Epigenome-wide association study of educational attainment

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Relevance

Educational attainment
Important correlate/indicator of:

- Cognitive and personality characteristics (e.g. intelligence, attention, memory, reading ability, persistence, self-discipline)
  - Advantage : well-documented in many cohorts

- Social environment in which the individual is born and raised

- Social outcomes of individual (occupation, income)

- Health
  - Average life expectancy at birth: 79,1 Dutch men, 82,8 Dutch women (RIVM reports 2012).

  - Difference in the Netherlands between high and low-educated groups:
    - 6.5 years for men
    - 6,1 years for women

Epigenetic mechanisms
(involved in / biomarkers of)

→ Cognition, personality

→ Social environment

→ Education-related health differences

Epigenome-wide association study

- **Aim**: Identify genomic regions where DNA methylation level correlates with educational attainment

- **Tissue**: peripheral whole blood

- **Approach:** 1. EWAS in individual BIOS cohorts

    2. Fixed-effects meta-analysis adjusting for bias and inflation[1]

- **Cohorts:**
    - Netherlands Twin Register (NTR)
    - Leiden Longevity Study (LLS)
    - Rotterdam Study (RS)
    - Lifelines-Deep (LLD)

Total sample size = 4179

[1] van Iterson, M. M., van Zwet, E. W., Slagboom, P. E., Heijmans, B. T., & Bios Consortium. (2016). Controlling bias and inflation in epigenome-and transcriptome-wide association studies using the empirical null distribution.*bioRxiv*, 055772.

Cohort	NTR	LLS	RS	LLD
N	2199	668	608	704
% female	68.6	52.5	57.7	57.67
Age, mean (sd)	38.2 (12.6)	59.1 (6.6)	68.6 (5.6)	47.32 (12.47)
birth year, mean (range)	1968 ('26-89')	1945 ('25'74)	1943 ('30-'60)	1965 ('31-'87)

# Educational attainment

Harmonization of the raw phenotype data:

1. Highest completed level of education at the age of 25 or higher – **7 categories**.

7 Levels
1. primary school only -lager onderwijs
2. lower vocational schooling -lager beroepsonderwijs (lbo)
3. lower secondary schooling (general) - middelbaar algemeen onderwijs (lavo, mavo)
4. intermediate vocational schooling - middelbaar beroepsonderwijs (mbo)
5. intermediate/higher secondary schooling (general) - voorgezet algemeen onderwijs (havo, vwo)
6. higher vocational schooling -hoger beroepsonderwijs (hbo)
7. University - wetenschappelijk onderwijs (wo)

