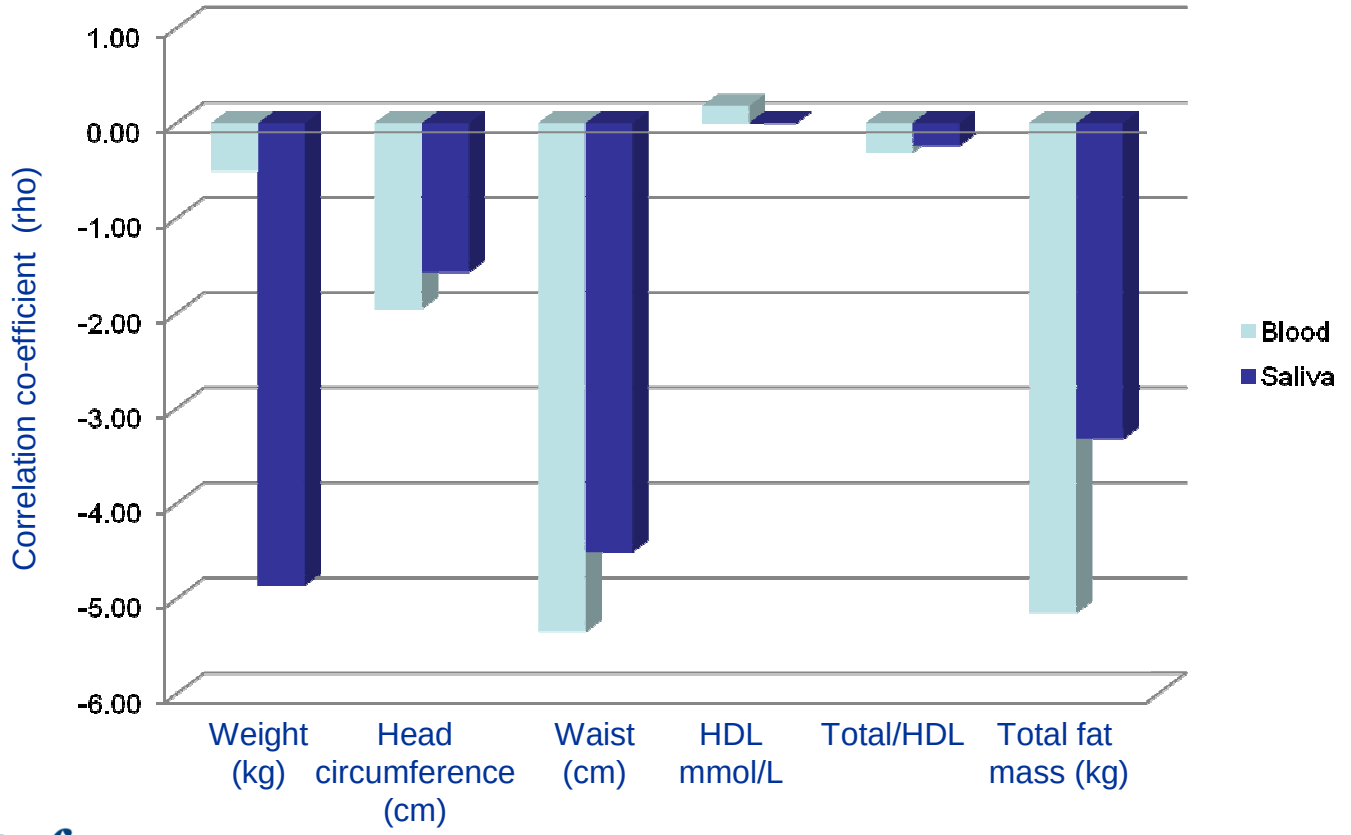
TACSTD2 methylation and childhood phenotype

Spearman correlation test showed the following variables to be associated with *TACSTD2* methylation ($p<0.05$)



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Variance in trait attributed to *TACSTD2* methylation

Linear regression analysis defined the level of variance (R^2) in each trait

Variable	Blood					Saliva				
	b	**95% CI**		**p-value**	**R^2**	**b**	**95% CI**		**p-value**	**R^2**
Weight (kg)	-0.50	-12.35	2.27	0.174		-4.86	-8.82	-0.91	**0.016**	0.057
Head circumference (cm)	-1.95	-3.61	-0.29	**0.022**	0.061	-1.57	-2.41	-0.73	**<0.001**	0.129
Waist (cm)	-5.35	-11.57	0.87	0.091		-4.51	-7.97	-1.05	**0.011**	0.064
HDL (mmol/L)	0.18	-0.04	0.39	0.103		0.00	-0.14	0.13	0.960	
Total/HDL	-0.31	-0.75	0.14	0.179		-0.24	-0.53	0.06	0.112	
Total fat mass (kg)	-5.15	-9.37	-0.93	**0.017**	0.061	-3.32	-5.53	1.12	**0.003**	0.085

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Summary

- Differences in catch up growth were associated with changes in gene expression at age 12y
- Investigation of the differentially expressed candidate gene *TACSTD2* demonstrated differential methylation
- Differential methylation of *TACSTD2* was associated with childhood phenotype
- Further work is required to establish the causal nature of the observed association
  - *Are changes in methylation caused by childhood phenotype?*
  - *Are changes in methylation caused by early growth patterns?*

Principal Investigator

Caroline Relton	HNRC/Institute for Ageing and Health

Focus team

Heather Cordell	Institute of Human Genetics
Nick Embleton	Newcastle Neonatal Unit, RVI
John Mathers	HNRC/Institute for Ageing and Health
Mark Pearce	Lifecourse Epidemiology
Dan Swan	Bioinformatics Support Unit

Lab team

Hannah Elliott	HNRC/Institute for Ageing and Health
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Clinical team

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Nick Embleton	Newcastle Neonatal Unit, RVI
Murthy Korada	Newcastle Neonatal Unit, RVI

Funding

BBSRC bioscience for the future

Newcastle Healthcare Charity

Institute for Ageing and Health

hnrc molecules to populations

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Epigenetics and Developmental Programming Conference

Newcastle upon Tyne, UK
21st -22nd March 2011

Photographs by Graeme Peacock

Topics

- The environment and the epigenome
- Epigenetic variation and phenotype
- Epigenetic variation and common genetic variation
- Identifying and quantifying epigenetic variation
- Bioinformatic challenges in epigenetic analyses

Confirmed speakers

- Dr Andrea Baccarelli
- Dr Graham Burdge
- Prof Patrick Chinnery
- Prof George Davey-Smith
- Dr Daniele Fallin
- Dr Bas Heijmans
- Prof Tom Kirkwood
- Prof John Mathers
- Dr Jonathan Mill
- Dr Sue Ozanne
- Dr Vardhman Rakyan
- Prof Wolf Reik
- Dr Caroline Relton
- Prof Seif Shaheen

To register interest please email;

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Conference Organisers
Alix Groom, Jill McKay, John Mathers & Caroline Relton

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