Transcriptomic gender differences in newborns upon prenatal exposure to Polycyclic Aromatic Hydrocarbons in relation to birth weight

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universiteit hasselt
KNOWLEDGE IN ACTION

Contents

Background

- Polycyclic Aromatic Hydrocarbons (PAHs)
- Why newborns?
- Health implications: birth weight
- Why gender differences?
- Toxicogenomics

Results

Polycyclic Aromatic Hydrocarbons

Group of organic compounds that occur naturally in mixtures

Incomplete combustion:

- Tobacco smoke, wood smoke
- Air pollution
- Grilled, smoked foods
- Occupational exposure

Health implications are a public concern

- Carcinogens
- Immunotoxicants
- Developmental toxins

In utero: a critical window of exposure

13th century

Renaissance

1940s

- Fetal vulnerability
  - > Cell proliferation
  - < Detoxification system
  - < DNA repair
  - < Immune system

Health implications fetal exposure PAHs

- Cross the placental barrier and affect:
  - Respiratory symptoms, asthma and wheezing
  - Neurological and cognitive health outcomes
  - Birth outcomes

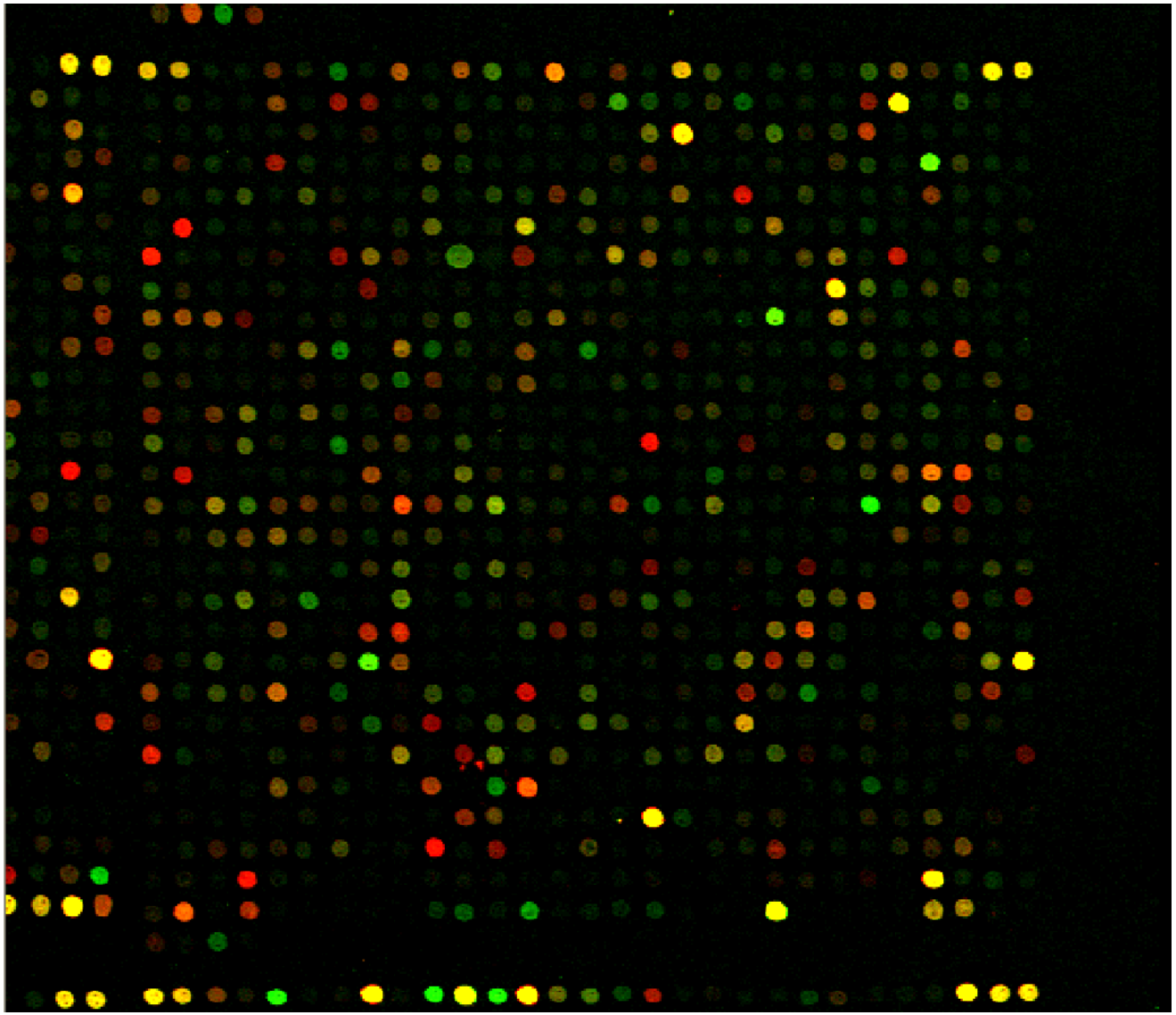
- Birth weight influences
  - Survival and perinatal morbidity
  - Subsequent health and development.
  - Associated with leukemia and other chronic diseases.