Educational attainment as a function of birth year

university

primary school
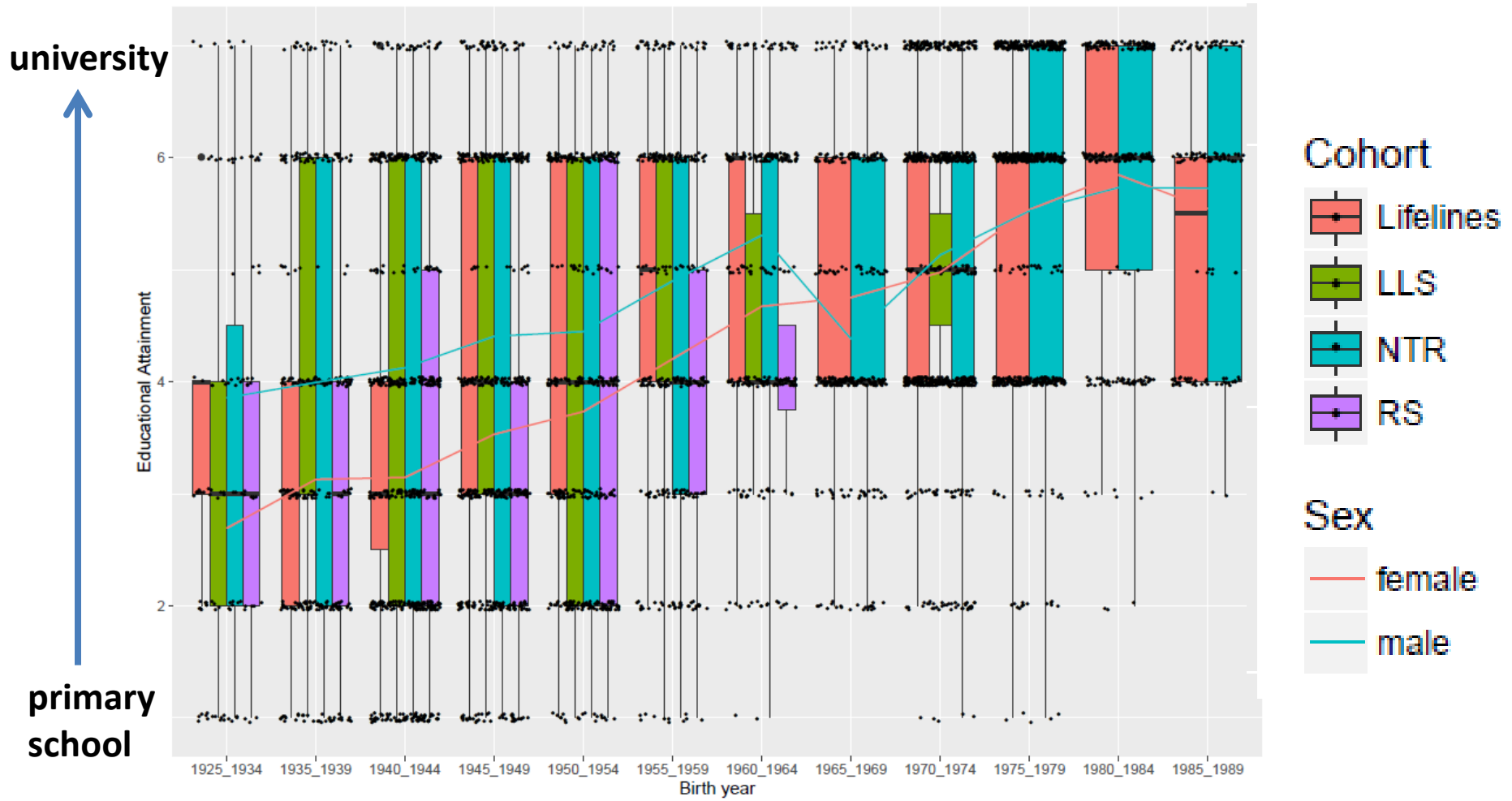
| **Compulsory education**	**1901**	**1968**	**1970**	**Currently:**
	6 years	9 years	10 years	11-13 years
	(age 6-12 years)			(age 5 – age 16 or 18: depending on whether a qualification has been obtained)

EWAS

- Linear relationship DNA methylation (outcome variable) - education level (predictor)

- Covariates
  - Sex
  - Age
  - White blood cell counts
  - 96-wells plate, 450k row

- Additional analyses:
  + covariate smoking status

Meta-analysis: 58 significant CpG sites

chromosome 2q37.1   *AHRR*
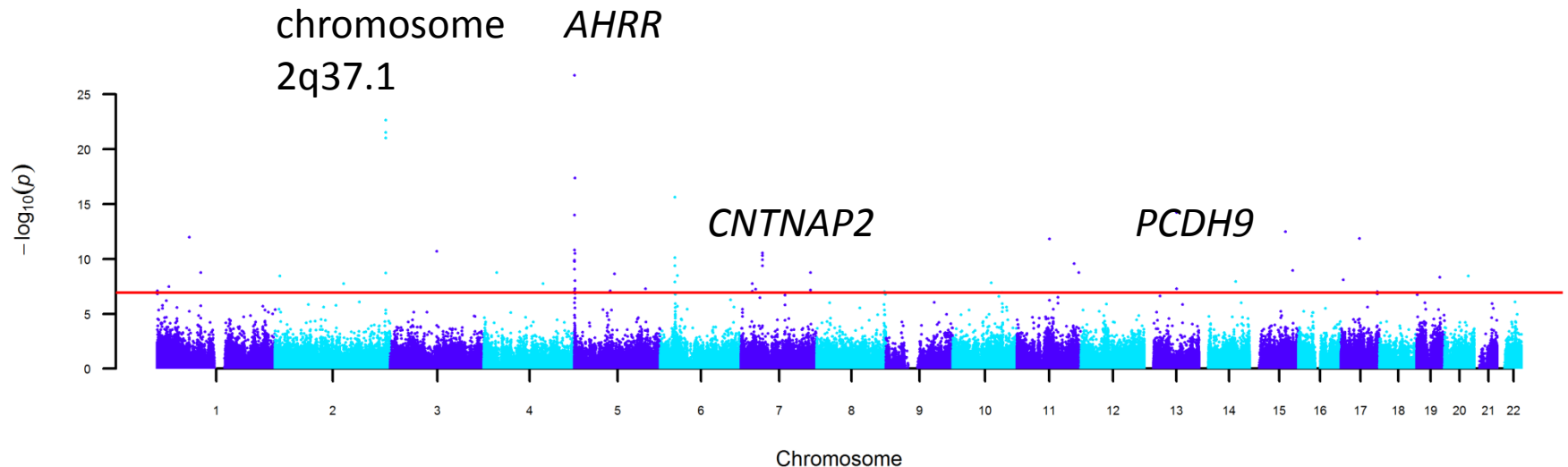
CNTNAP2: Contactin Associated Protein-Like 2- a neuronal transmembrane protein (neurexin family).
- *CNTNAP2* = target of transcription factor *foxp2*
- Genetic variants in *CNTNAP2* associated with neurodevelopmental phenotypes: language impairment, autism, intellectual disability, dyslexia, schizophrenia

