MANCHESTER
1824

The University
of Manchester

Healthy ageing and growth in early life: the interaction between genes, the environment and development

Adam Stevens

Institute of Human Development,
University of Manchester

Outline

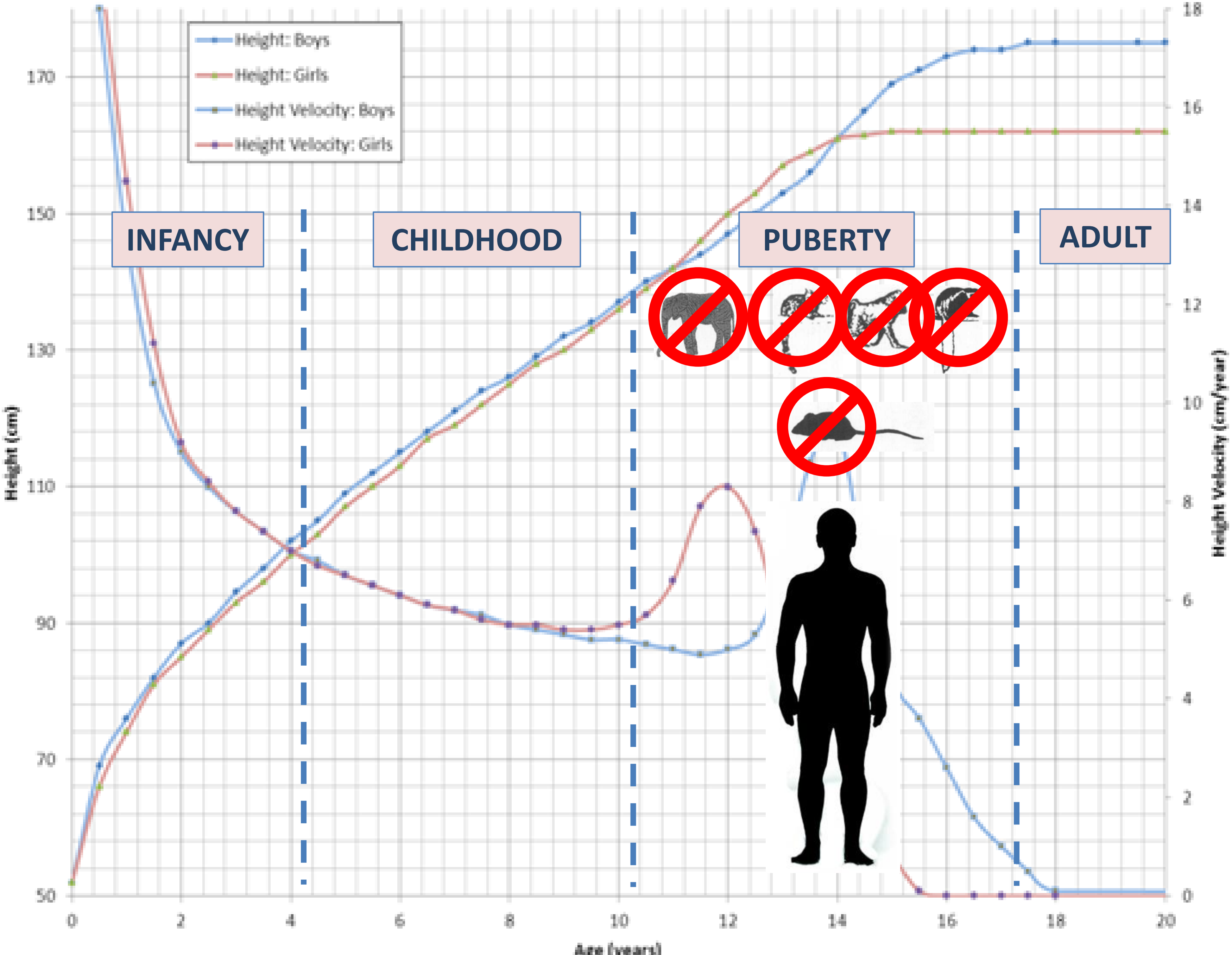
- **Background**
    - Human growth is unique
    - The interaction between growth, the environment and development
    - What is ‘omic data
    - Network models

- **Age-dependent gene expression & the effect of the environment on child growth**
    - Age-related changes in gene expression – defining networks of gene interactions
    - The effect of latitude & summer daylight exposure on growth
    - Evolutionary age of a gene is related to growth and metabolism

- **Growth trajectories and links to health in later life**
    - Network models of rate of growth
    - Age of puberty and health
    - Leukaemia as an example

- **Conclusions**

Human Growth



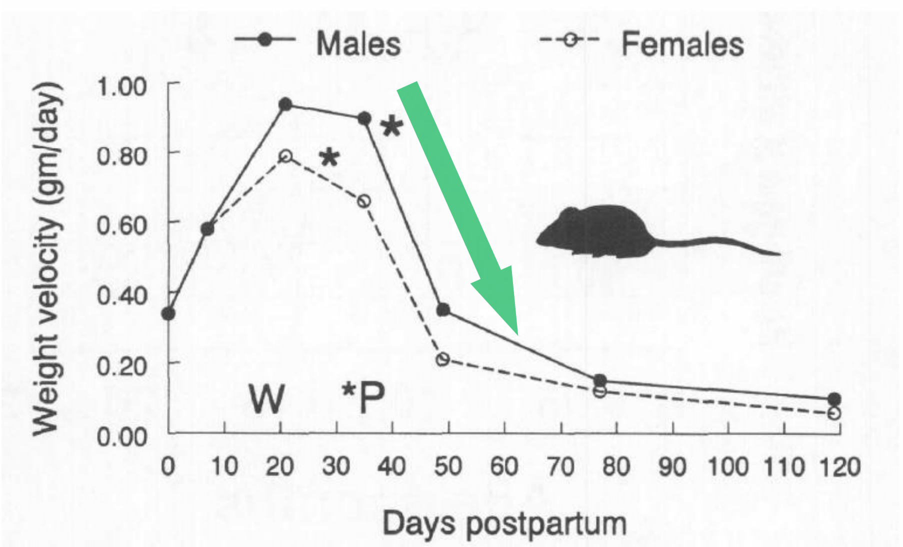
INFANCY

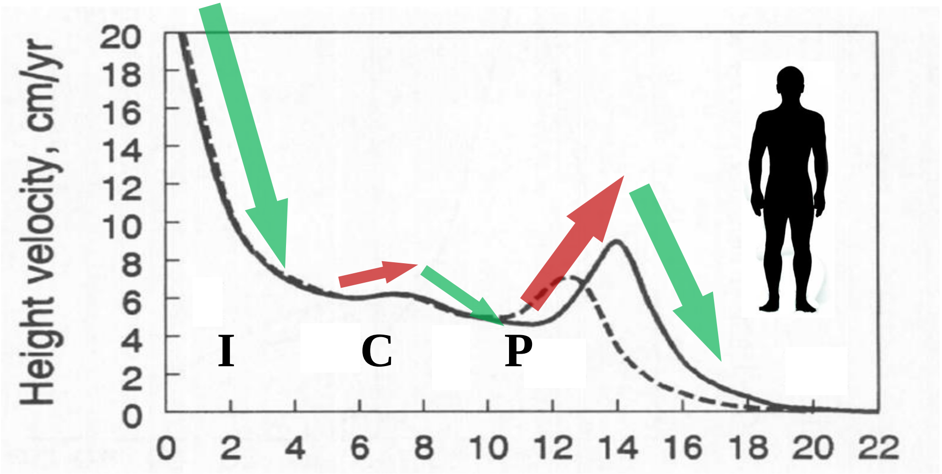
CHILDHOOD

PUBERTY

ADULT

Human growth pattern is unique





W = weaning, *P = puberty (Tanner 1962 redrawn by Bogin 1999)