- Birth weight more strongly affected in males

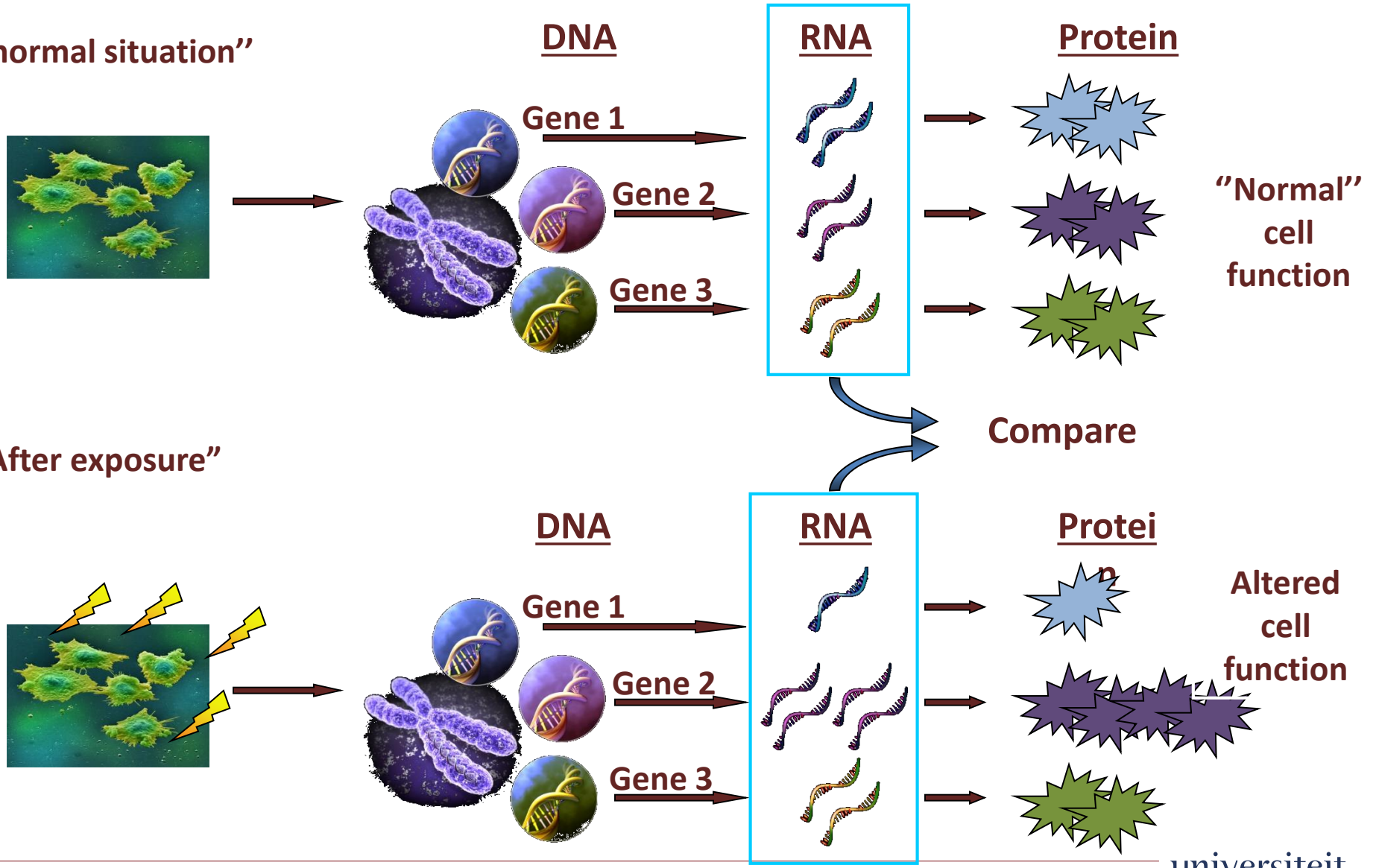
- Gender differences in gene expression responses