PCDH9 : protocadherin 9.
- Copy-number variants: autism spectrum disorder
- knock-out mice: social and object recognition deficits.
- also described as a tumor-suppressor gene

AHRR (top site cg05575921) .
- Aryl-Hydrocarbon Receptor Repressor
- One of the most strongly associated and best replicating hits in previous EWAS of smoking phenotypes (also increased RNA of *AHRR*)

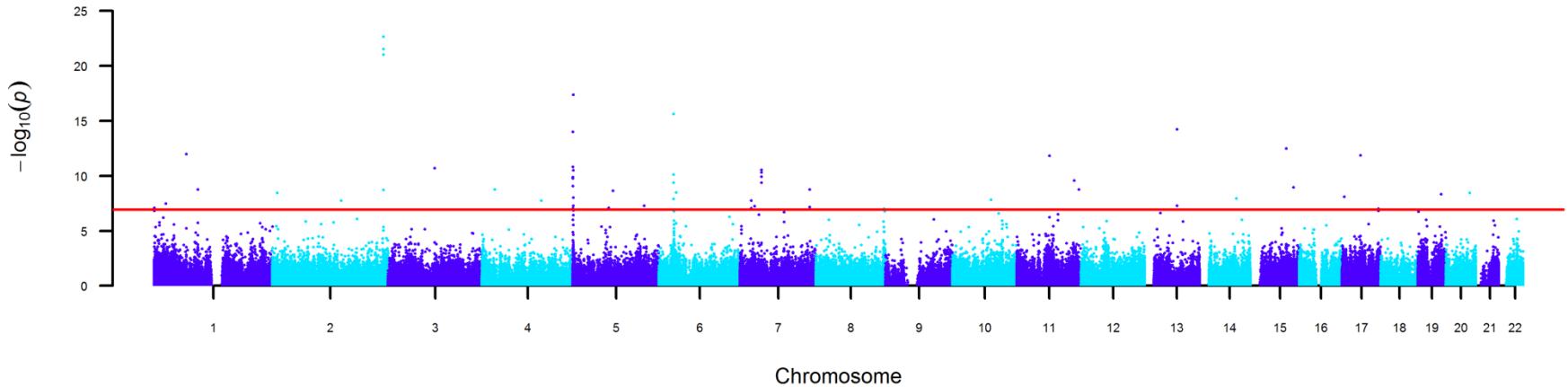# Overlap: EWAS educational attainment – smoking-associated CpGs
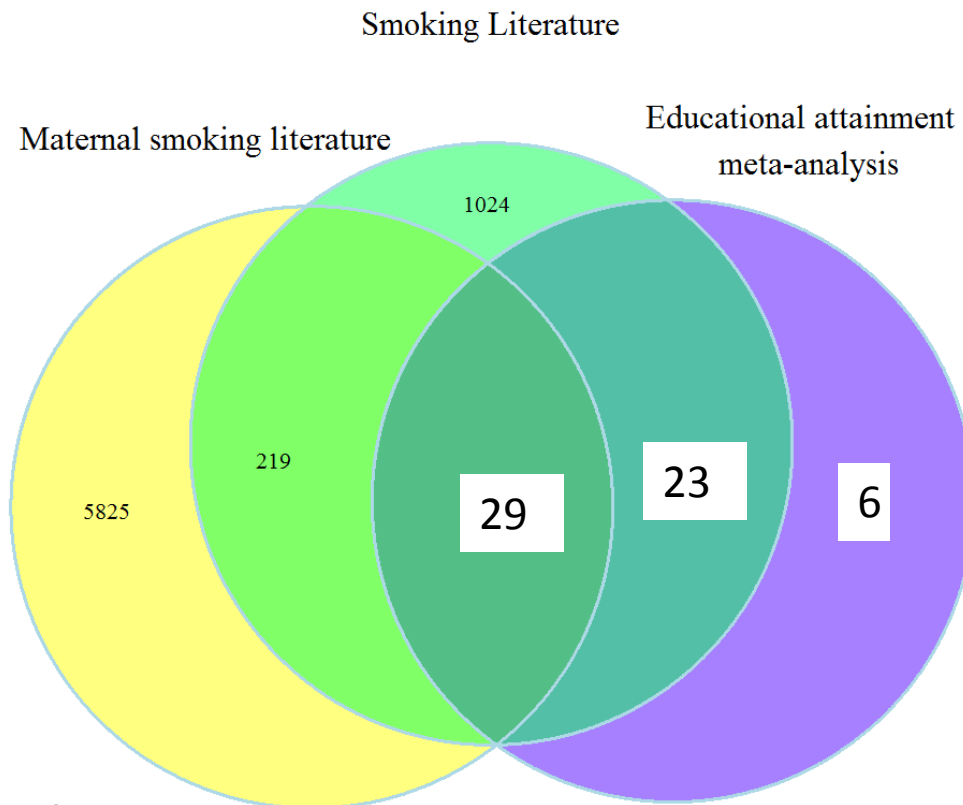
Smoking-associated CpGs