I = Infancy, C = Childhood, P = puberty (from Bogin 1999)

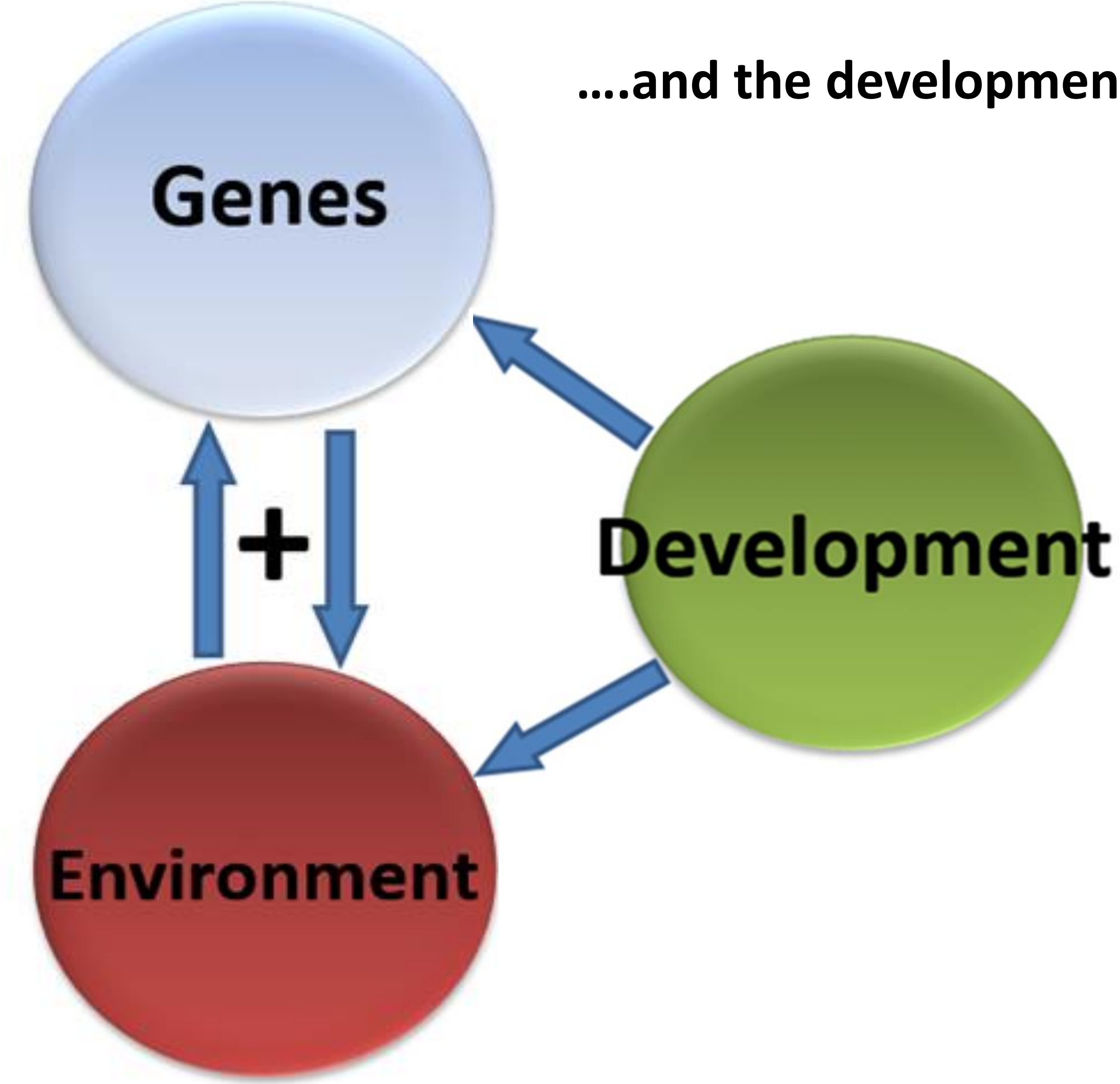
- Age-related, tissue-independent gene expression shown in mice

Finkielstain GP *et al.* Endocrinology 2009;150(4):1791-800

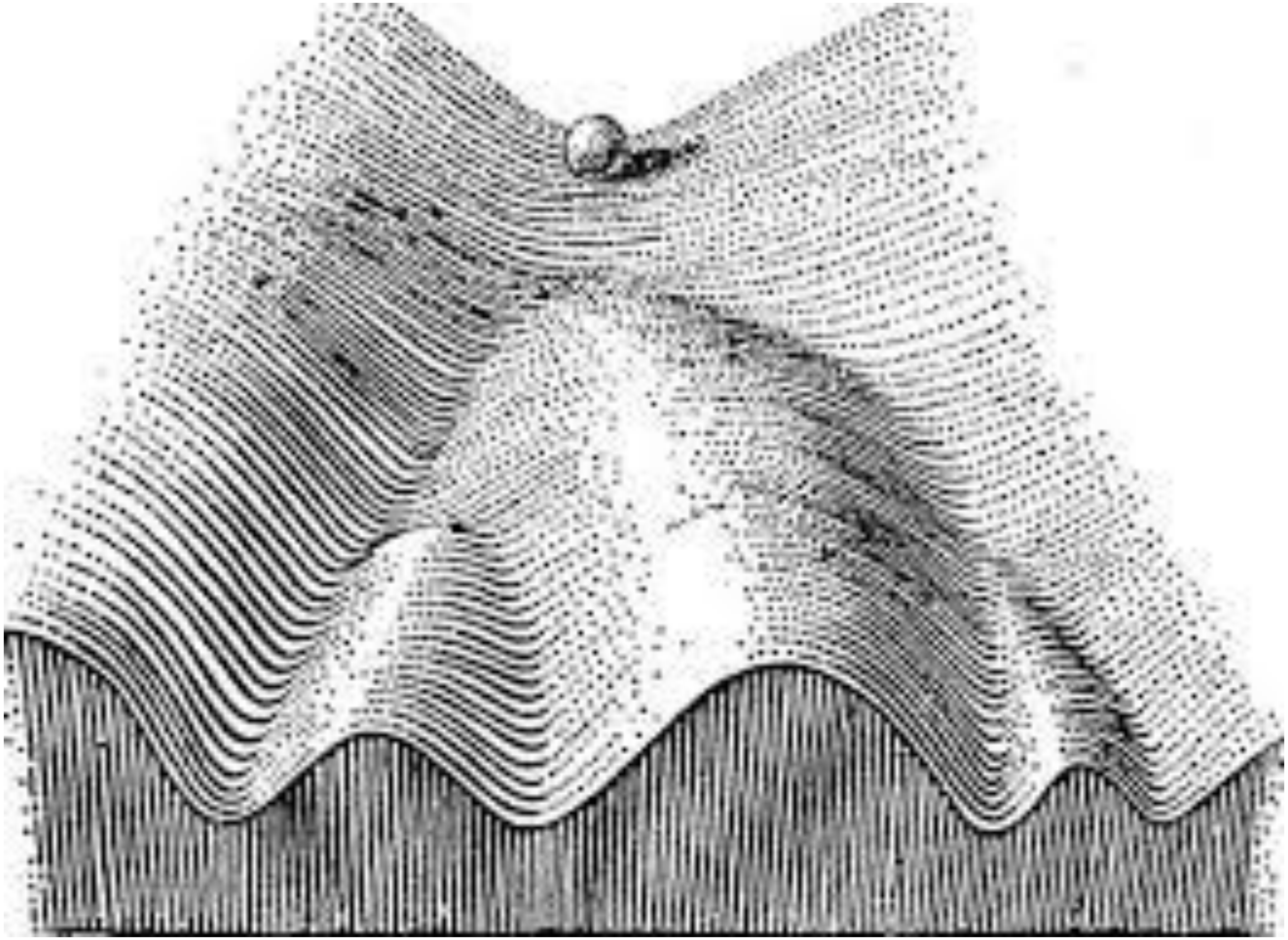
- ?