Environ Res. 2009; 109(4): 447–456

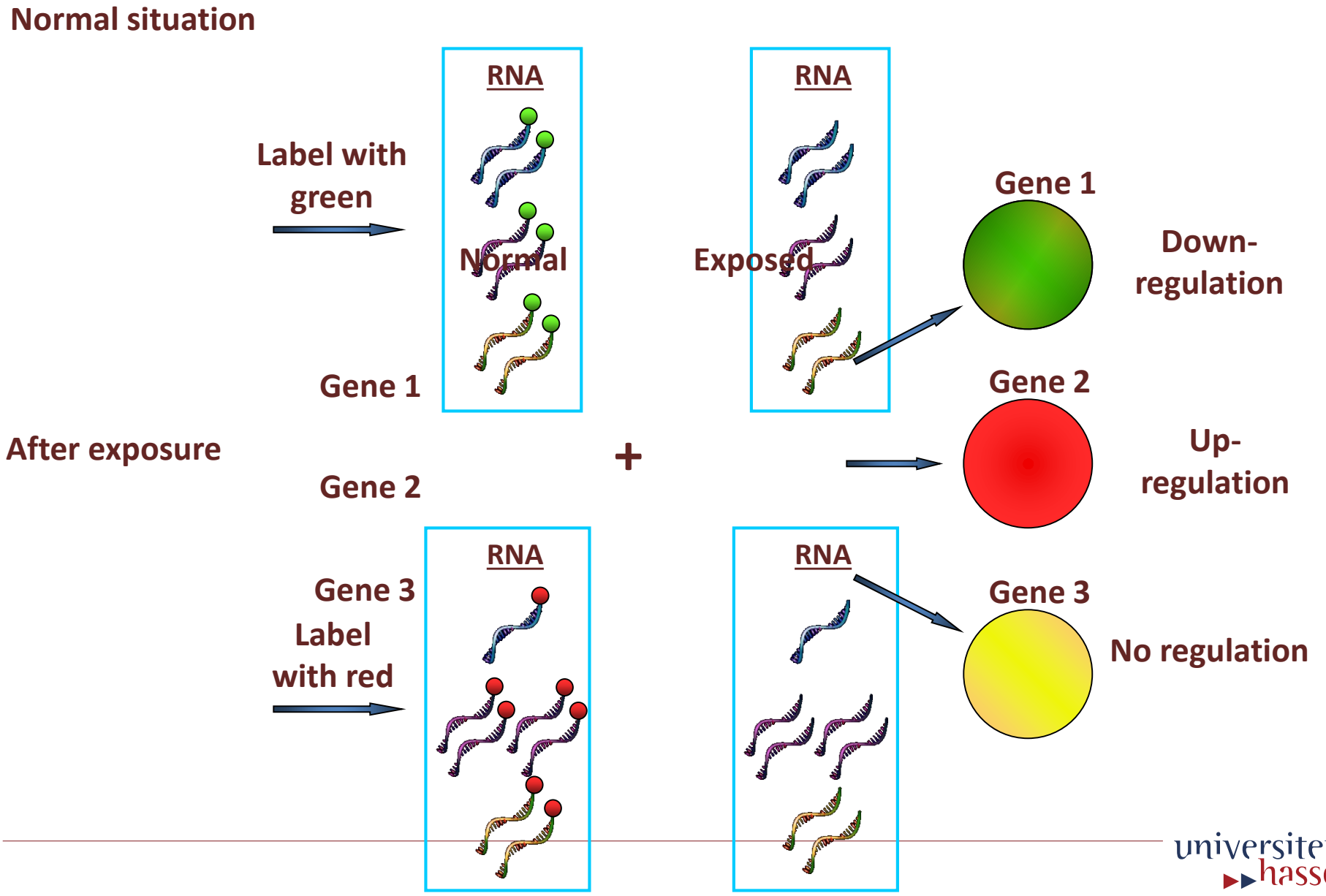
Toxicogenomics



Toxicogenomics



Toxicogenomics



Transcriptomic gender differences

Cancer Epidemiology, Biomarkers & Prevention

Research Article

Global Gene Expression Analysis in Cord Blood Reveals Gender-Specific Differences in Response to Carcinogenic Exposure *In Utero*