- Guida,F. *et al.* Dynamics of smoking-induced genome-wide methylation changes with time since smoking cessation. *Human molecular genetics*ddu751 (2015).
- Zeilinger,S. *et al.* Tobacco smoking leads to extensive genome-wide changes in DNA methylation. *PloS one* **8**, e63812 (2013).
- Ambatipudi,S. *et al.* Tobacco smoking-associated genome-wide DNA methylation changes in the EPIC study. *Epigenomics* **8**, 599-618 (2016).
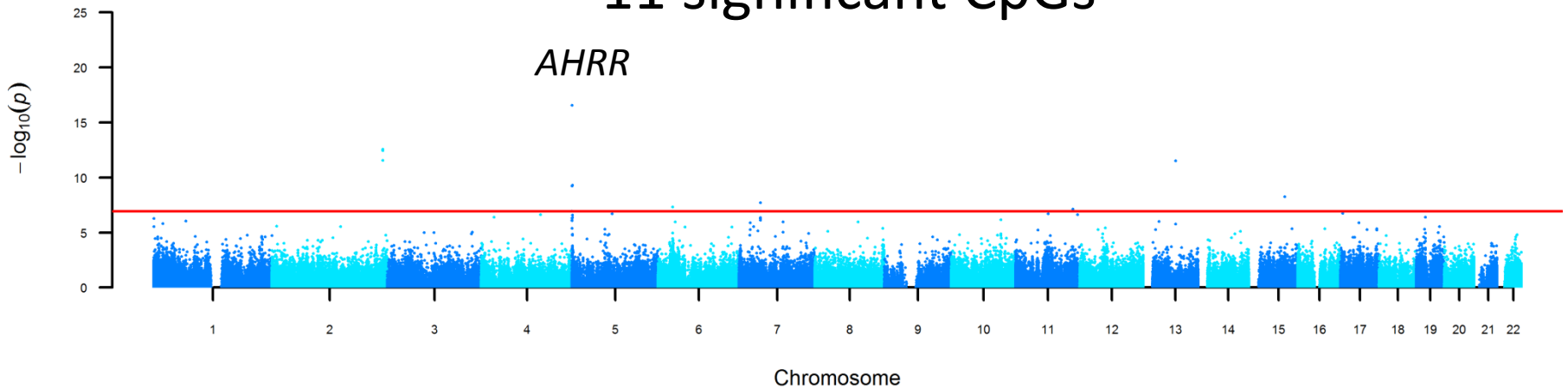
Maternal prenatal smoking-associated CpGs