Genes interact with the environment

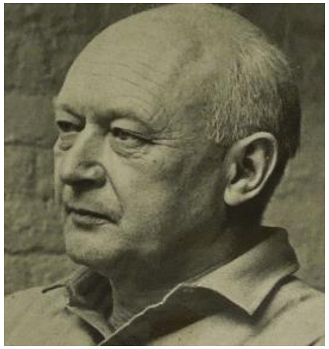
….and the developmental process



How do genes effect development?



Waddington's Landscape



C.H. Waddington 1905-1975

….is a metaphor for how **<u>gene regulation</u>** modulates development

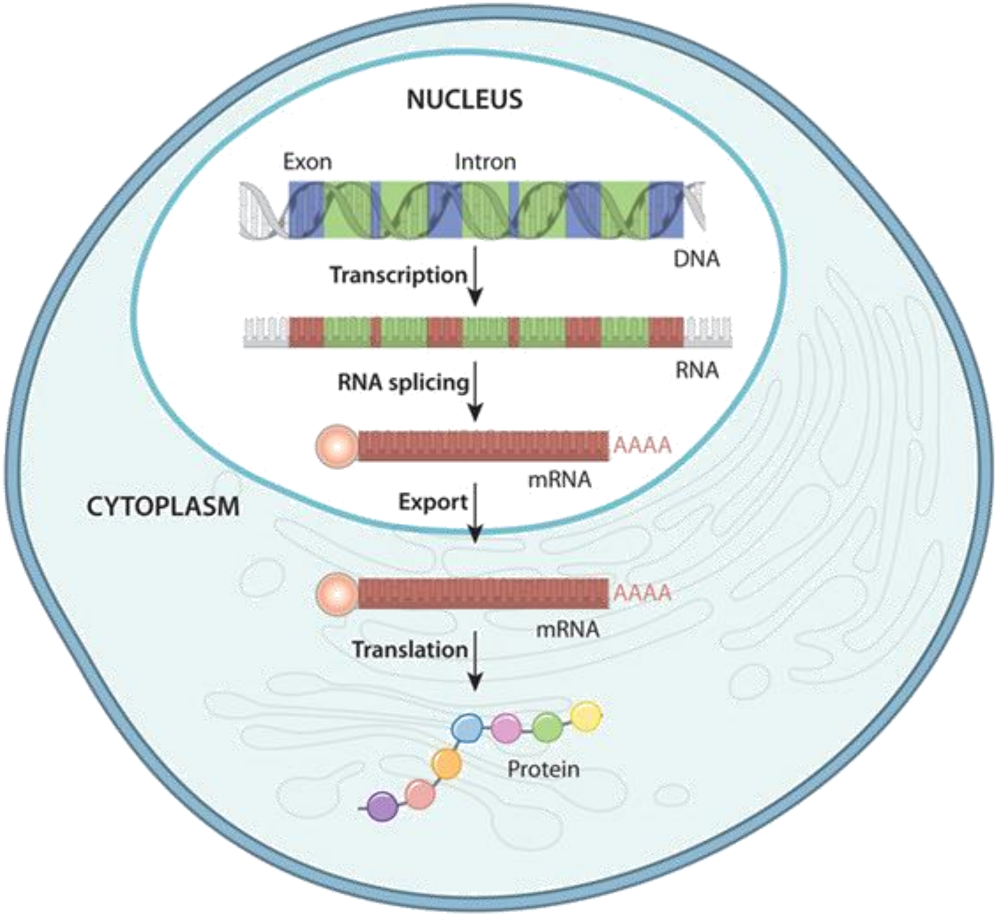
What is 'Omic Data

"big data" - a complete set of information about a feature of cell

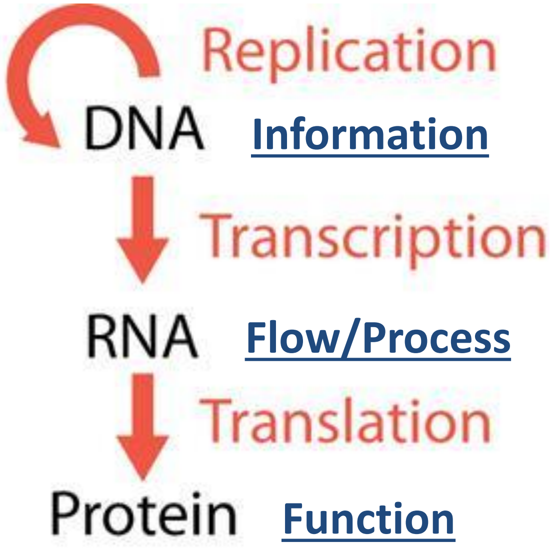
Genes to messenger to proteins

DNA —▷ mRNA —▷ Protein

Biological information flow



Central Concept of Molecular Biology



Information

Flow/Process

Function

What is ‘Omic Data

‘Omic data sets include:

