Maternal hyperglycemia and foetal epigenetic adaptations

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Early Nutrition Project – The Power of Programming

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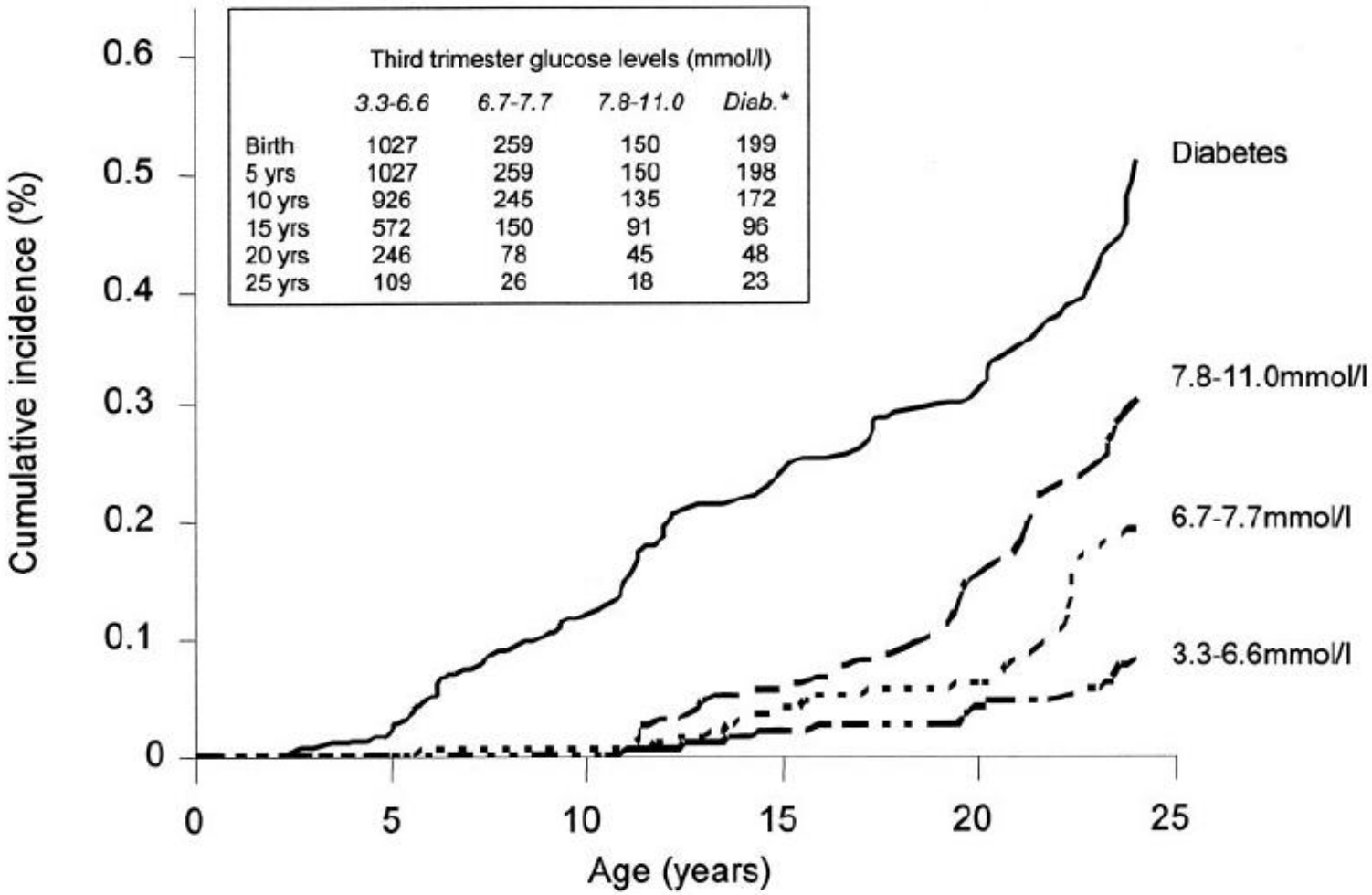
Note: for non-commercial purposes only

Outline

- Maternal hyperglycemia and risk of metabolic disorders in offspring
- What is epigenetics?
- Foetal epigenetic adaptations associated with maternal hyperglycemia
  - Candidate genes
  - Epigenome-wide approaches
- Limitations and future perspectives

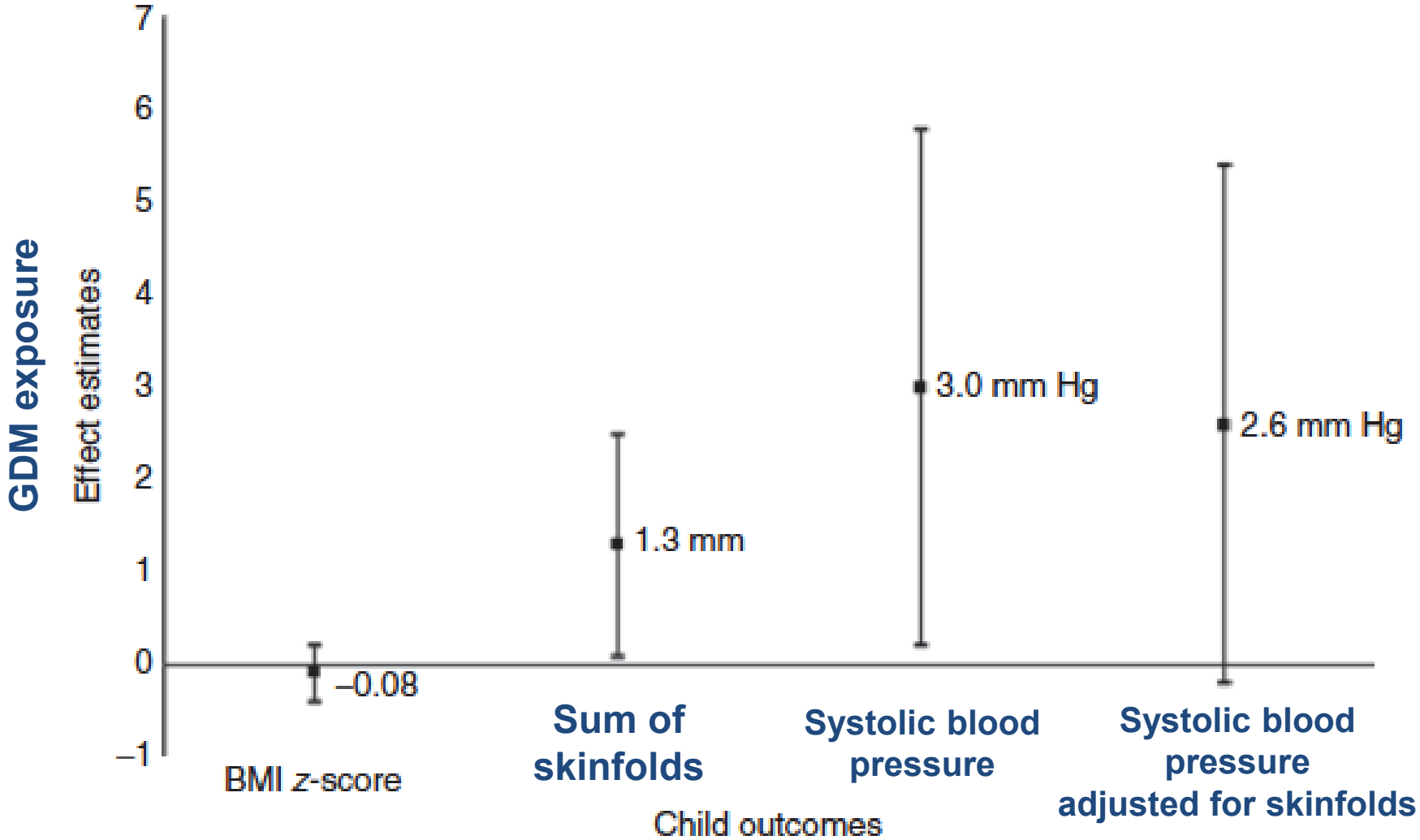
Cumulative incidence of T2D in Pimas offspring according to maternal 2h-glucose at third trimester



Franks PW et al. Diabetes 2006

Gestational Diabetes Mellitus (GDM)

association with childhood adiposity and blood pressure at 3 years old – Project Viva (Boston)