Joubert,B.R. *et al.* DNA Methylation in Newborns and Maternal Smoking in Pregnancy: Genome-wide Consortium Meta-analysis. *Am. J. Hum. Genet.* **98**, 680-696 (2016).
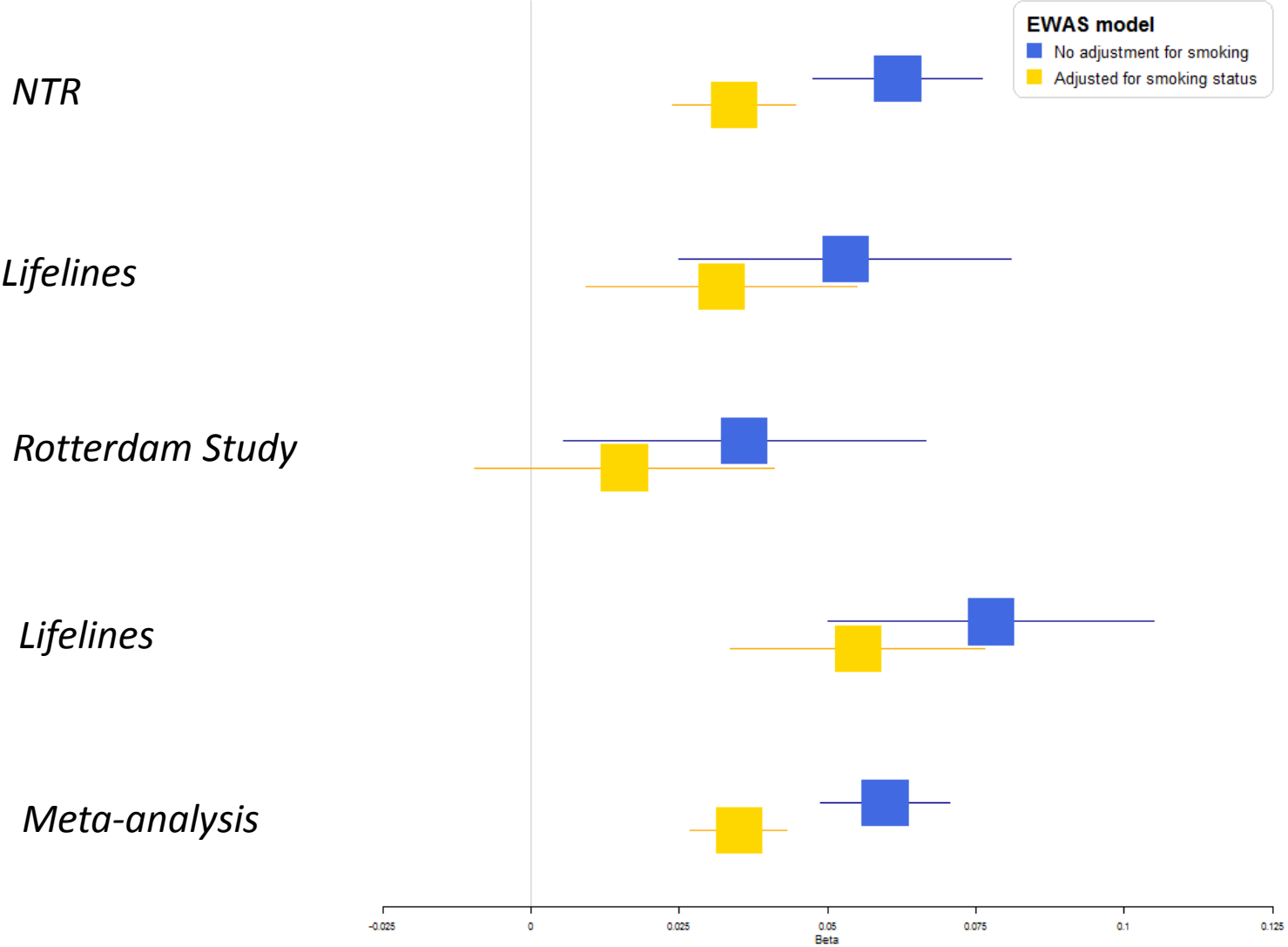
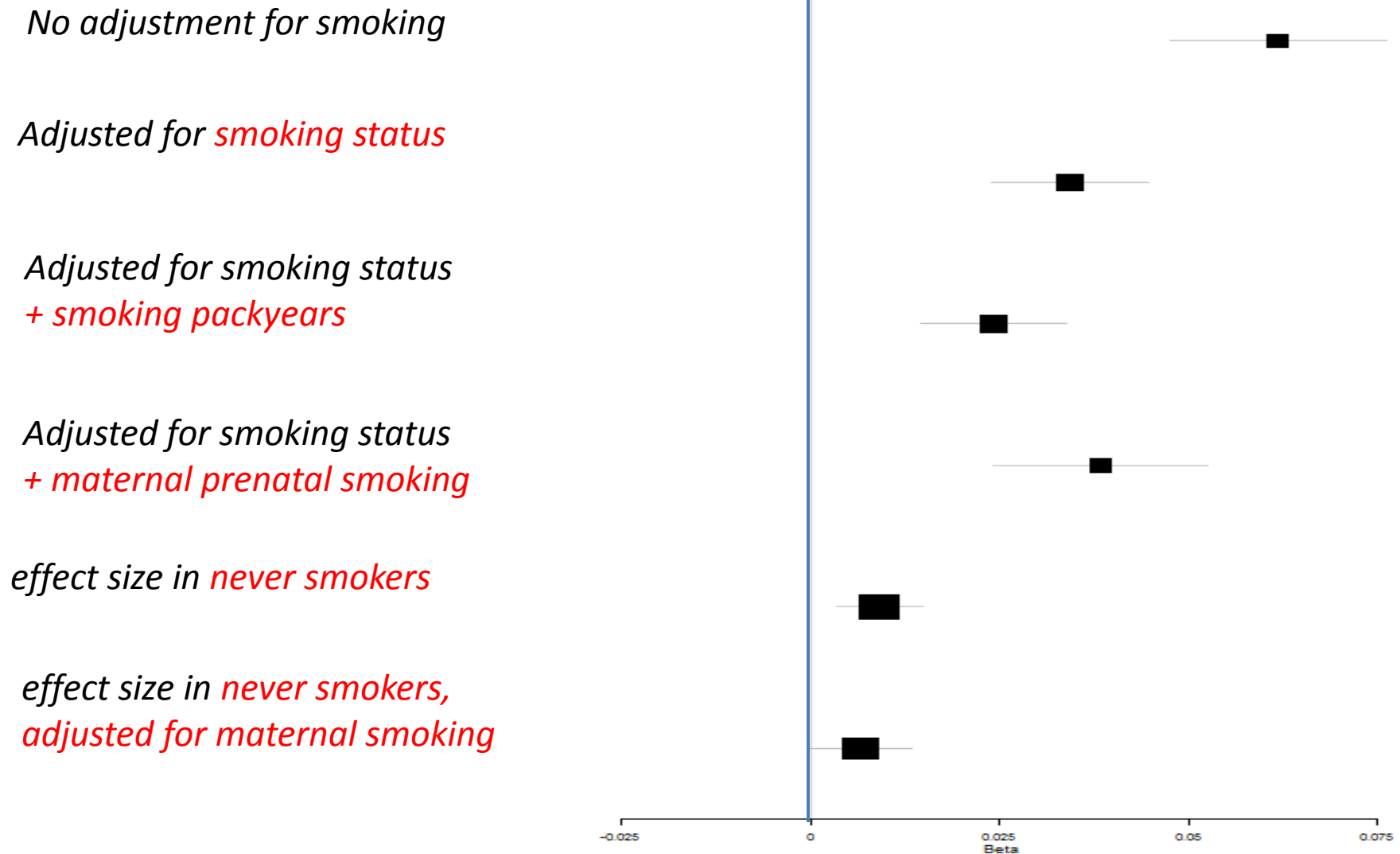# EWAS education, unadjusted for smoking status: 58 significant CpGs