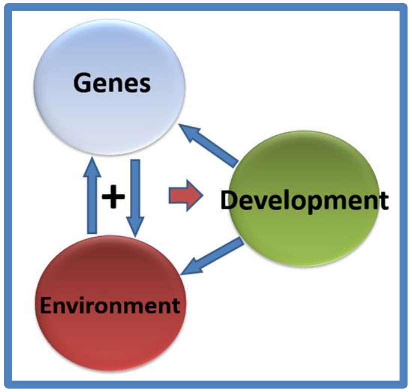
- Genetic

Fixed

- Transcriptomics – Gene Expression
- Proteomics
- Metabolome

Gene:Environment:
Development

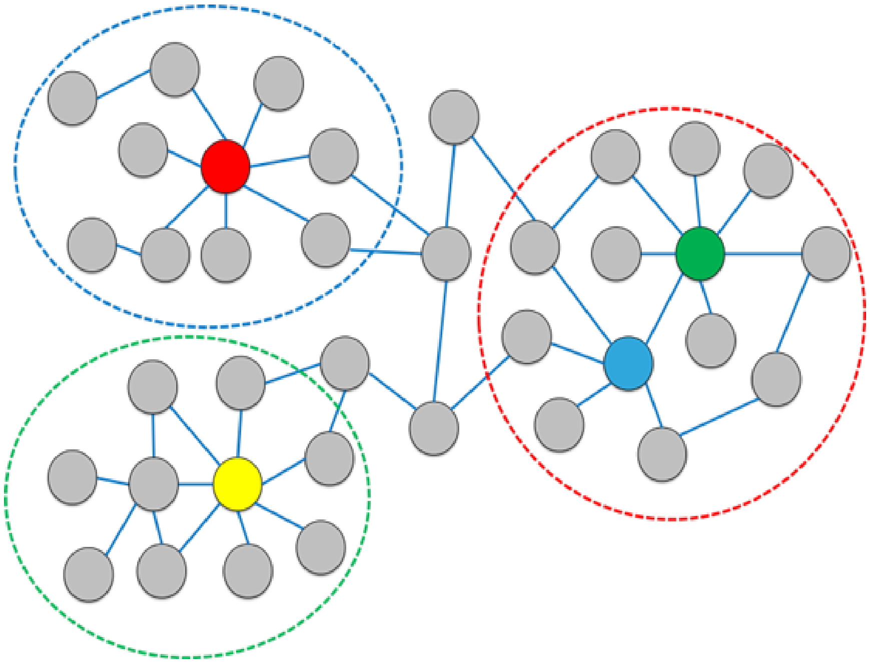
~ 22 000 genes in humans



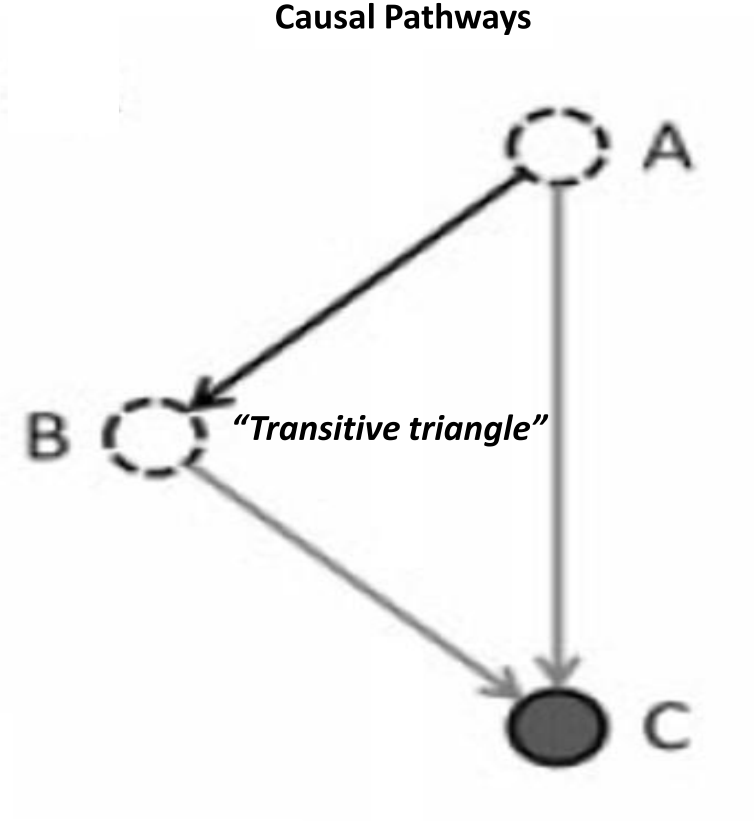
How is ‘omic data analysed?

