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

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Metabolomics in Children and Adults

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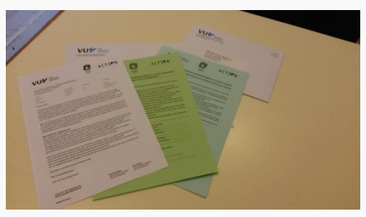
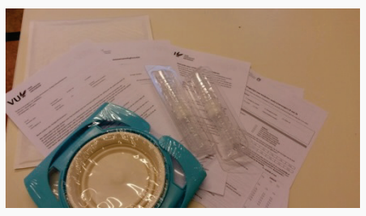
1. Urinary biomarkers & metabolomics in children

- **Introduction:** Research in the biochemical basis of aggressive disorders has focused on putative biomarkers of various classes in isolation. Aggression biochemistry research will benefit from a more holistic approach as provided by metabolomics (Hagenbeek et al. 2016).
  - **Project aim:** By identifying urinary biomarkers of aggression **ACTION** aims to unravel processes and pathways leading to childhood aggression.
- **Methods:** ACTION simultaneously collects DNA material, urine samples, health information & aggression scores in children of 7 to 12 years of age registered with NTR.



Invitation & informed consents



Urine collection material & questionnaires

DNA collection kit

- **Pilot studies:** Prior to start data collection a **Practical Pilot** was conducted to test the urine collection protocol in 6 non-aggressive children. The **Technical Pilot** showed that 14/19 selected biomarkers, a GC-MS biogenic amines platform and a UPLC-MS/MS organic acids platform could be reliably and reproducibly measured in urine samples of 20 non-aggressive twin children.
- **Discovery:** In the **Biochemical Study** urinary biomarkers and metabolites have been measured in 100 cases and 100 controls. By combining a range of univariate and multivariate statistical approaches the Biochemical study aims to discover the metabolite profile associated with childhood aggression.
- **Validation and replication:** Results obtained in the Biochemical Study will be validated and replicated in cohorts of 600 monozygotic twins pairs registered with the NTR and 400 clinical cases (Curium, Leiden). Data collection for both cohorts is still ongoing.

2. Heritability of fasting blood metabolites in adults

- **Introduction:** Blood metabolites reflect individual differences in i.e. gender, age, health, disease, diet, and lifestyle (Chaleckis et al. 2016).
  - **Project aim:** How much of the individual differences in metabolite levels can be explained by genetics?
- **Methods:** Jointly estimate narrow-sense and SNP heritability (h^2; Zaitlen et al. 2013) for fasting blood metabolites of 4 different metabolomics platforms as measured in participants of the Netherlands Twin Register (NTR) using GCTA software (Yang et al. 2011).

Fig. 1 Narrow-sense and SNP heritability of metabolites included on the Brainshake ^{1}H-NMR platform.

