

## Epigenome-wide association study meta-analysis of aggressive behavior

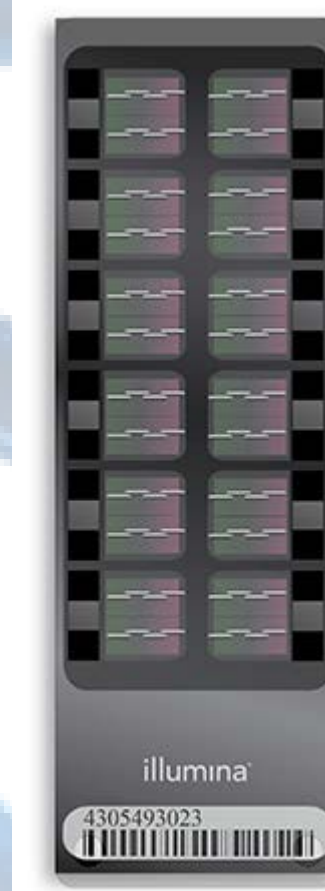
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### Introduction

- Previous small animal and human studies: associations between aggression and loci-specific DNA methylation in brain cells and white blood cells (Provencal *et al* 2012, Provençal *et al* 2013, Guillemin *et al* 2014).
- Previous epigenome-wide association study (EWAS) of aggression in adults from the Netherlands Twin Register (N=2029): no genome-wide significant methylation sites, but significant enrichment of various central nervous system functions among higher-ranking loci (van Dongen *et al* 2015).
- We currently are performing an EWAS meta-analysis.

### EWAS meta-analysis



- **DNA Methylation data:** Illumina Infinium HumanMethylation450 BeadChip
- **Tissue:** whole blood (peripheral or umbilical cord)
- **Standardized analyses in individual cohorts:**
  - EWAS aggressive behavior
  - Association analysis epigenetic clock
- **Summary statistics** + cohort information shared on SFTP server
- **Meta-analysis:** P-value-based fixed effects

Table 1: Cohorts

Study abbreviation	Study	DNA source	Aggression data	N (PWB/UCB)
NTR	Netherlands Twin Register	PWB	ASEBA Adult self-report (ASR) aggression scale	2029
FT12	FinnTwin 12	PWB	Multidimensional Peer Nomination Inventory (MNPI) – aggressive behavior	757
GenR	Generation R	UCB	Child Behavior Checklist (CBCL) 1½ – 5 years Aggressive Behavior scale	806
LLD	Lifelines-DEEP	PWB	“I am known for being short-tempered and irritable” (NEO personality)	683
ALSPAC	Avon Longitudinal Study of Parents and Children	PWB /UCB	SDQ conduct problem scale age 7	865/808
NFBC1966	Northern Finnish Birth Cohort 1966	PWB	“I lose my temper more quickly than most people” (TCI-NS4 Temperament and Character Inventory- Novelty Seeking)	803
NFBC1986	Northern Finnish Birth Cohort 1986	PWB	ASEBA Youth self-report (YSR) aggression scale	593
Gecko	Groningen Expert Center for Kids with Obesity	UCB	SDQ conduct problem scale age 6	198
INMA	Infancia y Medio Ambiente	PWB/UCB	SDQ conduct problem scale age 7	~200/~380
<b>N total</b>				<b>~6249</b>