Network Analysis

Clusters of genes

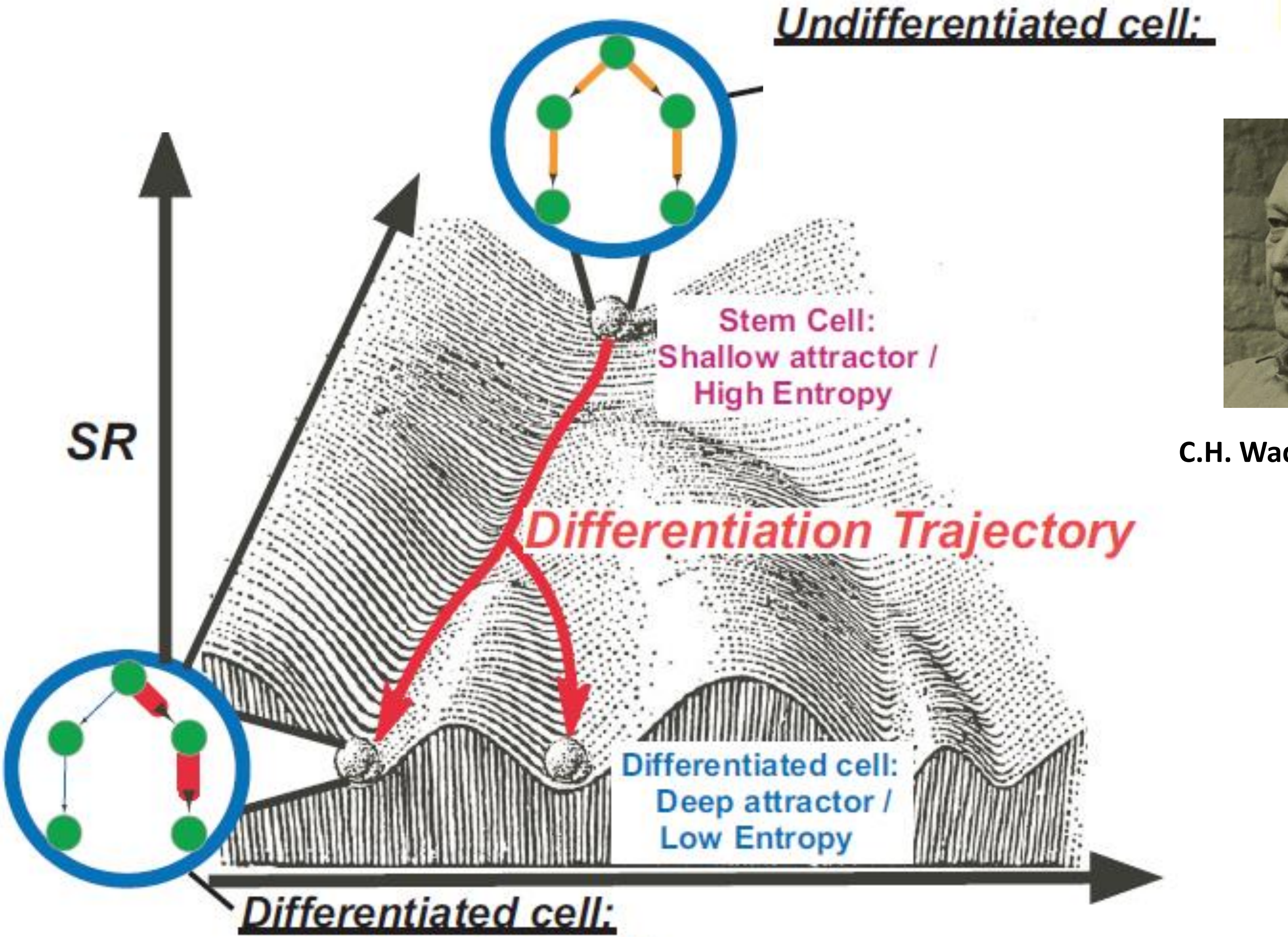


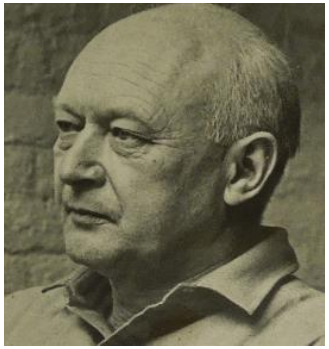
Causal Pathways



- **Function**
- **Prediction**

Waddington's Differentiation Landscape

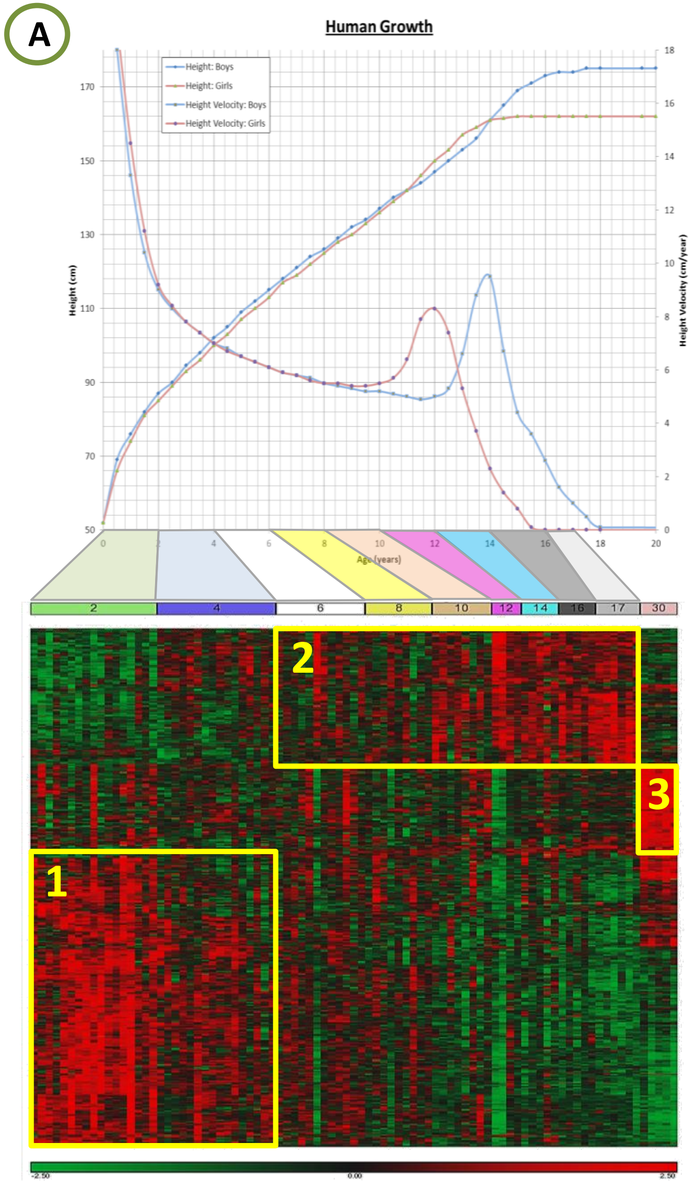




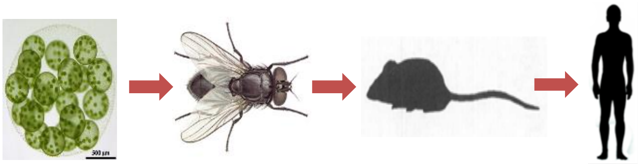
C.H. Waddington 1905-1975

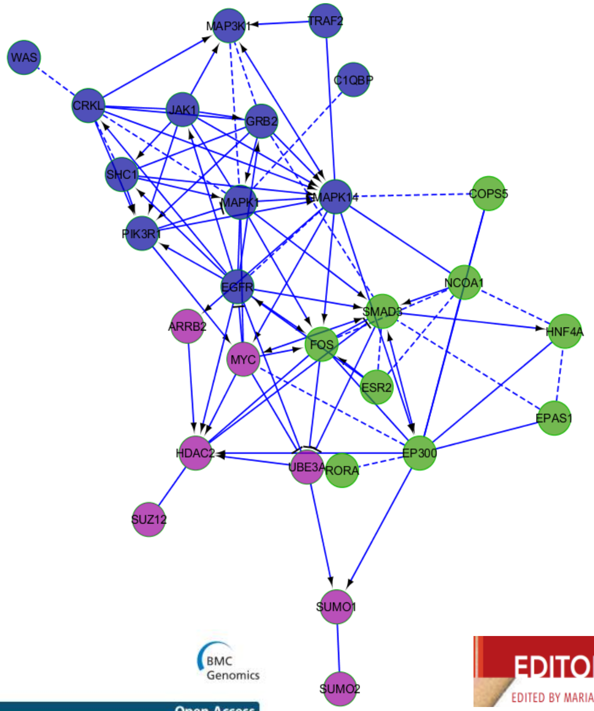
SCIENTIFIC REPORTS | 3 : 3039 | DOI: 10.1038/srep03039

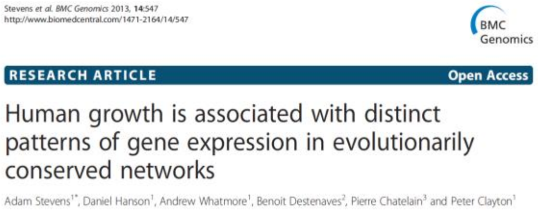
Evolutionary conserved growth pathways are associated with the the phases of childhood growth



Evolutionarily Conserved Growth Pathways







Stevens *et al. BMC Genomics* 2013, **14**:547
http://www.biomedcentral.com/1471-2164/14/547

BMC Genomics

RESEARCH ARTICLE **Open Access**

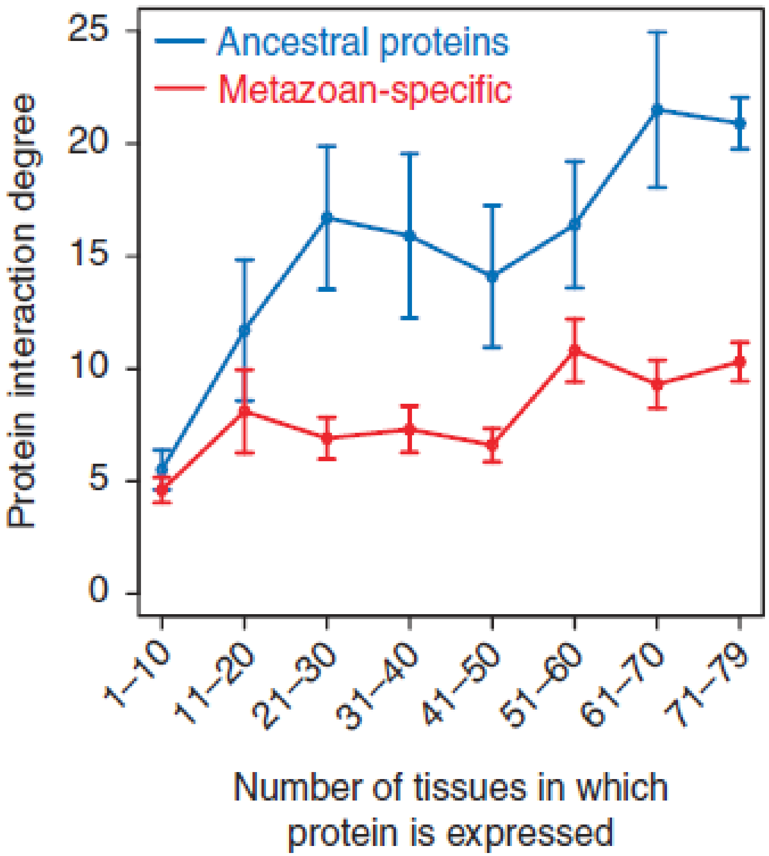
Human growth is associated with distinct patterns of gene expression in evolutionarily conserved networks

Adam Stevens[1*], Daniel Hanson[1], Andrew Whatmore[1], Benoit Destenaves[2], Pierre Chatelain[3] and Peter Clayton[1]

EDITORS'CHOICE
EDITED BY MARIA CRUZ AND SACHA VIGNIERI

SCIENCE VOL 341 20 SEPTEMBER 2013

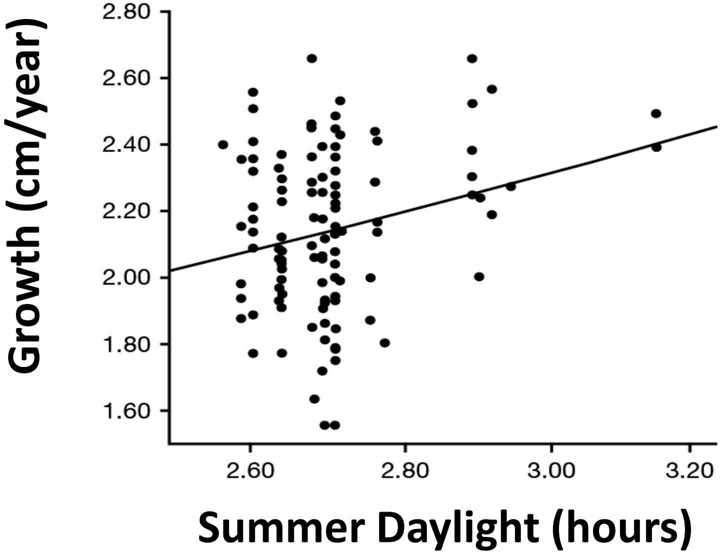
The evolutionary age of genes is associated with network properties