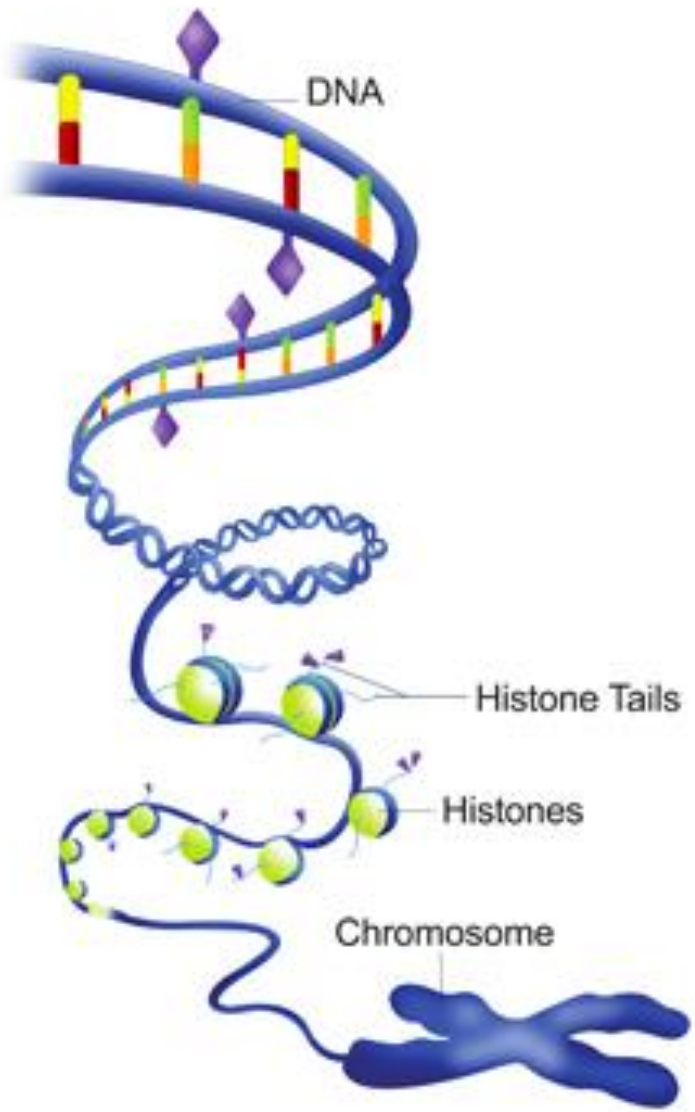
Wright CS et al. Am J Hypertension 2009

Mechanisms involved in foetal metabolic programming

- Malleable – environmental exposure
- Durable – long lasting effect

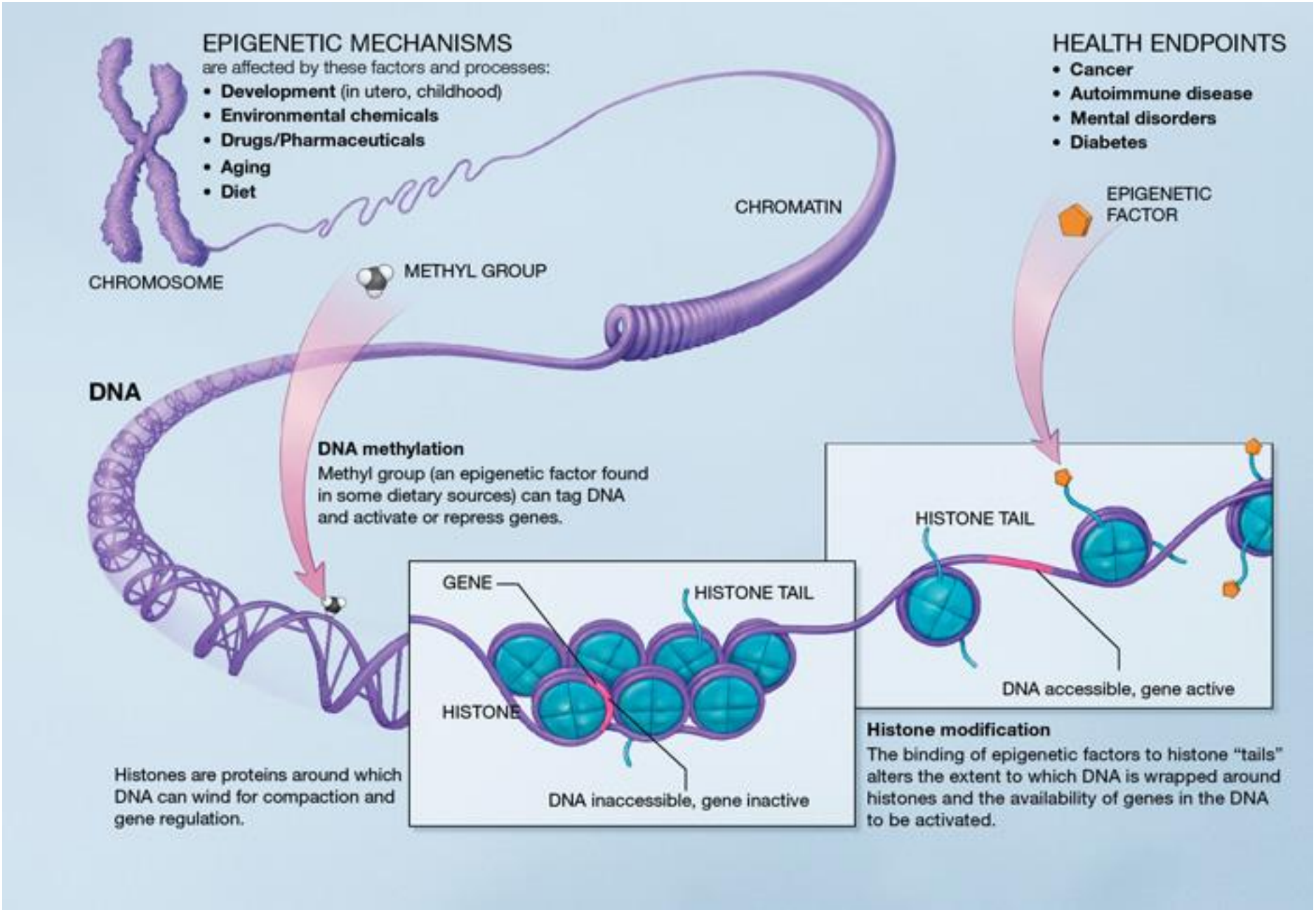
Epigenetics:

Study of variations in gene expression caused by mechanisms other than the underlying DNA sequence



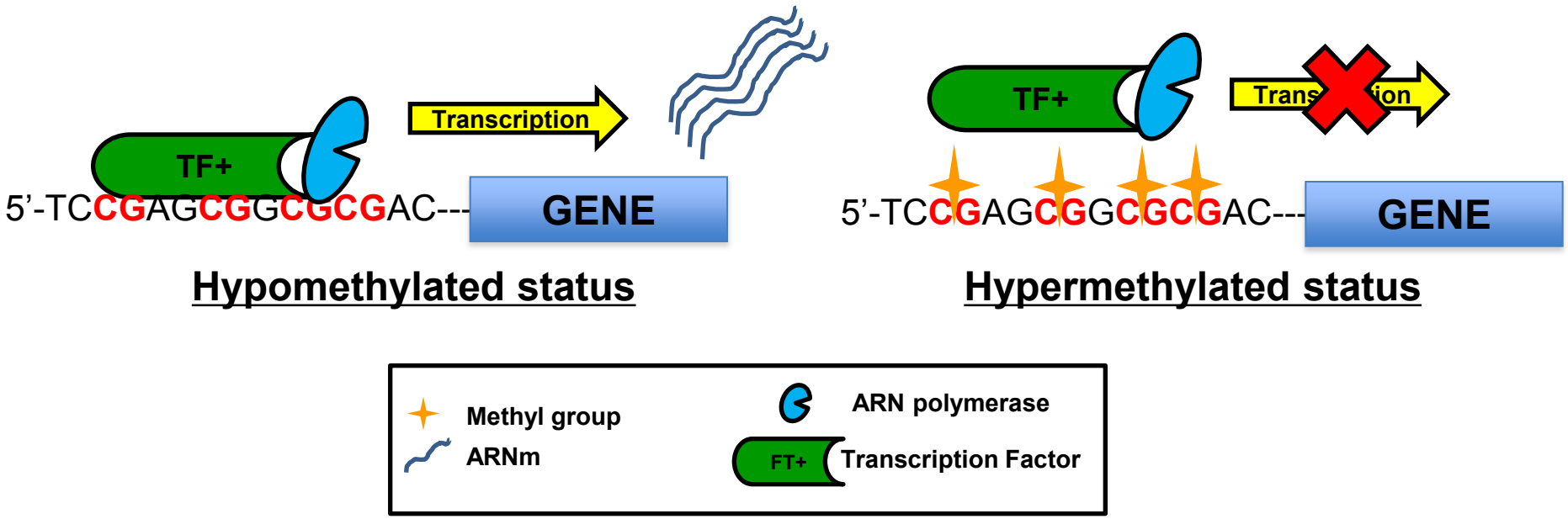
Epigenetics

- Most epigenetic phenomena are mitotically-stable and enduring, conveying long-term effects
  - Over decades in some humans studies
- Epigenetic phenomena can also be modulated by stochastic environmental stimuli
  - Modulated by environmental factors (pollutants, diet, smoking, etc.) during pre and post natal life
  - Particularly sensitive to in utero events
  - Tissue differentiation during foetal development


EPIGENETIC MECHANISMS
are affected by these factors and processes:
• Development (in utero, childhood)
• Environmental chemicals
• Drugs/Pharmaceuticals
• Aging
• Diet
HEALTH ENDPOINTS
• Cancer
• Autoimmune disease
• Mental disorders
• Diabetes
CHROMOSOME
CHROMATIN
METHYL GROUP
EPIGENETIC FACTOR
DNA
DNA methylation
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.
GENE
HISTONE TAIL
HISTONE
DNA inaccessible, gene inactive
HISTONE TAIL
DNA accessible, gene active
Histones are proteins around which DNA can wind for compaction and gene regulation.
Histone modification
The binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.