Kevin Hochstenbach[1], Danitsja M. van Leeuwen[1], Hans Gmuender[4], Ralf W. Gottschalk[1], Martinus Løvik[5], Berit Granum[5], Unni Nygaard[5], Ellen Namork[5], Micheline Kirsch-Volders[6], Ilse Decordier[6], Kim Vande Loock[6], Harrie Besselink[2], Margareta Törnqvist[7], Hans von Stedingk[7], Per Rydberg[7], Jos C.S. Kleinjans[1], Henk van Loveren[1,3], and Joost H.M. van Delft[1]

Cancer Epidemiol Biomarkers Prev. 2012;21(10):1756-67

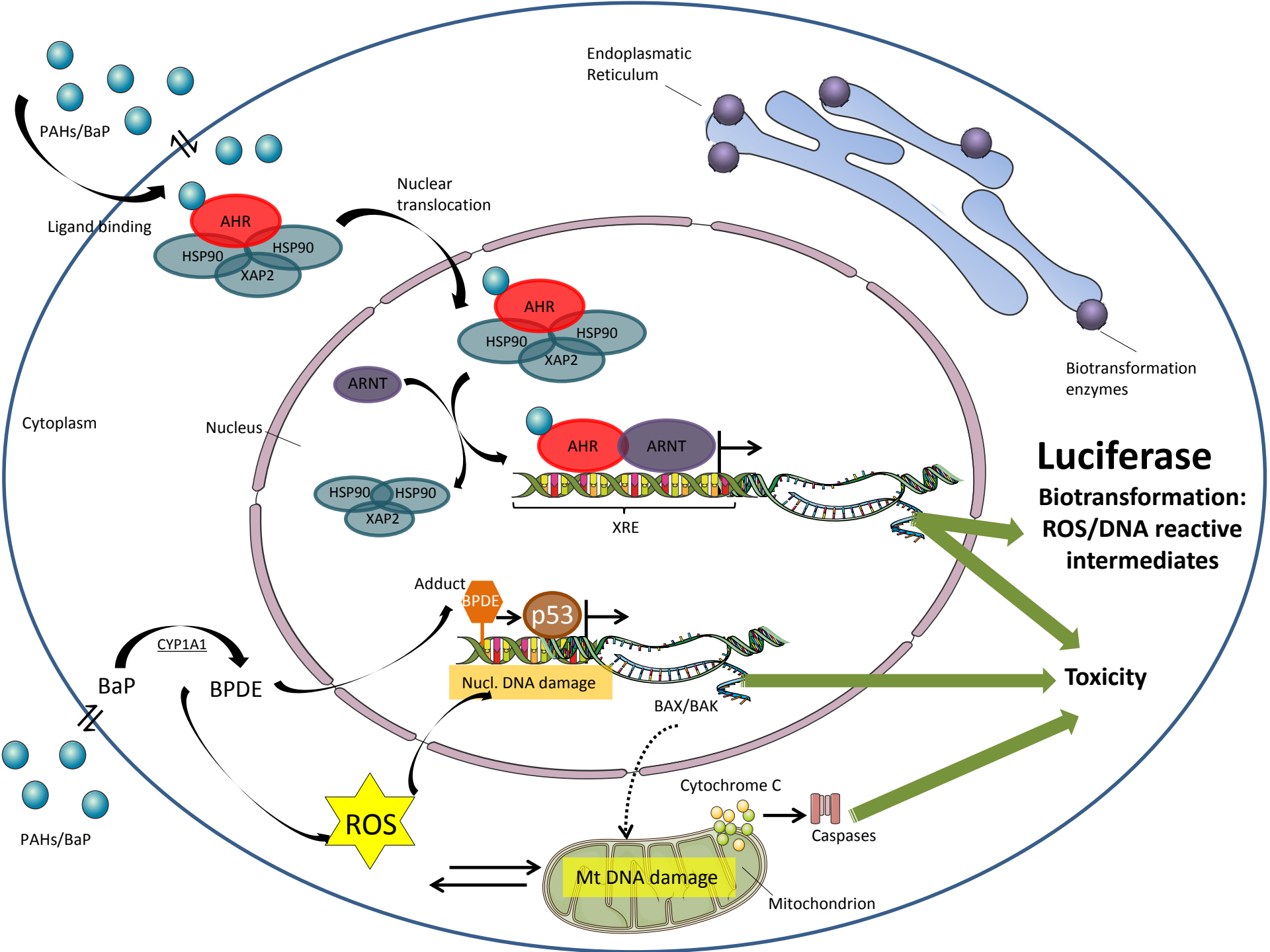
Transcriptomic gender differences

Biomarker	Process	# Significant Processes Males/Females	*T*-Value Males	*P*-Value Males	*T*-Value Females	*P*-Value Females