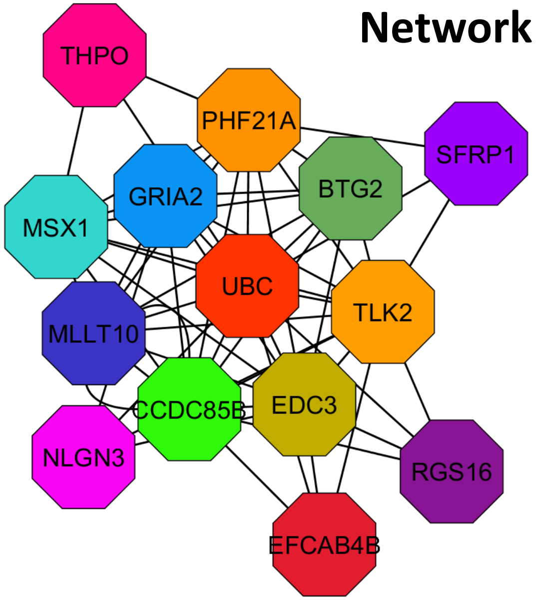
Recently evolved proteins make few protein interactions.

Bossi A, Lehner B: **Tissue specificity and the human protein interaction network.** *Mol Syst Biol* 2009, **5:260**

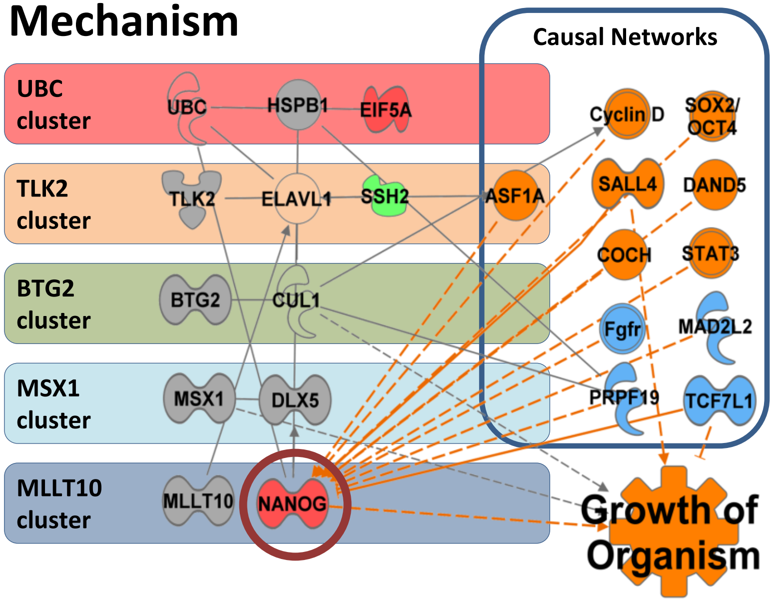
The Effect of Latitude and Summer Daylight Exposure on Growth