DNA methylation

- More likley at CpG site, enriched in promoters
  - Commonly in regions called CpG islands
- Highly methylated = low transcription
  - Most of the time, but not universal



Hivert MF, et al. Current Nutrition Reports 2013

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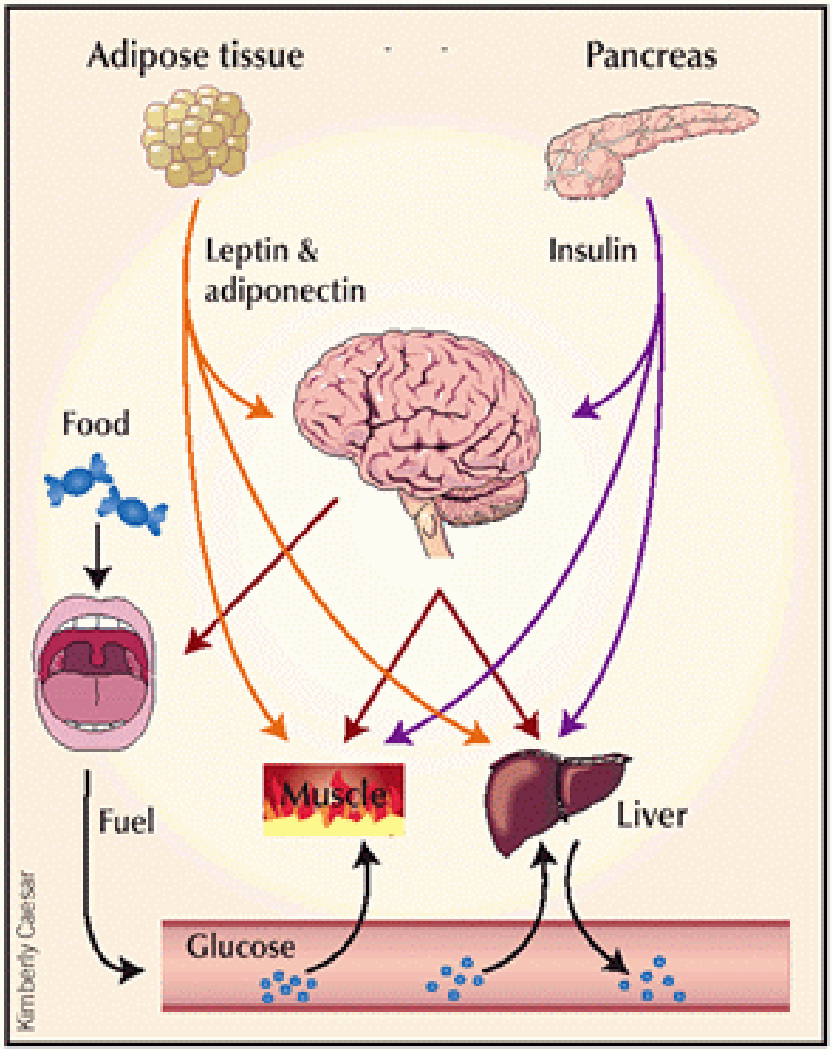
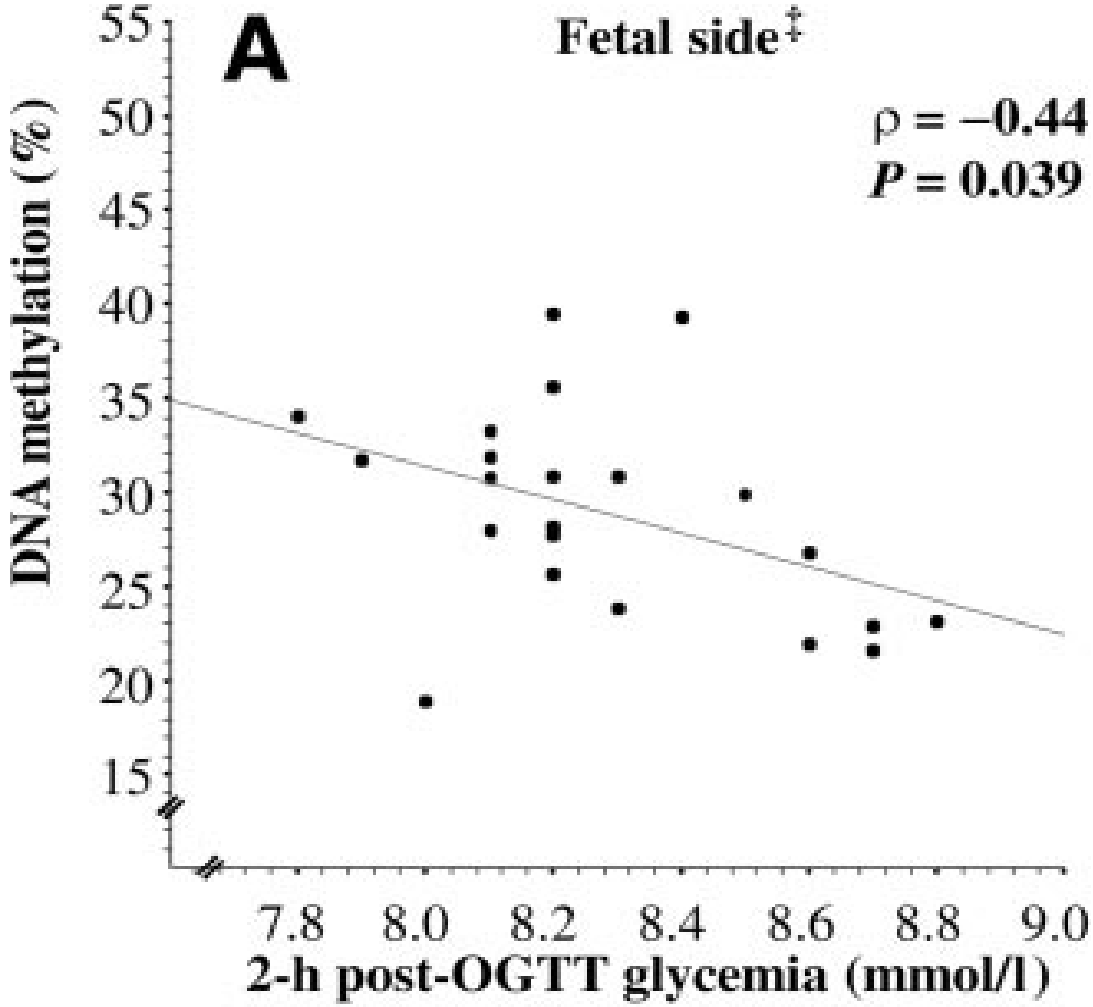
Adipokines: role in energy balance and glycemic regulation



- *LEP* encoding for leptin
  - 'Adipostat' role
  - lower levels = stimulate positive energy balance
  - Source: adipocytes, placenta during pregnancy
- *ADIPOQ* encoding for adiponectin
  - Potential role in insulin sensitivity
  - Higher levels associated with lower risk of T2D