DR CALUX		5/29				
	Nucleosome assembly		4.1	0.154	6.4	<0.001
	T-cell receptor signaling pathway		−2.7	1.000	−4.5	0.001
	B-cell receptor signaling pathway		−0.6	1.000	−4.1	0.005
	TNF-alpha-NF-kB Signaling Pathway		2.9	0.551	−4.2	0.010
GA Hb-adducts		8/12				
	Wnt signaling pathway		4.2	0.032	0.2	1.000
‰MNBN		30/13				
	Translational elongation		8.5	<0.001	−5.7	<0.001
	Spliceosome		4.6	0.002	−5.4	<0.001
	mRNA processing		4.0	0.012	−4.1	0.002
	Pathways in cancer		4.8	0.001	1.8	1.000
	Translational elongation		8.5	<0.001	−5.7	<0.001

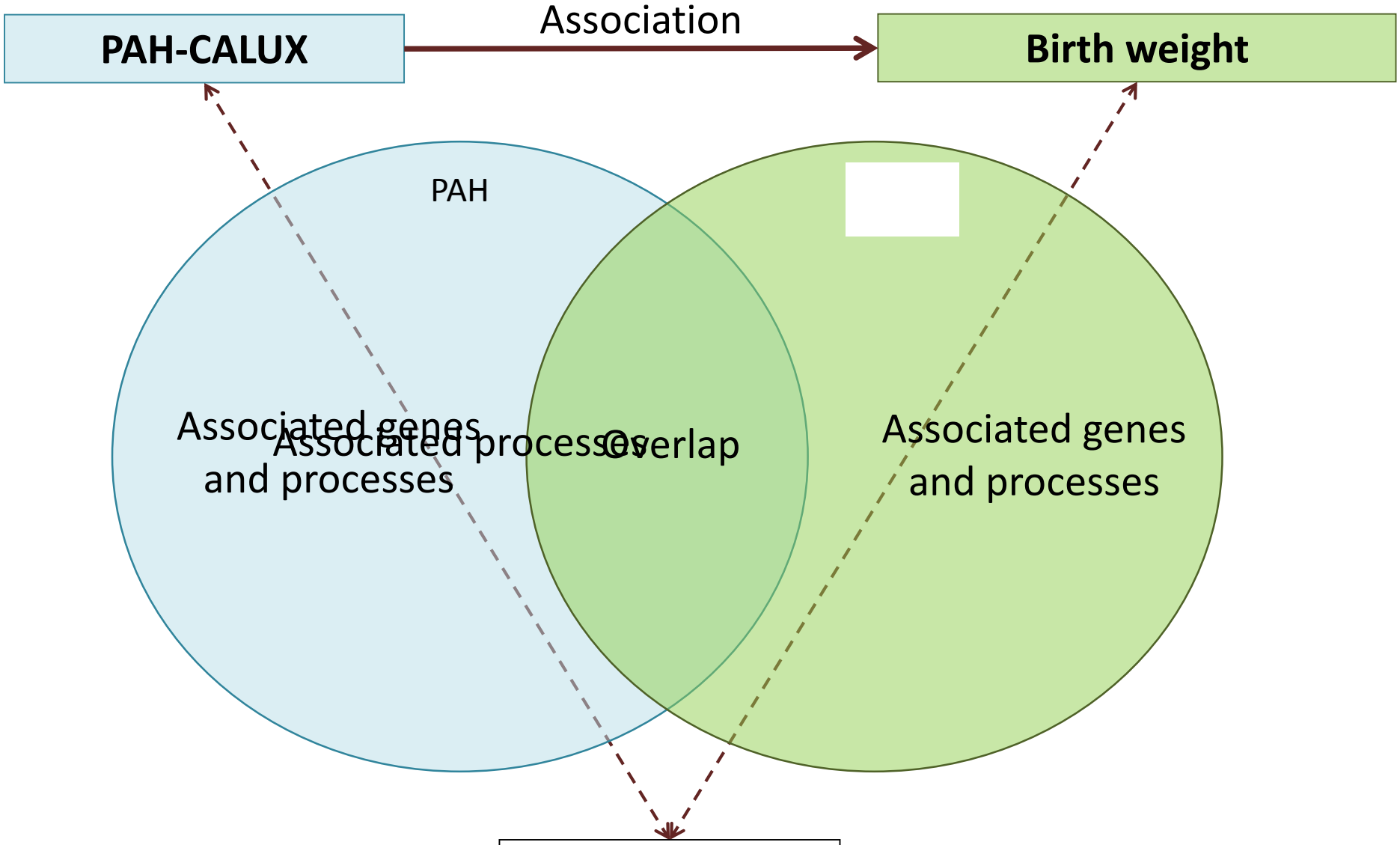
Cancer Epidemiol Biomarkers Prev. 2012;21(10):1756-67