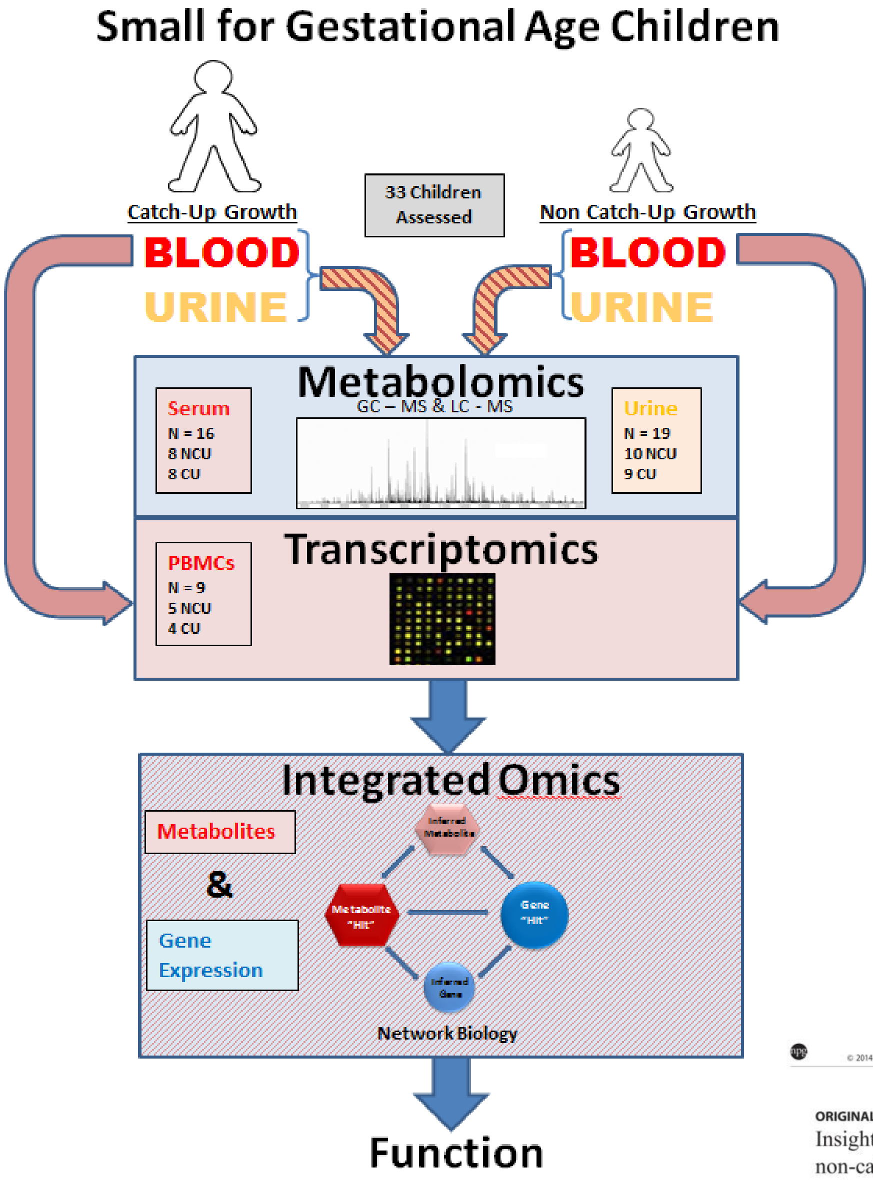
Network Model



Mechanism



Catch-Up Growth in SGA children



Small for Gestational Age Children

Catch-Up Growth

33 Children Assessed

Non Catch-Up Growth

BLOOD

URINE

BLOOD

URINE

Metabolomics

GC – MS & LC - MS

Serum
N = 16
8 NCU
8 CU

Urine
N = 19
10 NCU
9 CU

Transcriptomics

PBMCs
N = 9
5 NCU
4 CU

Integrated Omics

Metabolites

&

Gene Expression

Network Biology

Function

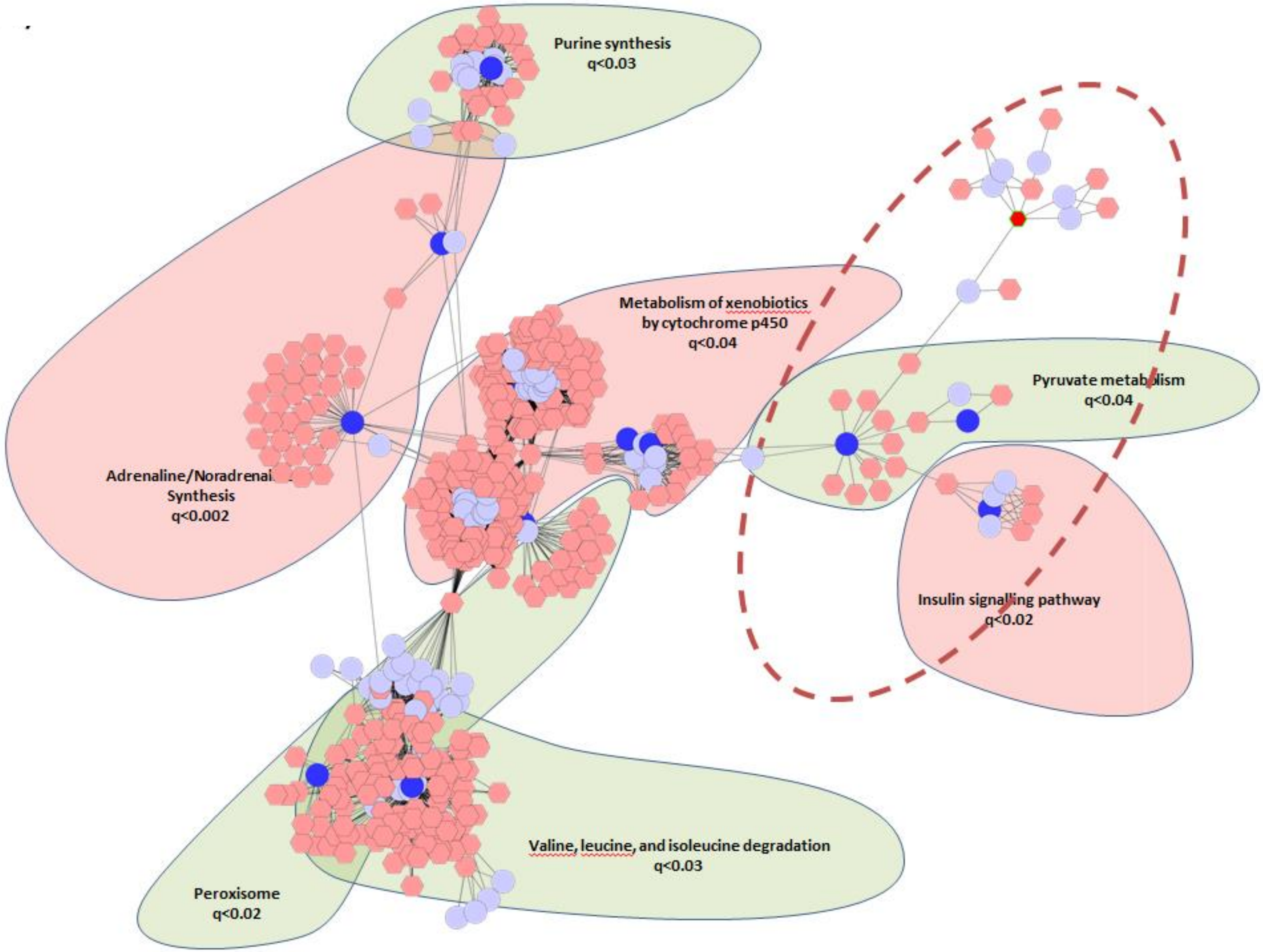
The Pharmacogenomics Journal (2014) 14, 376–384
© 2014 Macmillan Publishers Limited All rights reserved 1470-269X/14
www.nature.com/tpj

ORIGINAL ARTICLE

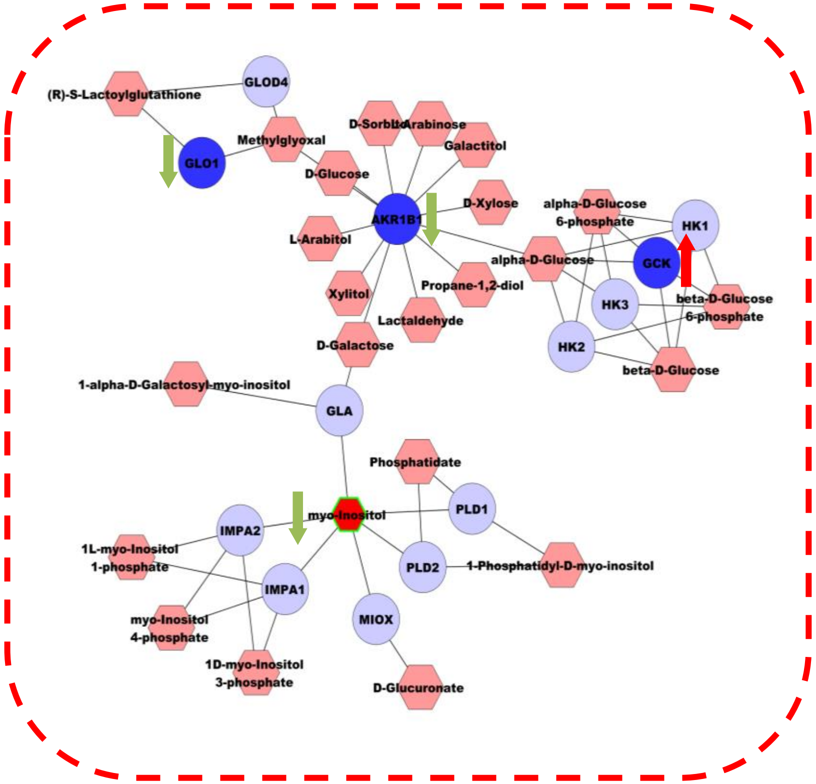
Insights into the pathophysiology of catch-up compared with non-catch-up growth in children born small for gestational age: an integrated analysis of metabolic and transcriptomic data