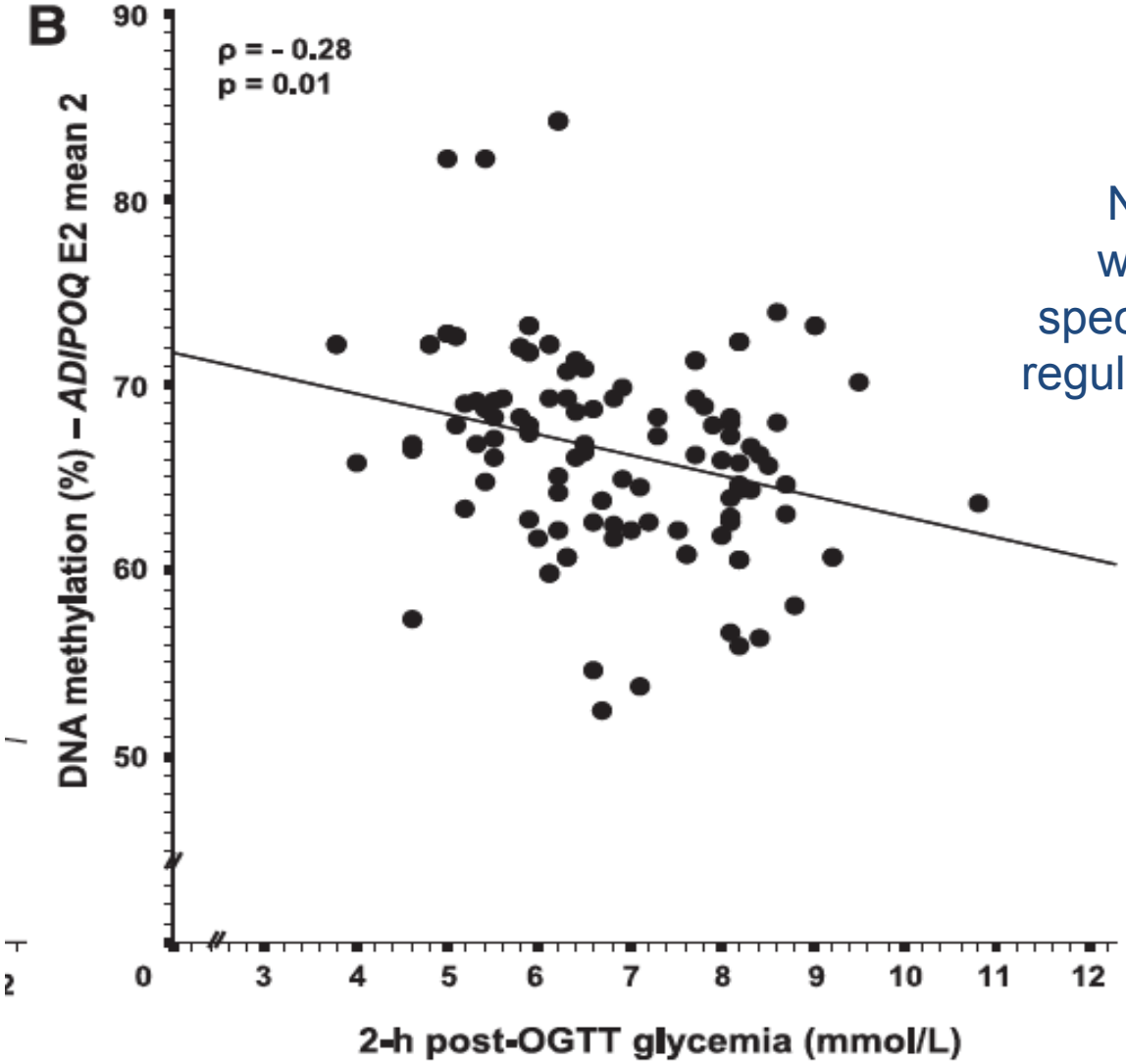
Maternal hyperglycemia is associated with lower DNA methylation at *LEP* in foetal placental tissue



N= 23 offspring of women with impaired glucose tolerance (IGT) during pregnancy

Bouchard L et al. Diabetes Care 2010

Maternal glycemia is associated with DNA methylation at *ADIPOQ* in foetal placental tissue



N= 98 offspring of women across the spectrum of glycemic regulation (NG–GDM)

Bouchard L, Hivert MF, et al. Diabetes 2012

Maternal glycemia and DNA methylation at other metabolism candidates genes

- In lipid metabolism:
  - *ABCA1*
    - Higher 2h-glucose = associated with lower DNA methylation in fetal circulating cells cord blood
  - *LPL*
    - Higher 2h-glucose = associated with lower DNA methylation in placenta on the foetal side
- IGF pathways
  - *IGF1R* and *IGFBP3* showed lower DNA methylation in foetal placenta associated with higher 2h-glucose
- Energy regulation
  - *PRDM16, BMP7* and *PGC1α* methylation levels in foetal placenta associated with fasting glucose and/or 2h-glucose

Houde AA et al. *Epigenetics* 2013
Houde AA et al. *Journal of DOHaD* 2014

Exposure to GDM and DNA methylation at candidates genes: imprinted loci and metabolic/inflammatory pathways

- Cord blood and placenta of offspring
  - GDM-diet (n= 88)
  - GDM-insulin (n=98)
  - Normoglycemia (n= 65)
- Tested list of candidate genes
  - 7 imprinted genes
    - Maternally : *LIT1*, *MEST*, *NESPAS*, *PEG3*, and *SNRPN*
    - Paternally: *H19* and *MEG3*
  - Metabolic and inflammatory pathways
    - *NR3C1, PPARA, NDUFB6, IL-10, APC, LEP, and OCT4*
  - Global methylation markers
    - ALU and LINE1 repeats

El Hajj N et al. Diabetes 2013

Exposure to GDM and DNA methylation at candidates genes: imprinted loci and metabolic/inflammatory pathways

- Imprinted gene *MEST* was hypomethylated in GDM exposed (diet or insulin) compared to control group in both placenta and cord blood cells
  - Lower methylation at *MEST* in circulating blood cells was associated with adult obesity in independent cohort of case-control (age-sex matched)
- *MEST* potential role – animal studies
  - Potential role in fetal and placental growth; adult behavior, particularly in maternal care
  - *MEST* expression is up-regulated by early post-natal overnutrition
  - *MEST* overexpression = enlargement of adipocytes and fat expansion

El Hajj N et al. Diabetes 2013

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Suggestive differential methylation in cord blood cells

El Hajj N et al. Diabetes 2013

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El Hajj N et al. Diabetes 2013

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1% lower in both tissues

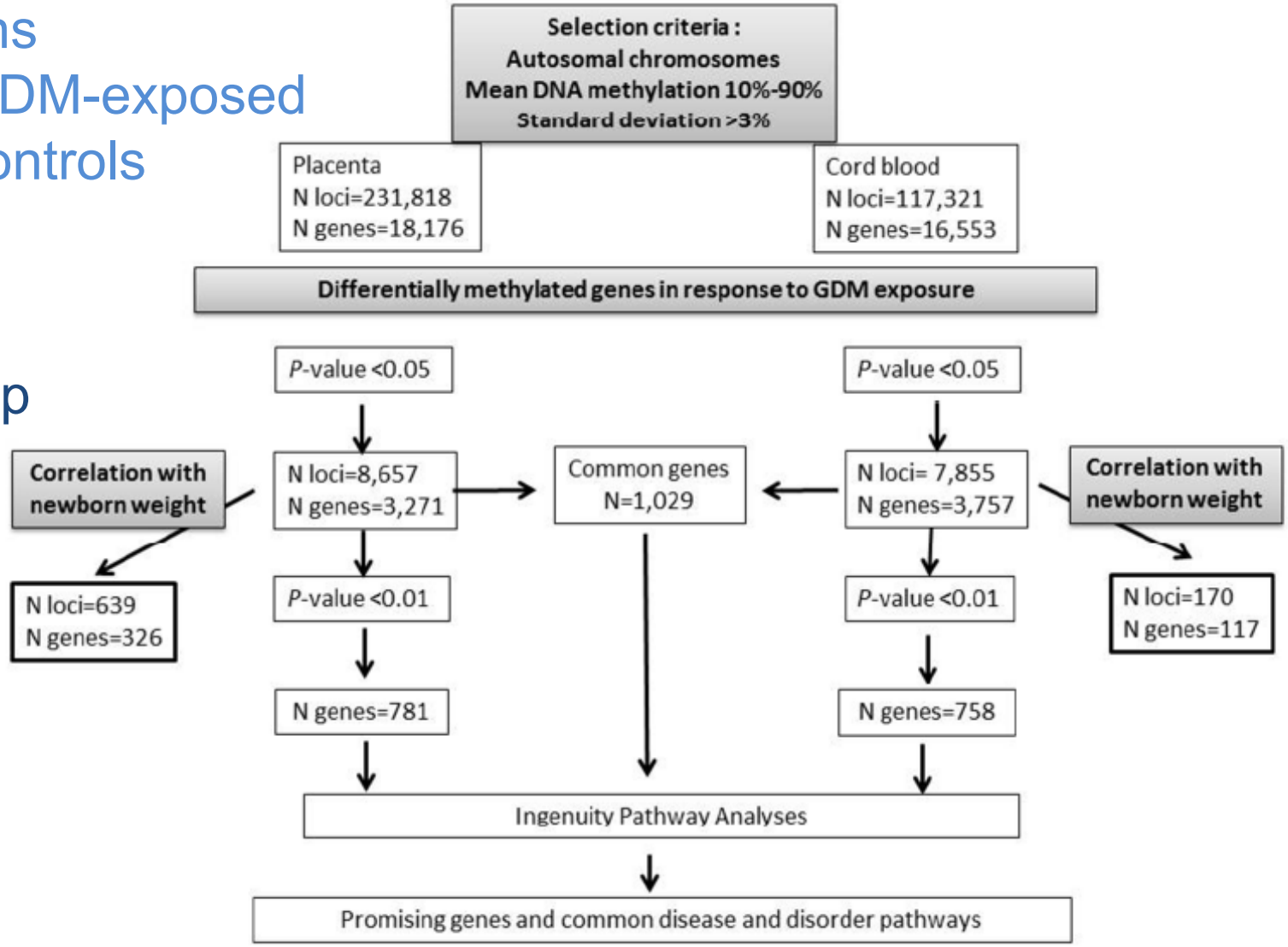
3% lower in fetal placenta
3% higher in cord blood cells