Are there transcriptomic gender differences in newborns upon prenatal exposure to PAHs in relation to birth weight??

ERC project	ENVIR*ON*AGE
Coordinator:	Prof. Tim Nawrot
Funding	FWO grant


Endoplasmatic
Reticulum
PAHs/BaP
Ligand binding
AHR
HSP90
HSP90
XAP2
Nuclear
translocation
AHR
HSP90
HSP90
XAP2
Biotransformation
enzymes
Cytoplasm
Nucleus
ARNT
AHR
ARNT
HSP90
HSP90
XAP2
XRE
Luciferase
Biotransformation:
ROS/DNA reactive
intermediates
Adduct
BPDE
p53
Nucl. DNA damage
BAX/BAK
Toxicity
CYP1A1
BaP
BPDE
PAHs/BaP
ROS
Cytochrome C
Caspases
Mt DNA damage
Mitochondrion

Meet-in-the-middle approach



PAH-induced gene expression - Common

category	#
Replication/Transcription/Translation	29
Cell cycle/division/proliferation	12
Immune response	6
GPCR	2
Proteosome	2
DNA repair	1
Embryogenesis	1

Consensus
Enrichment analyses
Q value 0.05

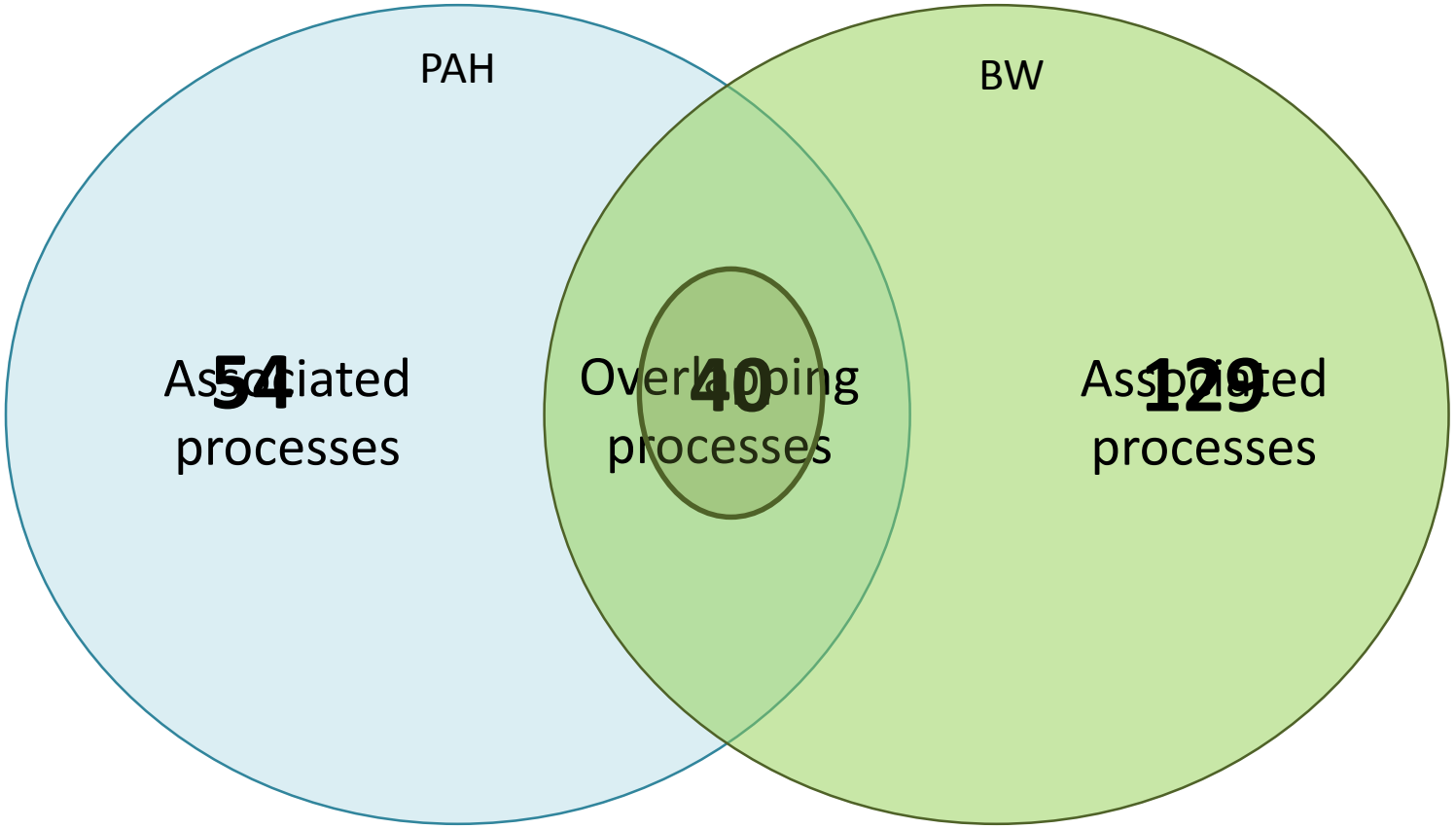
PAH-induced gene expression - Females

category	PAH
TCA cycle	8
Disease	3
Cell cycle/division/proliferation	2
Replication/Transcription/Translation	2
DNA damage response	1
Proteasome	1
Cancer	1
Integrin	1

PAH-induced gene expression - Males

category	#	category	#
Signal transduction	103	Vascular system	6
Immune response	18	Mitochondrial	5
Neurobiology	14	DNA damage response	4
Diseases	12	Senescence/Apoptosis	4
Cell cycle regulation	10	Biotransformation	3
Developmental Biology	10	Endocrine system/hormones	3
DNA packaging	10	Telomeres	3
Epigenetics	8	AhR-ER-AR	2
Cancer	7	Folate	1
Glycobiology	6	Vitamin E	1

