Aggression and Metabolomics

Fiona A. Hagenbeek, Harmen H.M. Draisma, Meike Bartels & Dorret I. Boomsma

1. Department of Biological Psychology, VU University, Amsterdam, The Netherlands

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

WP5: Metabolomics & Biomarkers

Background & aim
- Different aggression biomarkers have been investigated, including: Neurotransmitters (serotonin), hormones (testosterone), inflammatory markers (interleukin 6) and lipoproteins (LDL-C).
- The heterogeneous nature of aggression indicates different mechanisms may underlie aggression sub-types and be characterized by different biochemical disturbances.

Aim: Investigate the metabolomic profile of aggression to establish and validate biomarkers to aid the classification of sub-diagnoses.

Data collection (Figure 1)
- ~2000 Dutch children 7-12 years
- DNA (also parents & siblings) → epigenetics (for WP3: Genetic Epidemiology)
- Urine → enzyme immunoassays & LC-MS metabolomics
- Questionnaires → health, wellbeing, Child Behavior Check List (CBCL)

What’s next?
- Establishment and validation of aggression biomarkers (metabolomics + enzyme immunoassays)

Figure 1. Overview data collection ACTION

Practical pilot
- Participants: 6 control children
- Collection: 1-12ml urine

Technical pilot
- Participants: 10 MZ or DZ twin pairs
- Collection: 2x 11-24ml urine - 2x 16 buccal swaps - DNA

Biochemical pilot
- Participants: 50 high aggression MZ twin pairs
- 50 low aggression MZ twin pairs
- Collection: 11-12ml urine - 16 buccal swaps – DNA - Health & wellbeing - CBCL

Main study twins
- Participants: 400 MZ twin pairs discordant aggression
- 200 MZ twin pairs high aggression
- 200 MZ twin pairs low aggression
- Collection: 1-24ml urine
- 16 buccal swaps – DNA
- Health & wellbeing - CBCL

Main study clinical participants
- Participants: 400 children
- referred to clinic with aggression problems
- Collection: 1-24ml urine
- 16 buccal swaps – DNA
- Health & wellbeing - CBCL

Figure 2. Heritability estimates for metabolites under AE model not accounting for sex differences (lipidomics)

The dots indicate the point estimate for the standardized A variance component, the whiskers are the maximum likelihood based 95% confidence intervals for these point estimates. Lipids are ordered by an increasing number of carbon atoms and double bonds in their side chains for each of the lipid classes.

Metabolomics & Heritability
- Metabolomics is the comprehensive analysis of low-molecular weight compounds in biological samples such as cells, body fluids and tissues.

Lipidomics data

Methods
- Participants: 1387 MZ-twins & 1126 DZ-twins
- Measurement: 131 blood plasma lipids from 9 different classes via LC-MS.
- Analysis: AE genetic model (not accounting for sex differences) in OpenMx (Boker et al., 2011).

Results
- Low to moderate (~60%) heritability estimates for blood plasma lipids (Figure 2).
- Triglyceride heritability depends on the number of carbon atoms and double bonds in the fatty acid chains → consistent with pilot study Draisma (2011).

References:

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Contact: f.a.hagenbeek@vu.nl