El Hajj N et al. Diabetes 2013

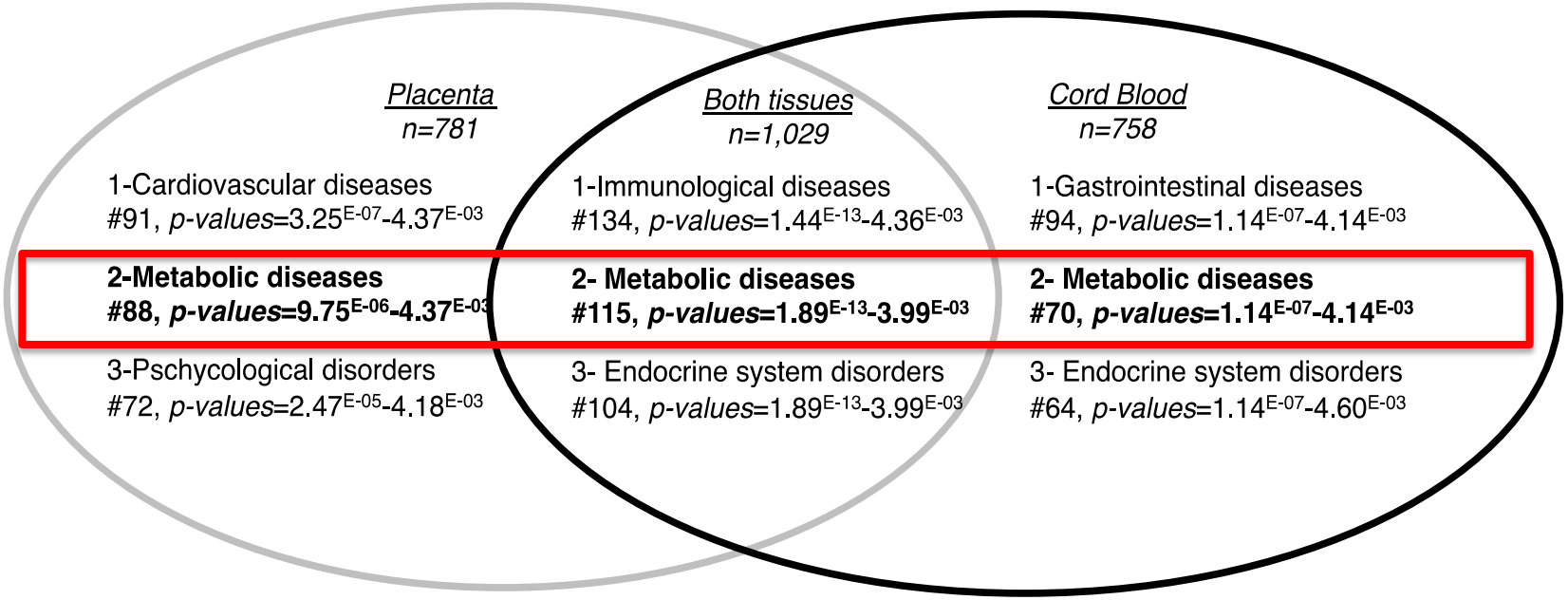
Epigenome-wide association study (EWAS) in GDM-exposed case-control study

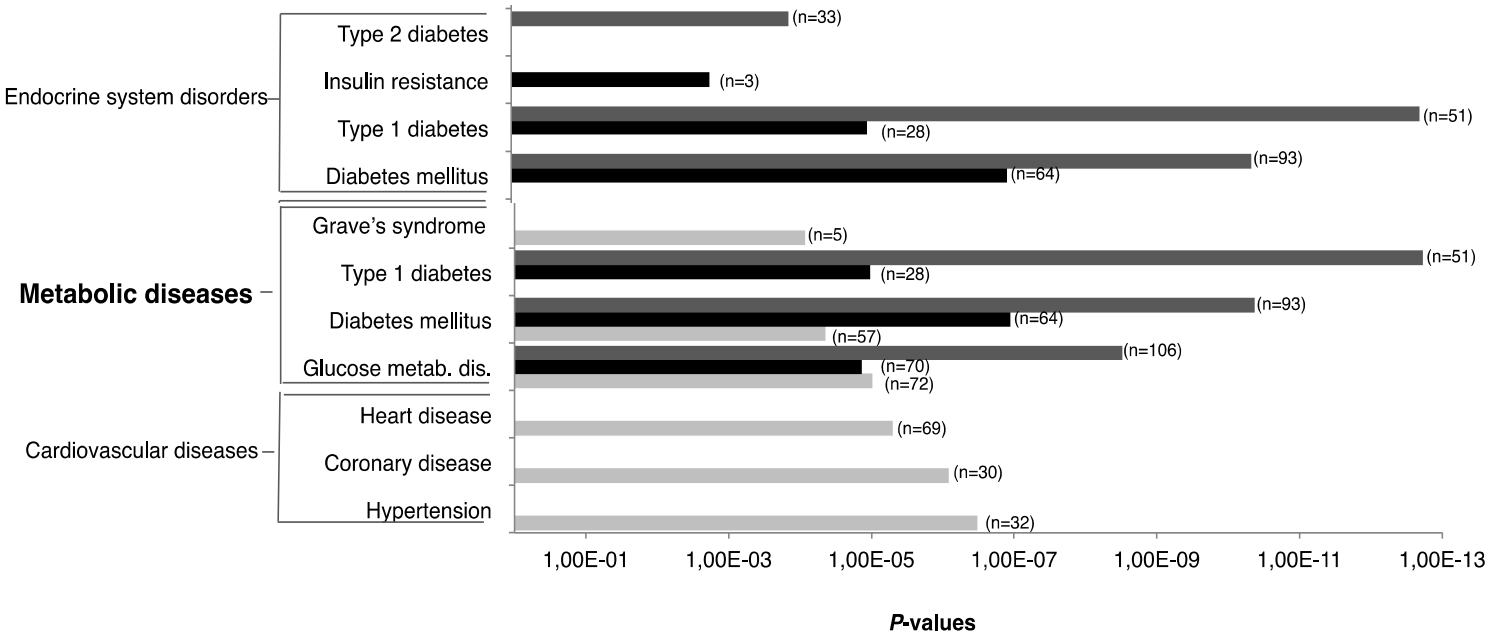
Newborns
N= 30 GDM-exposed
N= 14 controls

Illumina
450k
Beadchip



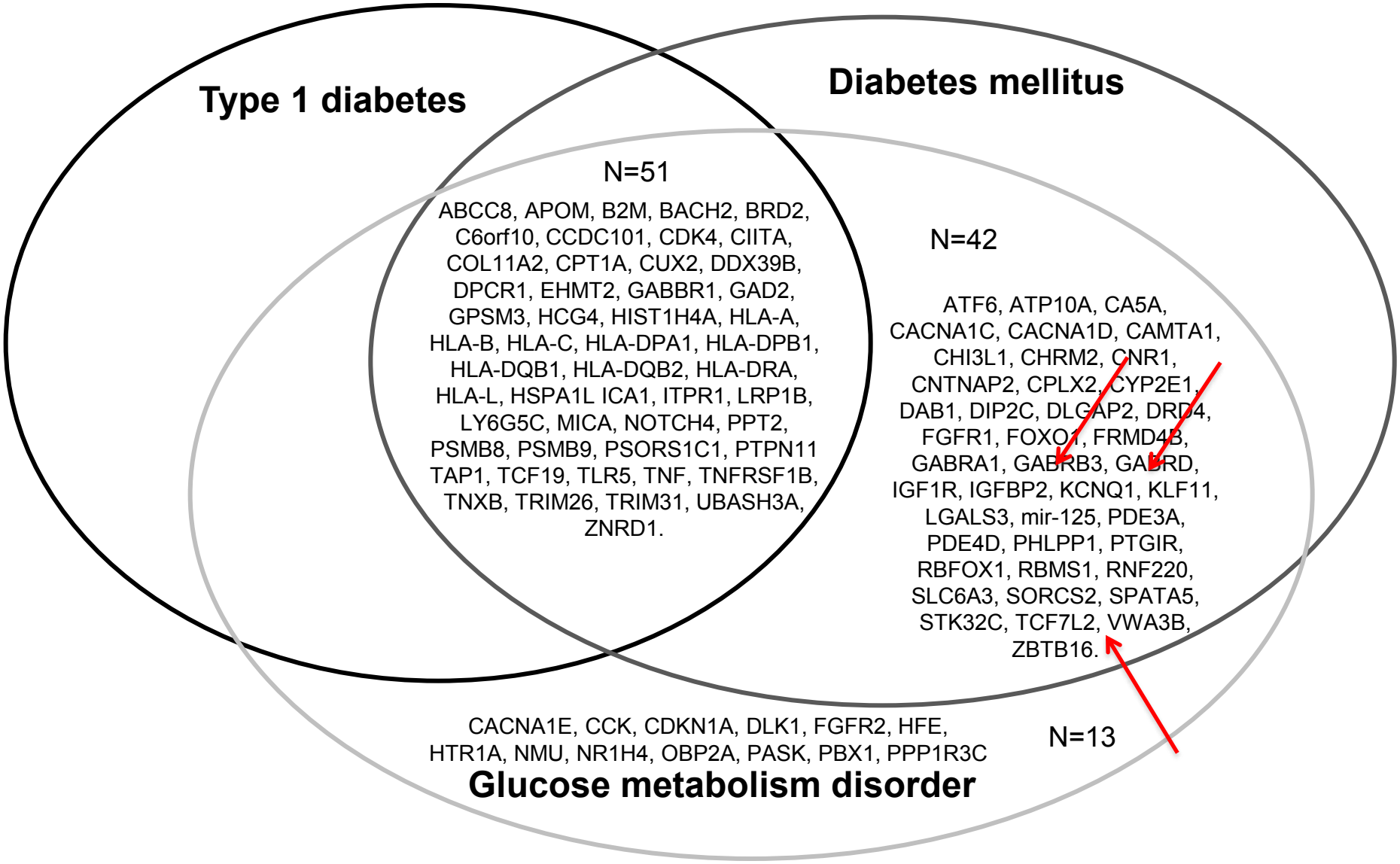
Ruchat SM, HoudeAA, et al. Epigenetics 2013