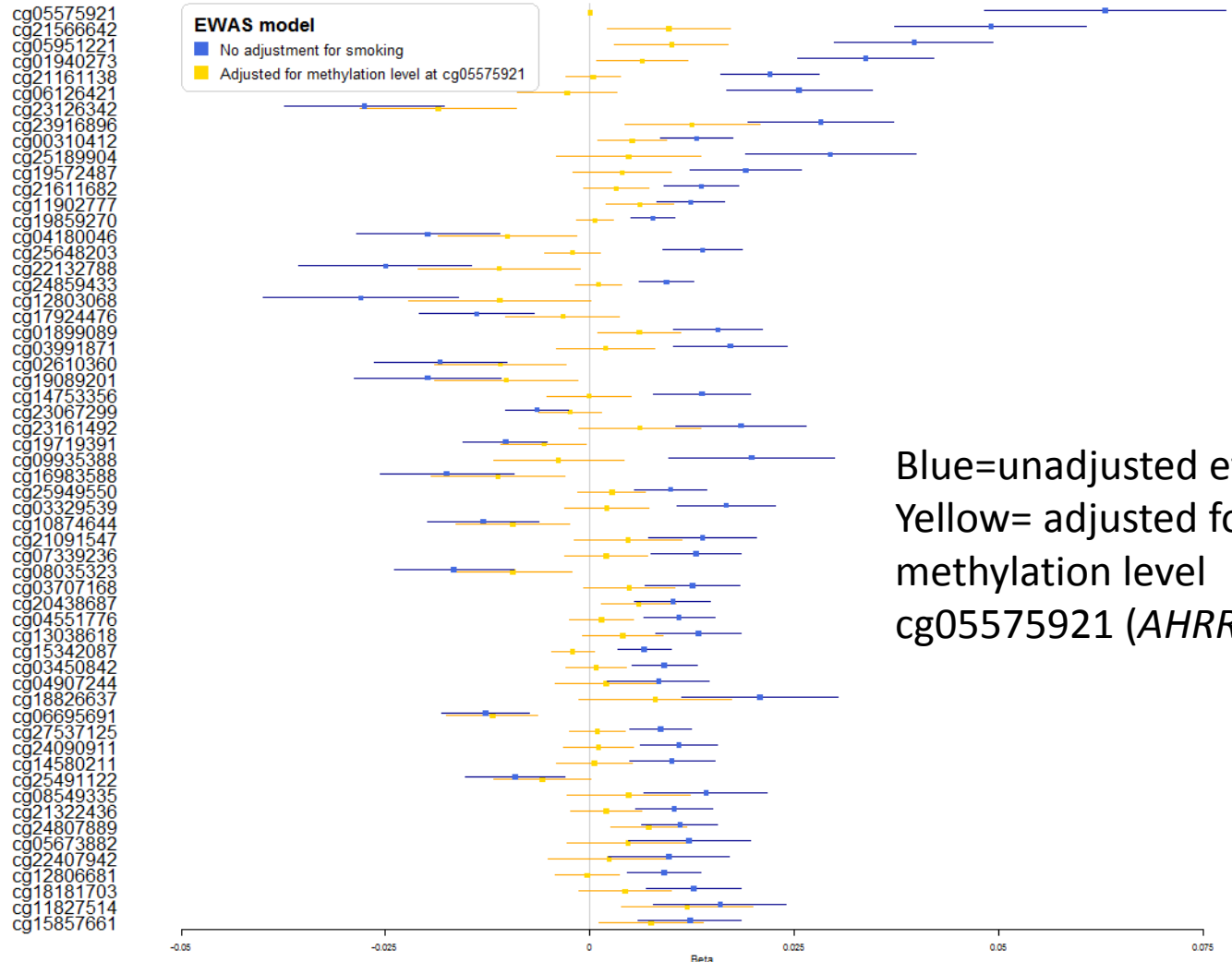# EWAS education, adjusted for smoking status: 11 significant CpGs