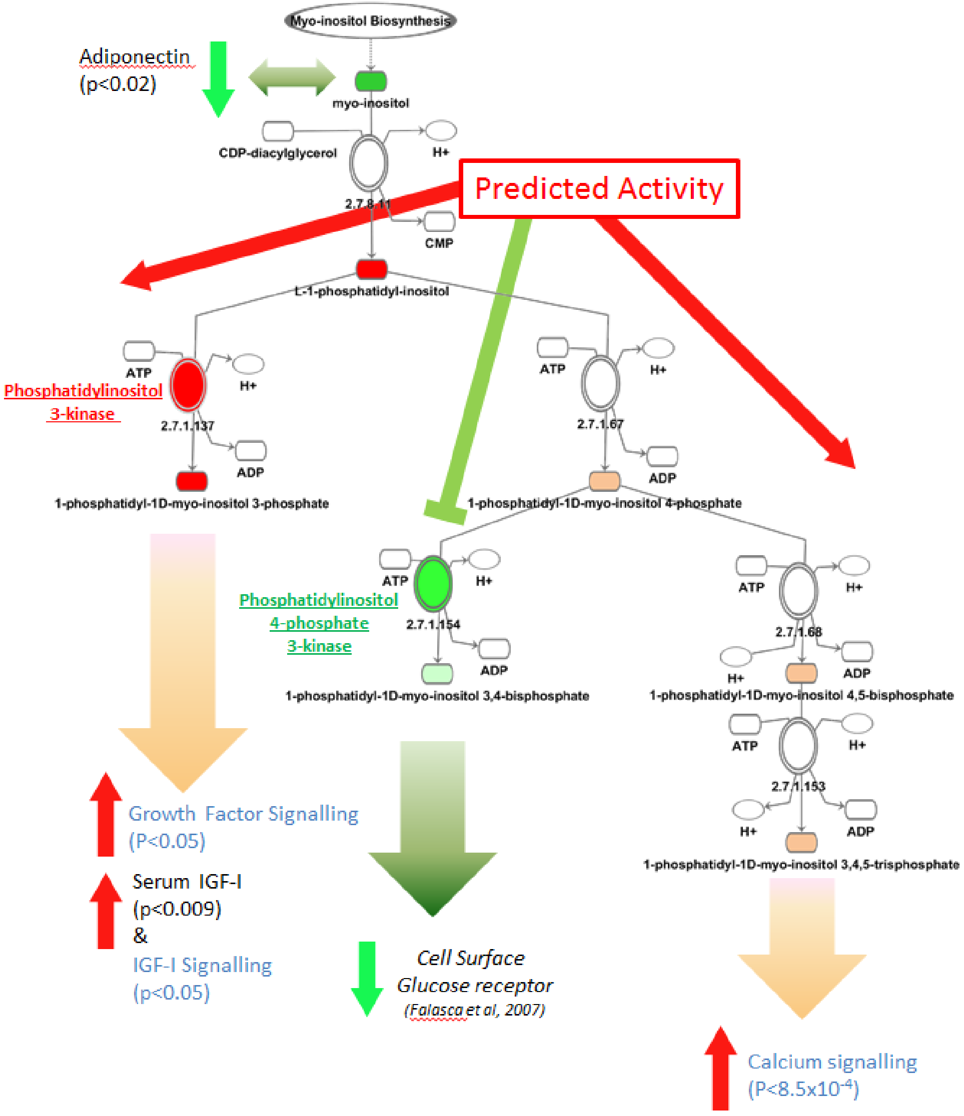
A Stevens[1,2,14], C Bonshek[1,2,14], A Whatmore[1,2], I Butcher[1,2], D Hanson[1,2], C De Leonibus[1,2], G Shaikh[3], M Brown[4,5], E O'Shea[1,2], S Victor[6], P Powell[7], P Settle[8], B Padmakumar[9], A Tan[9], E Odeka[9], C Cooper[10], J Birch[11], A Shenoy[12], M Westwood[13], L Patel[1,2], BW Dunn[4,5] and P Clayton[1,2]

Catch-Up Growth in SGA children



Catch-Up Growth in SGA children





Adiponectin
($p<0.02$)

Growth Factor Signalling
($P<0.05$)

Serum IGF-I
($p<0.009$)
&
IGF-I Signalling
($p<0.05$)

Cell Surface
Glucose receptor
(Falasca et al, 2007)

Calcium signalling
($P<8.5\times10^{-4}$)

Red= metabolomic change

Blue = gene expression change - protein “seed”

Female age and embryonic gene expression

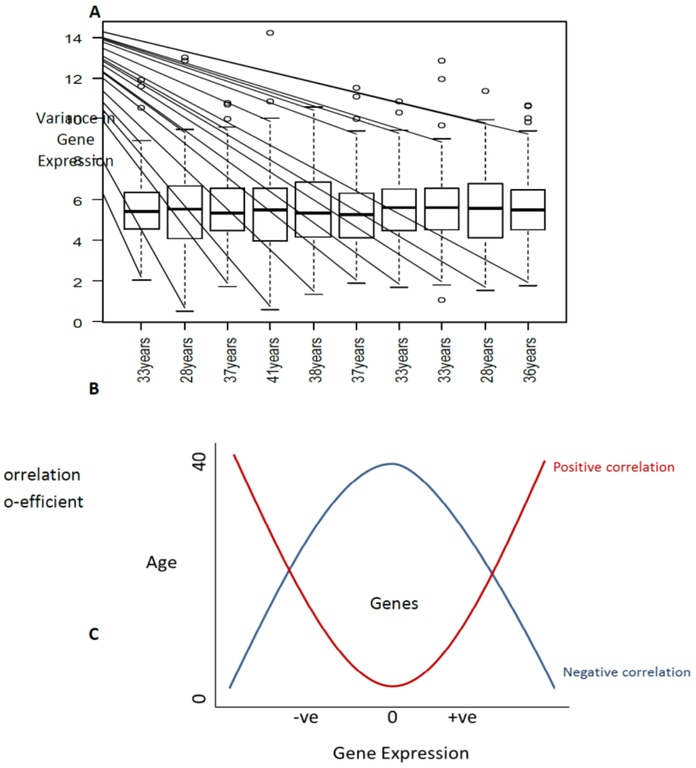


Figure 1. A) Boxplots displaying the variance of gene expression within individual blastocyst embryos with different maternal ages. **B)** Spearman's rank correlation co-efficient calculated for every gene, in relation to maternal age. Red dotted line represents correlation threshold cut-off of 0.75 **C)** Figure depicting positive and negative correlation analysis patterns.

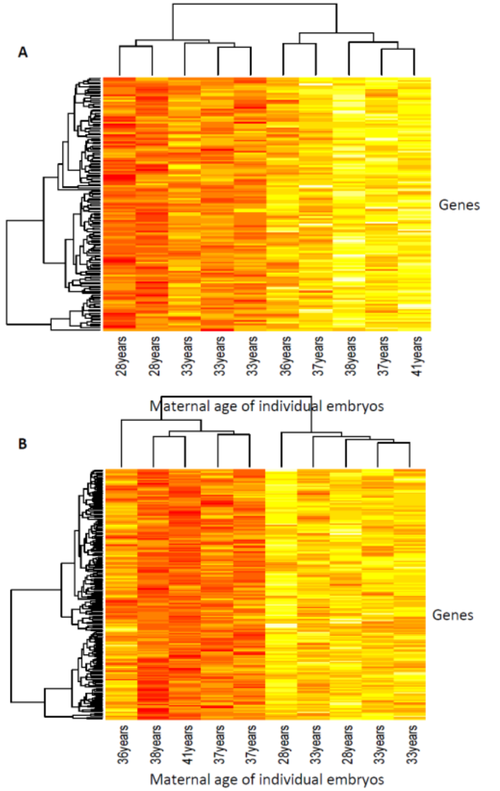


Figure 2. Genes highly correlated with maternal age within the blastocyst embryo. **A)** Genes positively correlated (R>0.76) with maternal age. **B)** Genes negatively correlated (R> 0.74) with maternal age. Yellow represents higher levels of expression and red represents lower levels of expression.

Human blastocysts (n=10)
329 genes correlated with maternal age: 139 positively, 190 negatively
Tipping point at female age = 35, maps onto decline in female fertility
Epigenetic regulators overrepresented (11 ZFPs, HIST1H2AE, METTL2B, L6)

Helen Smith

Conclusions

- Human growth has features that are unique in the animal kingdom
- ‘omic data and network modelling gives us the tools to relate gene:environment:development
- The evolutionary age of a gene can act as a marker to relate growth and metabolic function
- Changes of growth rate in early life are related to health in later life

University of Manchester

Chiara De Leonibus
Philip Murray
Dan Hanson
Andrew Whatmore
Peter Clayton

Stefan Meyer

Chris Knight
Neil Swainston

University of Lyon

Pierre Chatelain

predict

The Elimination of Leukaemia Fund
FOCUSING ON PATIENT-CENTRED WORK

CDL was supported by a European Society for Paediatric Endocrinology (ESPE) Research Fellowship, sponsored by Novo Nordisk A/S

MANCHESTER
1824
The University of Manchester

Manchester Institute for Collaborative Research on Ageing