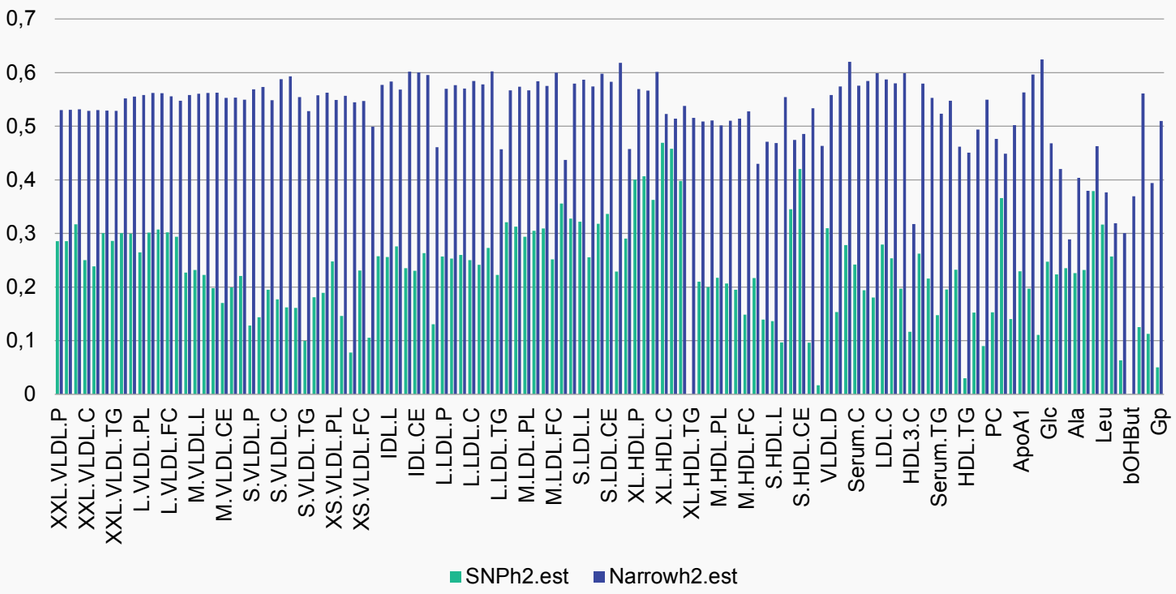
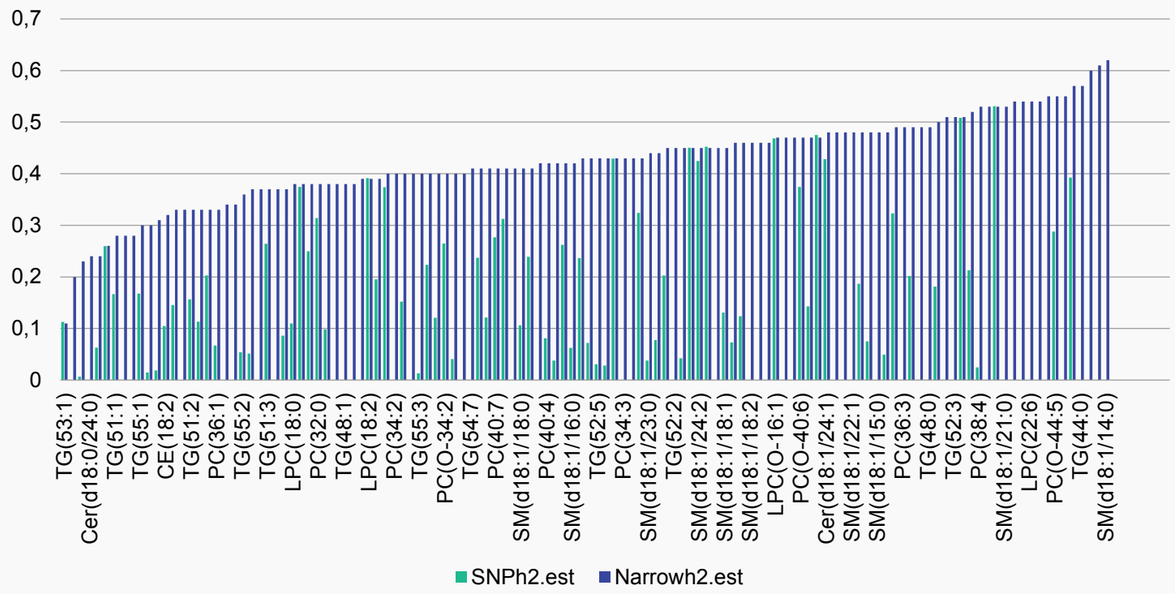


Fig. 2 Narrow-sense and SNP heritability of metabolites included on the UPLC-MS Lipidomics platform.



- **Results:** We observe similar mean narrow-sense and SNP h^2 estimates across platforms, with a large range of h^2 for the individual metabolites per platform (narrow-sense h^2: 0.2-0.9; SNP h^2: 0-.9). Overall, genome-wide SNP h^2 explains 28.1-45.3% of the observed narrow-sense h^2 per platform.
- **Discussion:** Narrow-sense h^2 estimates are similar to those obtained by classic twin-family studies of similar platforms and congruent with Rhee et al. (2016), while common SNPs can account for a large proportion of the narrow-sense h^2, common SNPs alone are insufficient to explain variation in all metabolite levels.
- **Follow-up:** Power is low for 3/4 platforms due to small N; in follow-up analyses we will compensate for power issues by reducing the GRM to include only SNPs previously identified by GWAS efforts.

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