AHRR

Effect size: *AHRR* methylation – educational attainment

Effect size: *AHRR* methylation – educational attainment in NTR

# 58 top sites for educational attainment in NTR

Conclusion

- Educational attainment–associated CpGs: very large overlap with the effects of smoking-related exposure

The AHR pathway

- AHR =Aryl-Hydrocarbon Receptor: binds to various environmental toxins (e.g dioxins, benzopyrene, PCBs) and endogenous substrates

- AHR is a transcription factor for:
  - Xenobiotic metabolism genes
  - Developmental genes
  - AHRR

- AHRR: represses the functioning of AHR (negative feedback)

- Increased expression of AHRR following prenatal and lactational dioxin exposure disturbs neural network formation in the developing mouse brain (Kimura et al 2015; 2016)
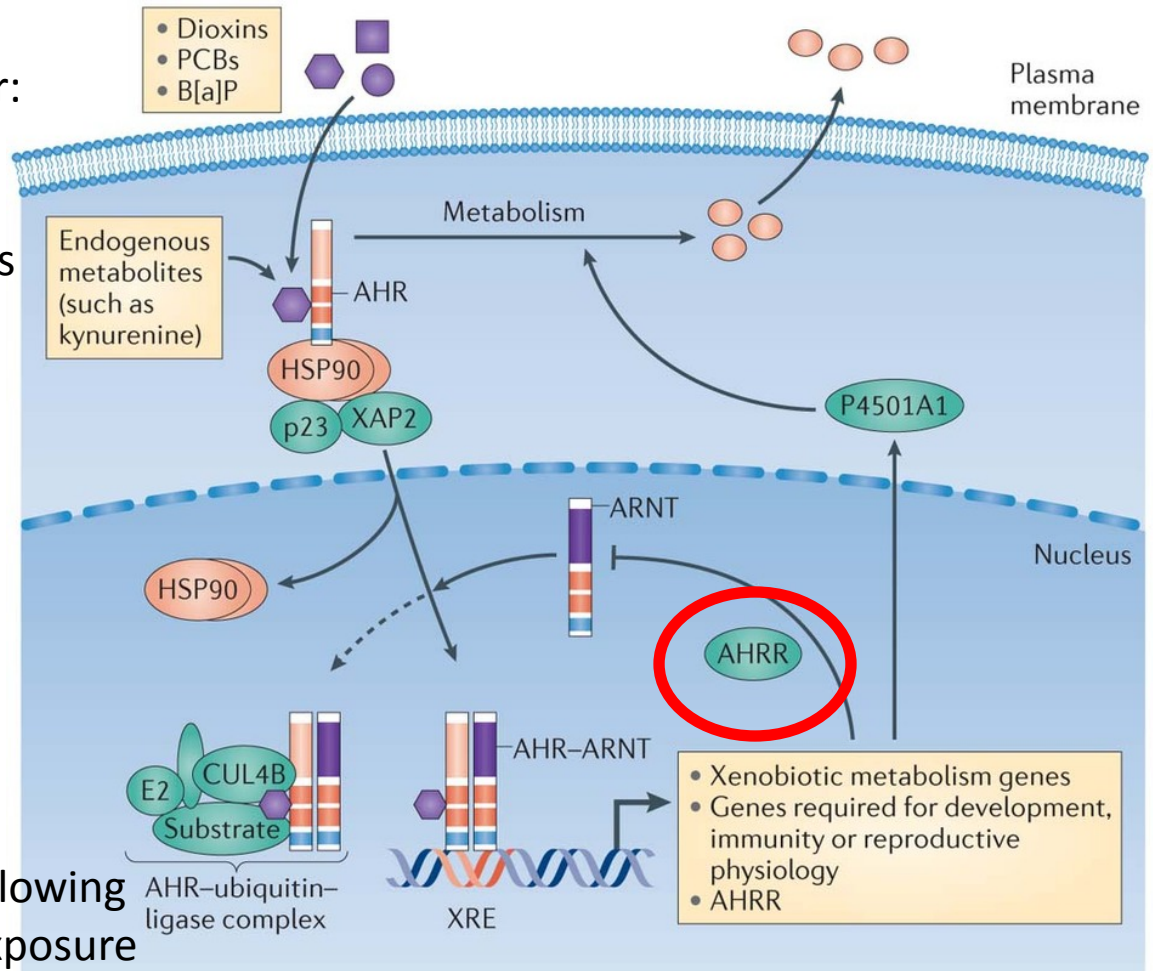
Bernsten et al. bHLH–PAS proteins in cancer. Nature Reviews Cancer 13, 827–841 (2013) doi:10.1038/nrc3621

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