Twin studies of metabolomics traits and metabo-phenotype associations

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Insomnia is one of the most common sleep disorders and Insomnia with short sleep (ISS) is the most biologically severe phenotype of the disorder. Cannabis use is associated with sleep problems, increased rates of insomnia, and decreased sleep duration. Research suggests that the endocannabinoid system is involved in sleep regulation and that various circadian rhythm and sleep related genes are associated with cannabis use. Furthermore, a small collection of studies has shown that early cannabis use can predict later sleep outcomes. In a population-based twin cohort of 1882 twins (56% female, mean age = 22.99) we explored the genetic/environmental etiology and the relationship between onset of regular cannabis use and insomnia-related outcomes via multivariate twin models. Controlling for current depression symptoms, prior diagnosis of an anxiety or depression disorder, and sex, adult twins who reported early onset for regular cannabis use were significantly more likely to have insomnia ($\beta = 0.07$, $p = 0.024$) and ISS ($\beta = 0.08$, $p = 0.003$). We found significant genetic contributions for the onset of regular cannabis use ($a^2 = 76\%$, $p < 0.001$), insomnia ($a^2 = 44\%$, $p < 0.001$) and ISS ($a^2 = 37\%$, $p < 0.001$). We found evidence of a significant genetic correlation between onset of regular use and both insomnia ($rA = 0.20$, $p = 0.047$) and ISS ($rA = 0.25$, $p = 0.008$), but failed to find environmental associations between these traits. Ultimately, we found evidence of significant overlapping additive genetic influences between onset of regular cannabis use and insomnia related outcomes, implying possible common genetic liabilities and a possible pleiotropic influence of genes on both traits.

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High-throughput technologies enable metabolite profiling, allowing for a holistic approach to biomarker discovery. Such approaches may lead to a better understanding of behavioral and psychiatric phenotypes. Metabolic profiles represent a functional read-out of the physiological state of the human body, referred to as *metabotype*. The association of metabotypes with phenotypes and with genetic variation can suggest new causal pathways, whereas genetic variants that associate with changes in the homeostasis of metabolites as a consequence of disease can inform on the biochemical context of such changes.

For metabolic profiling, several platforms exist that can be considered as combinations of sample work-up, chemical separation and detection technique (Mass Spectrometry or Nuclear Magnetic Resonance spectroscopy) and allow for reporting on a (specific) set of molecules. Combining platforms will optimize biochemical coverage. For adults in the Netherlands Twin Register (NTR) we measured metabotypes in blood across four platforms. For children, blood sampling was replaced by less invasive urine sampling and three platforms were used.

The metabolite database for 6585 adults and 1382 children with additional SNP-genotyping and extensive phenotyping allows to a) establish metabotypes—phenotypes association for aggression, externalizing problems, migraine, depression, cognition, diabetes, ageing and other traits; b) estimate by employing the classical twin design total heritability and SNP data to identify associations with genetic variants for the purpose of increasing the understanding of pathways that influence the metabotypes; c) establish whether such genetic variation associates to a diversity of clinical endpoints and phenotypes.

Genetic driven markers of Th2-type inflammation explain the link between asthma and exhaled nitric oxide in children

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Background: Asthma is the most common childhood disease which is obstructive and often inflammatory. Several phenotypes like exhaled nitric oxide (FE_{NO}), serum immunoglobulin E (IgE) and blood eosinophil count underlie the clinical expression of asthma.
Aim: Our aim is to disentangle the covariance between asthma and FE_{NO} into genetic and environmental contributions that can be accounted for Th2-inflammation using prominent biomarkers of IgE and counted blood eosinophils.
Methods: This is a population-based, cross-sectional twin study. Data were available in 612 individual twins including asthma status, FE_{NO}-values, IgE, and blood eosinophil blood count. Genetic model-fitting was applied for best fitting model. Multivariate structural equation modeling was utilized for separating the covariance between asthma and FE_{NO} into genetic and/or environmental effects taking IgE and eosinophils into account while controlling for inhaled corticosteroid use and re-weighted by sampling probability.
Results: We report that the majority, 80%, of the total variance in the phenotypic correlation of 0.18 (0.04–0.32) can be attributable to genetic effects due to IgE and eosinophils.
Discussion: As new phenotypes for asthma are discovered, twin studies provide a first effort in determining the contribution of genetic and environmental factors to these traits. Differentiating and diagnosing asthma with use of FE_{NO} in children should be done with caution, due to genetic effects and individual variations linked to influencing factors of IgE and eosinophils.
Conclusion: Th2-inflammatory markers of IgE and eosinophils are part of the same underlying construct which make asthma and FE_{NO} associate and this can mainly be attributable to genetic factors.

The nature and nurture of individual differences in internalizing and externalizing behavior problems: a nuclear twin family study

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Internalizing (INT) and externalizing (EXT) problem behavior is an established risk factor for many unpleasant outcomes and psychopathology in adulthood. Understanding the interplay between genes and environment has therefore several implications for practice. Among genetic studies on problem behavior, heritability estimates differ widely. Most research only uses twin data and therefore underlies certain limitations which could lead to biases. Our study is the first investigating genetic influences on INT and EXT by extending the Classical Twin Design to a Nuclear Twin Family Design. Self-reported INT and EXT of 3087 twins, a sibling, and their