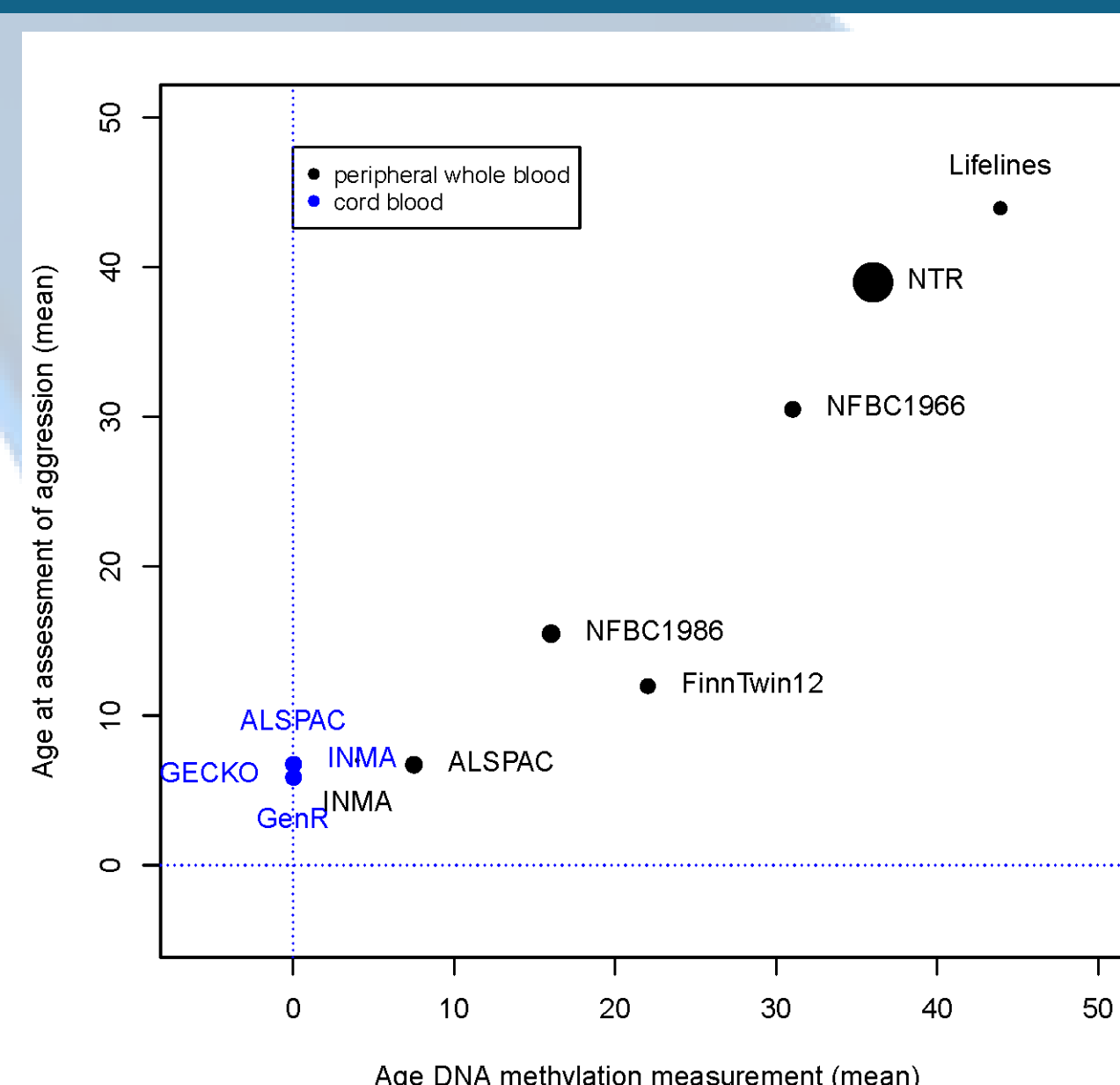
### Results

- **Table1:** Current sample size: ~6249 subjects from 9 cohorts UCB=umbilical cord blood. PWB=Peripheral whole blood.
- **Figure 1:** Aggressive behavior and DNA methylation were assessed across a broad age range (childhood and adulthood)
- **Preliminary EWAS results:** 3 cohorts (NTR, FT12, GenR)
  - N total=3622:
  - Meta-analysis: No genome-wide significant sites
  - 1 significant CpG site in Generation R (*IL1B* gene)

### Ongoing work - 1

- Meta-analysis of all cohorts
- Age-, tissue-, phenotype definition- specific associations
- Gene expression (RNA) analysis
- Correlation methylation blood-brain
- **Suggestions are welcome** if you know any cohorts with methylation data and aggression data!

Figure 1: Age of participants



### Ongoing work - 2

#### Sample collection in monozygotic twins

- Buccal DNA → genome-wide DNA methylation
- Aggression concordant/discordant twins (poster Fiona Hagenbeek)