Ruchat SM, HoudeAA, et al. Epigenetics 2013

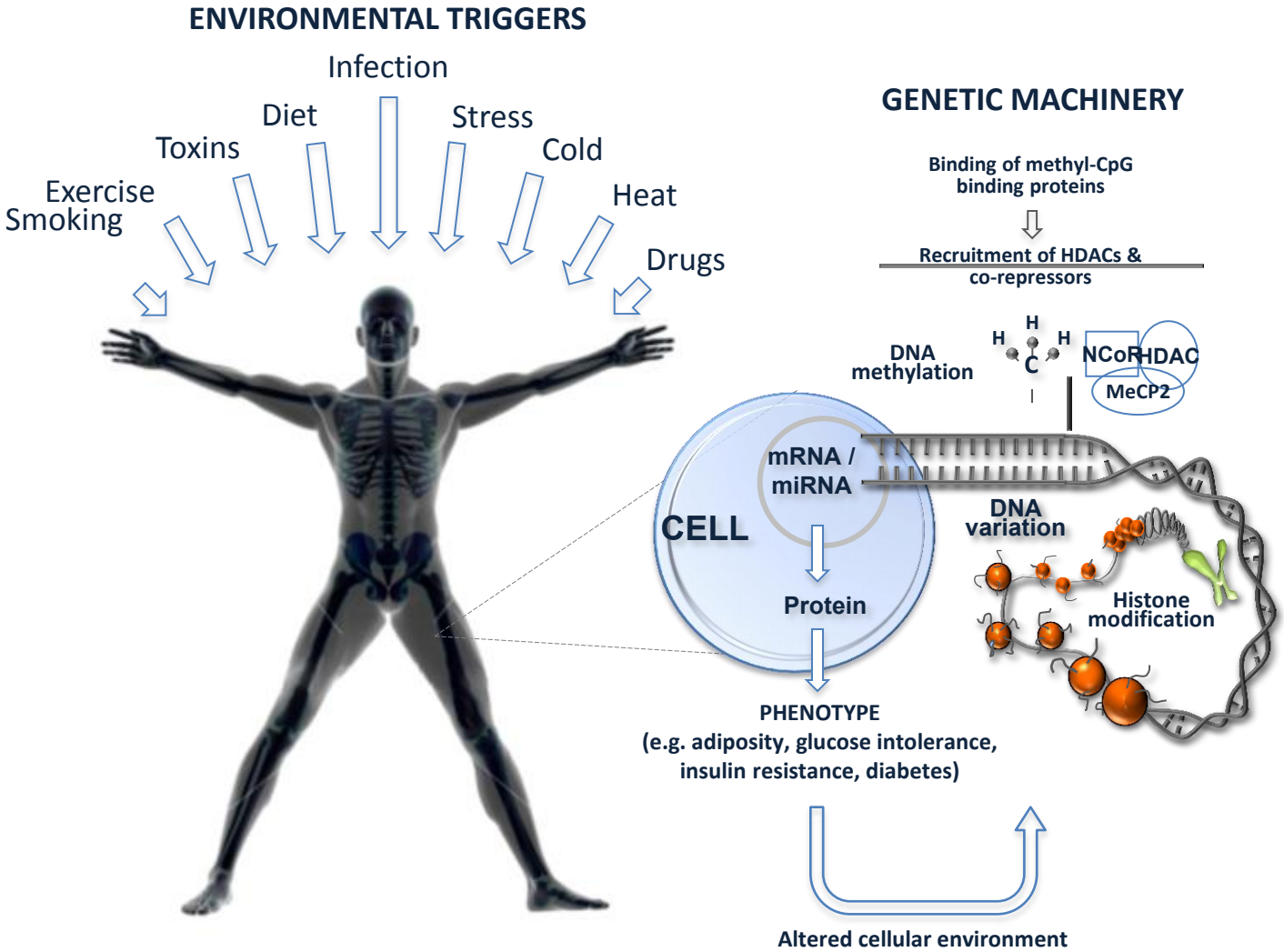
Genes classified in metabolic diseases pathways



Limitations of current studies and future challenges

- Often based on candidate genes
- Small sample size
- Access to tissues
  - Cord blood, placenta
- Assessment at birth only, need for longitudinal studies
- Integration of genetics, epigenetics, transcriptomics, metabolomics

Epigenetics: potential mechanism of foetal metabolic programming



Slide courtesy of Paul Franks

Franks P.W. & Ling C., *BMC Med*. 2010

Acknowledgements

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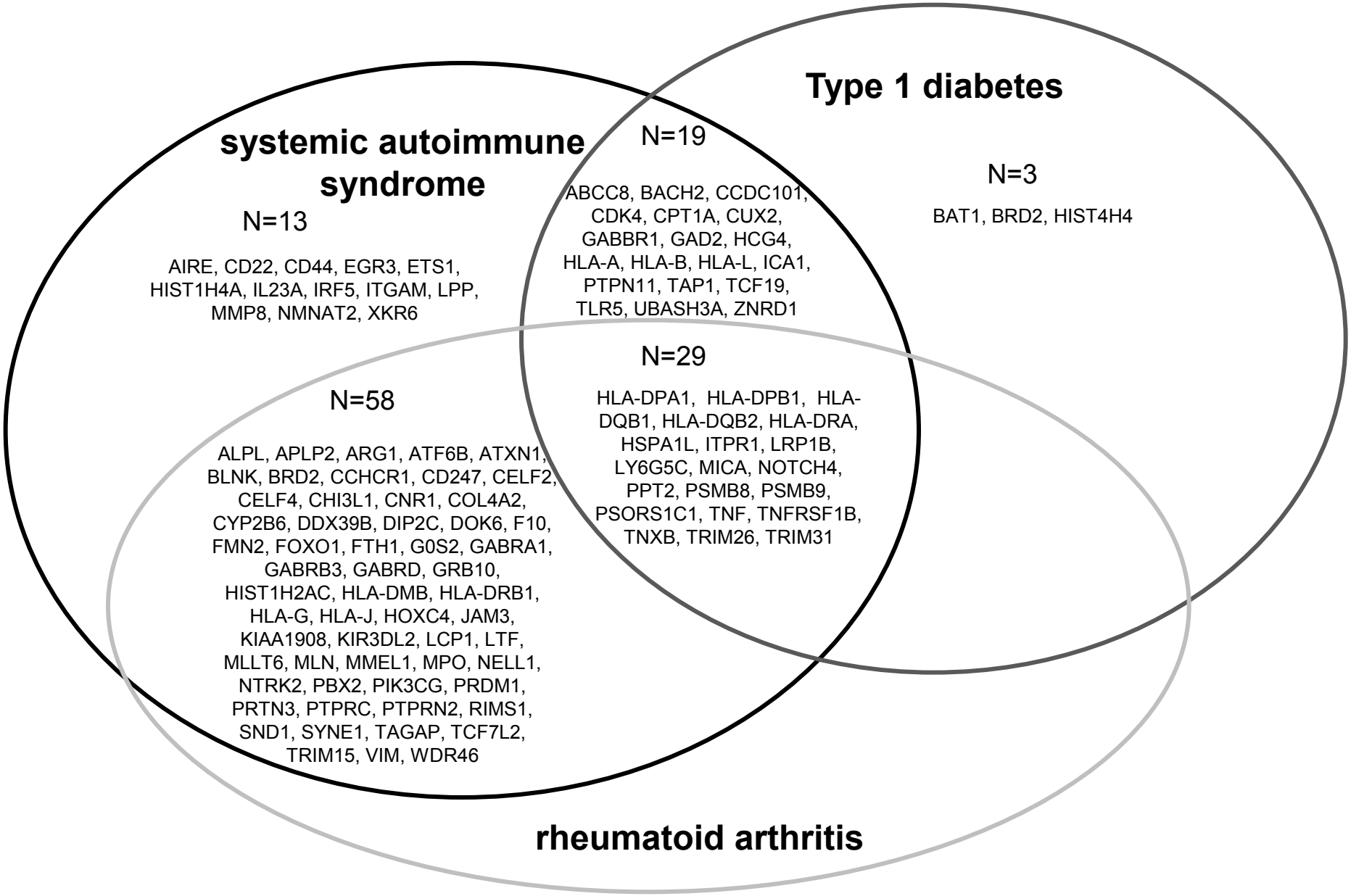
Diabète Québec