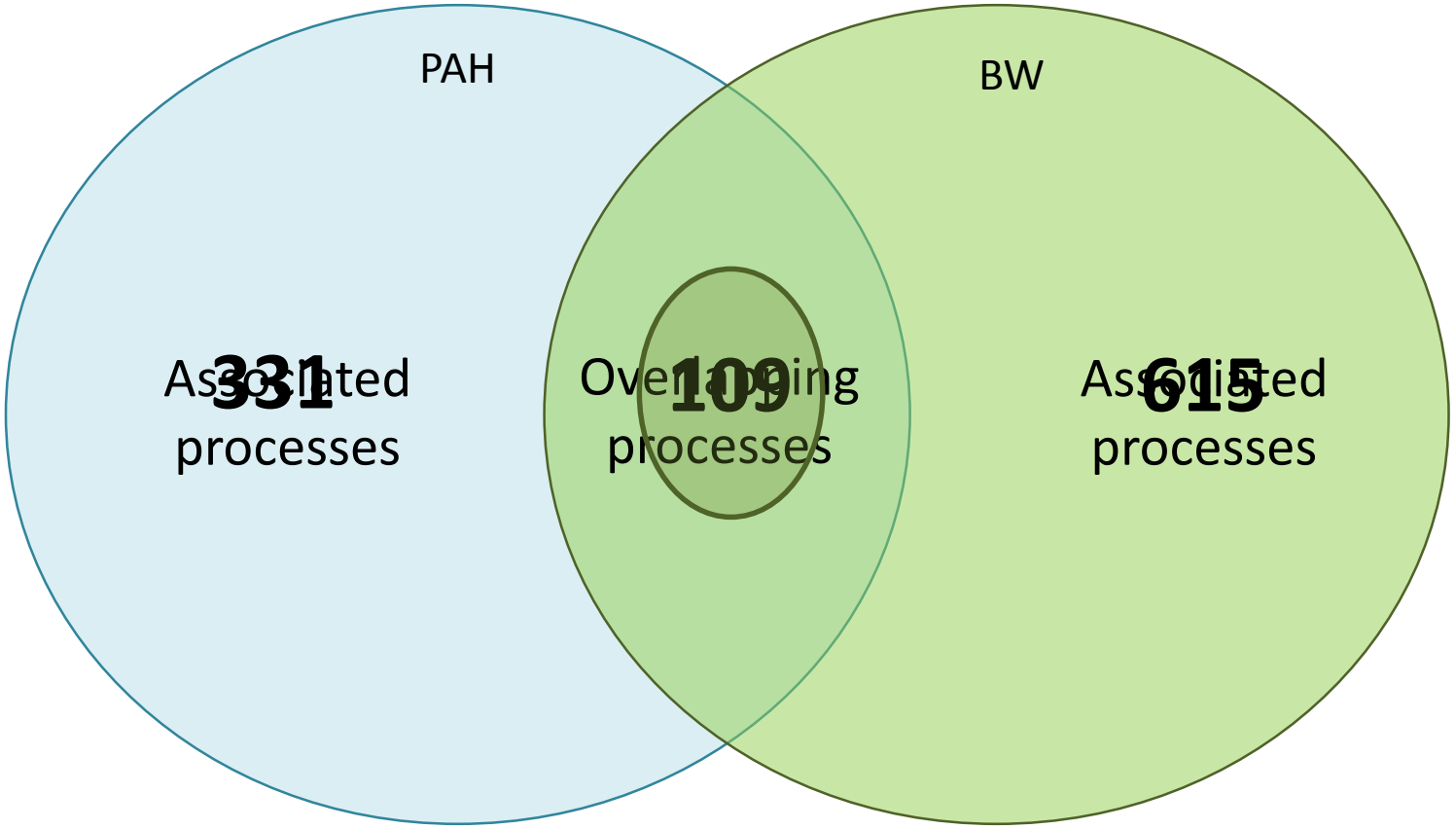
Meet-in-the-middle: Overlap common



Meet-in-the-middle: Overlap common

category	Overlap
Replication/Transcription/Translation	26
Cell cycle/division/proliferation	12
GPCR	1
DNA repair	1

Meet-in-the-middle: Overlap males



Meet-in-the-middle: Overlap males

EGF – Ras - ERK - PI3K-Akt

TCR signaling-NFkB cascade
IL-1 p38

Cyclin E during G1/S transition

ATM

BARD1

Cell cycle regulation	1	Senescence/Apoptosis	0
		Biotransformation	3
Cancer	4		
Glycobiology	2	Vitamin E	1

Wnt signaling

Complexation between folic

Protective against PAH-DNA adduct formation

Take home message!

- Gender-specific PAH-Birth weight association through modulation of the fetal transcriptome:
  - Higher transcriptomic response in male newborns upon prenatal PAH exposure
  - Possible gender-specific PAH mechanisms-of-action
    - Epigenetics
    - DNA damage:
      - Cell cycle regulation
      - P38/JNK
      - Apoptosis
    - Folate
    - Vitamine E

Ongoing and future research

Develop a toxicogenomics-based biomarker indicative of in utero exposure to PAHs

Apply additional PAH-CALUX on subset to validate developed biomarker

Measure PAH adducts and its newly developed transcriptome signature in cord blood of 850+ newborns within the ENVIRONAGE birth cohort by means of qRT-PCR

Identify transcriptomic profiles in cord blood associated with the effects of in utero PAH exposure on:

- Telomere length
- Neurodevelopment
- Follow up data on immune functionality.

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