Aggression in Children: Unraveling gene-environment interplay to inform Treatment and Intervention strategies

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Epigenome-wide association study meta-analysis of aggressive behavior

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Introduction


• 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

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

N total ~6249

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)

Figure 1: Age of participants

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!

Ongoing work - 2

Sample collection in monozygotic twins

• Buccal DNA → genome-wide DNA methylation

• Aggression concordant/discordant twins (poster Fiona Hagenbeek)

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