Fonds de la recherche en santé Québec

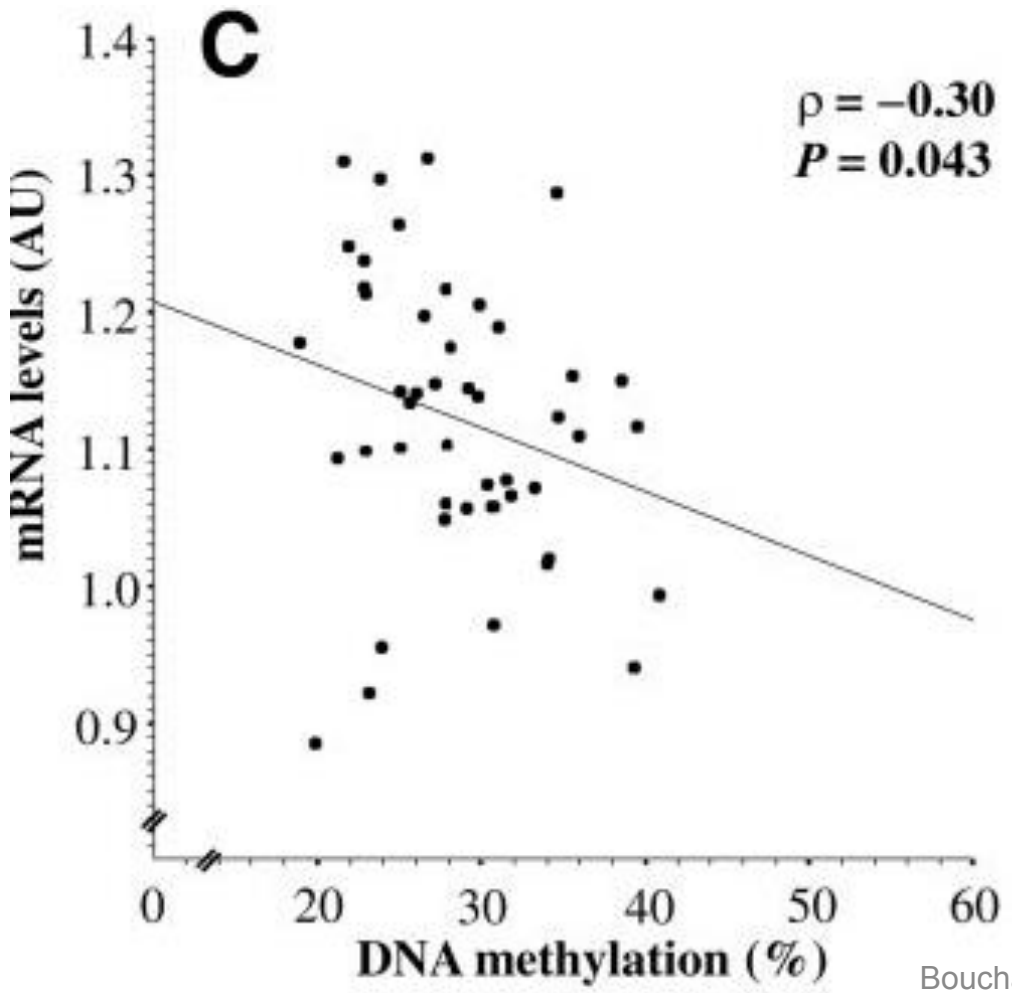
IRSC CIHR
Instituts de recherche en santé du Canada
Canadian Institutes of Health Research

Questions

Genes classified in immunological pathways

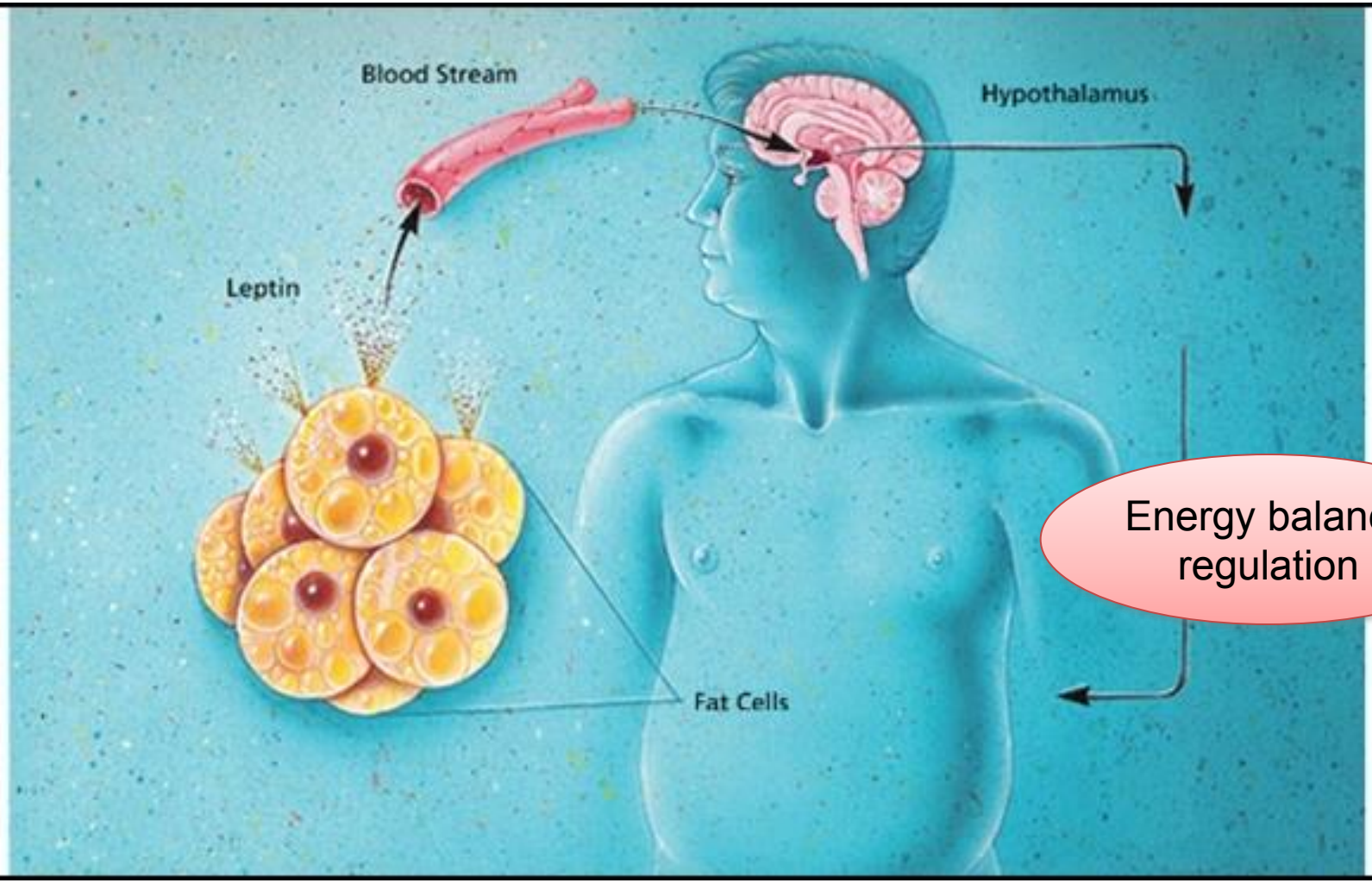


LEP promoter DNA methylation and mRNA expression of leptin on fetal side of the placenta



Bouchard L et al. Diabetes Care 2010

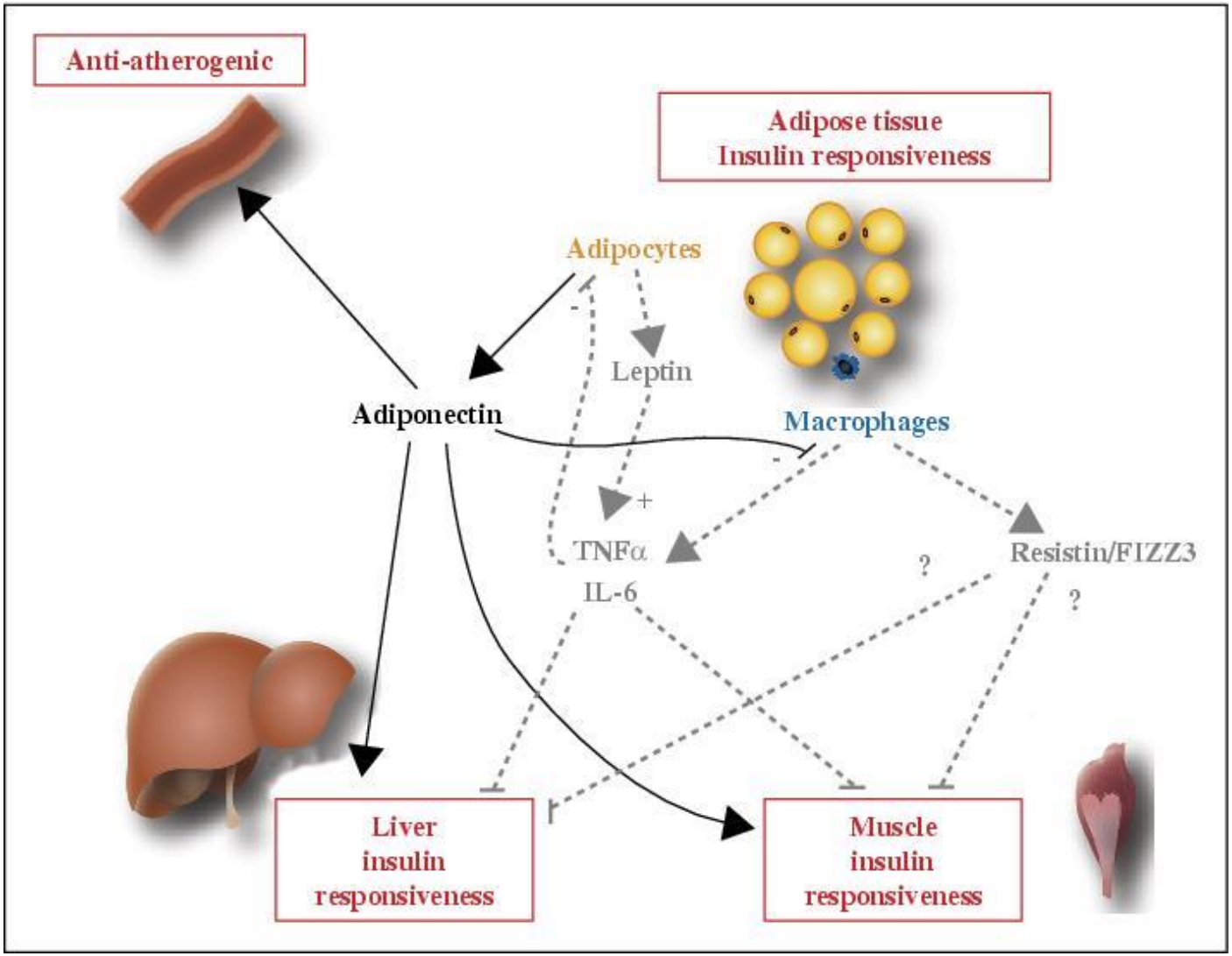
LEP encoding leptin



Energy balance regulation

Adipokines

hormones/cytokines produced by the adipose tissue potentially implicated in obesity and diabetes



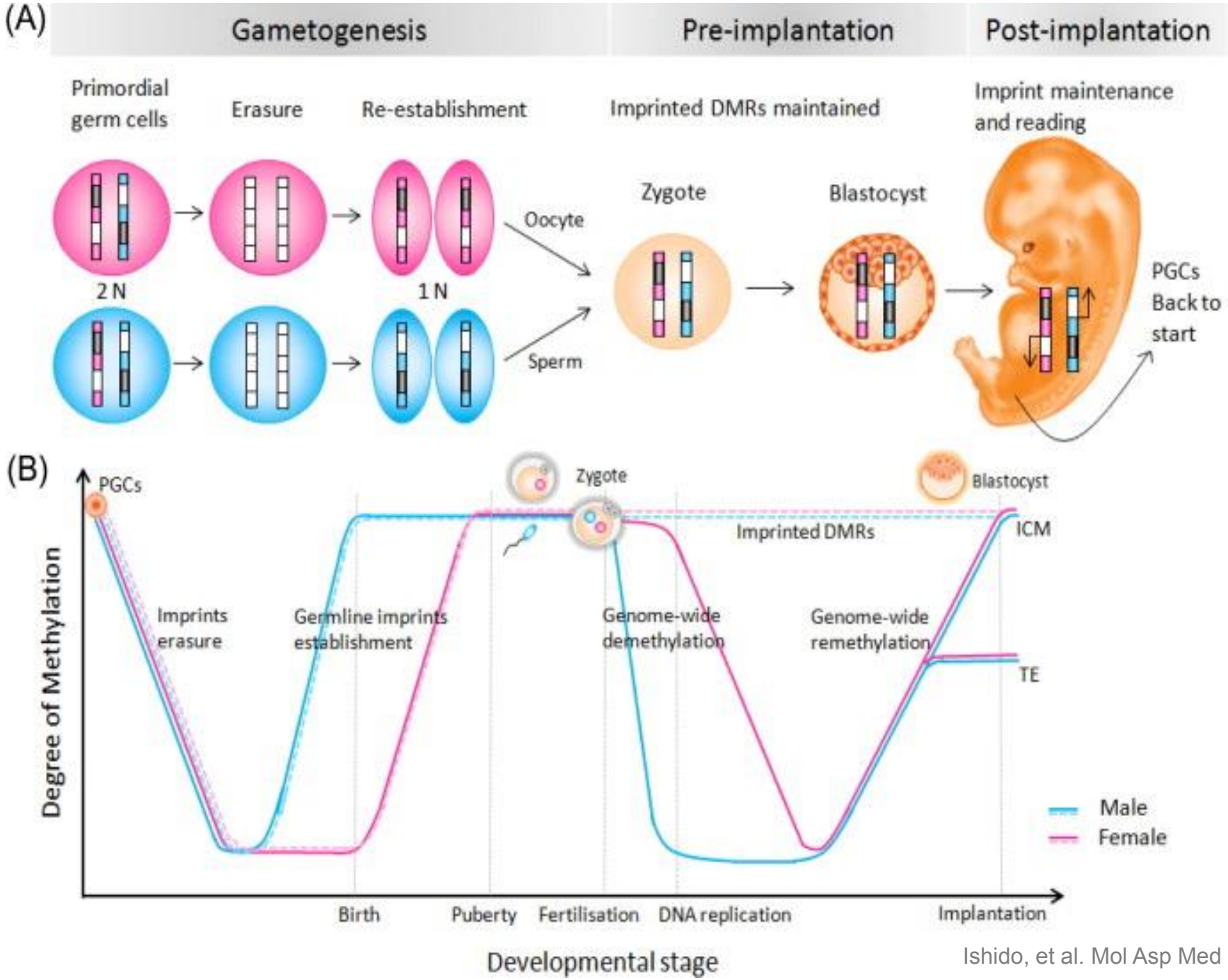
Candidates genes

- Other genes investigated by Bouchard lab
  - ABCA1 cord blood DNA methylation levels are negatively correlated with maternal glucose 2 h post-OGTT (r = -0.26; P = 0.02)
    - Ref: Houde AA Epigenetics 2013
  - LPL-CpG1 and CpG3 were also negatively correlated with maternal glucose (2-h post OGTT; r = –0.22; P = 0.02) and HDL-cholesterol levels (third trimester of pregnancy; r = –0.20; p = 0.03), respectively
    - Ref: Houde AA et al, Journal of DOHaD 2014
  - Both *IGF1R* and *IGFBP3* were hypomethylated in placentas exposed to IGT compared to NGT (12.9% vs. 17.2%; *p*=0.02 and 10.1% vs. 12.6%; *p*=0.01 respectively) and negatively correlated with 2h-glucose in the overall population (r=-0.23; *p*=0.01 and r=-0.20; *p*=0.03 respectively)
    - Veronique Desgagné
  - *PRDM16* and *PGC1α* DNA methylation was also correlated with the fasting glycemia at the end of the 2nd TofP (r=-0.19, *p*=0.048 and r=0.32, *p*=0.001; respectively) whereas DNA methylation levels at *BMP7* and *PGC1α* genes were correlated with the 2h post-OGTT glucose concentration (r=-0.20, *p*=0.029 and r=0.26, *p*=0.006; respectively)
    - Sandra Côté

Genome-wide approach

- Using 27k illumina platform
- Circulating blood cells – children 8-12yo from the EPOCH study (white, Kaiser)
  - N = 11 offspring exposed to GDM
  - N= 10 normoglycemic mothers (controls)
- No findings reaching FDR p-value

West NA et al. *Immunometabolism* 2013



Ishido, et al. Mol Asp Med 2013