and covariance of indirect maternal and direct offspring genetic effects. We apply DINGO to publicly available summary results statistics from a recent GWAS of birth weight from deCODE and the Early Growth Genetics (EGG) consortium. Our method dramatically increases the number of robustly associated genetic loci for birthweight and implicates new biological pathways involving DNA methylation and epigenetic modifications. Finally, we illustrate how conditional estimates of indirect genetic effects provided by DINGO can be used downstream in informative two sample Mendelian randomization analyses to estimate, for example, the causal effect of adverse maternally mediated intrauterine exposures on offspring health.

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E3 Ubiquitin-Protein Ligase Hakai (CBLL1) Gene, is Hypomethylated and Correlates with Cortical Thickness in Transgender Men Before Gender Hormone Affirming Treatment

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Keywords: CBLL1, cortical thickness, DNA methylation, gender dysphoria, MRI

Gender identity refers to the psychological experience of being a man, a woman or other condition. Generally, it is congruent with the assigned sex at birth; however, for some people, it is not. If the incongruity is distressing, it is defined as gender dysphoria (GD) according to the DSM-5 (American Psychiatric Association, 2013). Here, we measured DNA methylation (Illumina Infinium Human Methylation array), and reported its correlation with cortical thickness (CTh) in 22 transgender men (TM) experiencing GD versus 25 cisgender men (CM) and 28 cisgender women (CW). Main findings: firstly, TM showed differences in the methylation in CBLL1 and DLG1 genes that correlated with global and left hemisphere CTh. Both genes were hypomethylated in TM with respect to cisgender groups. Secondly, when early and late onset of GD were considered, late onset TM showed thicker cortex than early onset TM, and the cisgender groups. Thirdly, early onset TM showed a positive correlation between CBLL1 and several cortical regions. Methylation of CBLL1 positively correlated with CTh in the frontal (left caudal middle frontal), temporal (right inferior temporal, left fusiform) and parietal cortices (left supramarginal and right paracentral). This is the first study that relates CBLL1 methylation with cortical thickness and gender variants.

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The Heritability of Living Area

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Keywords: heritability, living area, MIDUS twins, Wisconsin Longitudenal

It is known that living in an urban versus rural area is associated with individual attitudes and preferences. Using the Swedish Twin sample (292 MZ and 537 DZ twins) provided by ICSPR, we investigated whether the type of living area has to some extent a heritable component. In this sample, living is is encoded as 1) rural area, 2) smaller community, 3) town, and 4) large city. We did run an ACE model in umx; after reducing the model, only an AE model remained with a heritability of 0.52; MZ twin correlation is 0.49 and DZ correlation is 0.29. These results indicate that living area seems to have a substantial heritable component. We further investigated on basis of the Wisconsin Longitudinal Study (n = 5,693) whether any of the polygenic scores provided by this data set are associated with the size of the living area (ranging from lower as 50 to more than 600,000). We found that the particularly the PGS of mathematical aptitude, cognitive performance, education, and taking part in religious communities are significantly positively whereas depression, narcissism, delayed discounting and neuroticism are significantly negatively associated with the size of the living area. The frequently claimed assumption, that people adopt their attitude according to their living area thus seems to be only "half the truth". Rather our data suggest that living area is in part the result of a genetic predisposition and polygenic scores may deliver a glance of this association in detail.

The Validity of Self-Rated Health for Mortality: Family-Background and Genetic Precursors in IGEMS

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Keywords: validity of self-rated health; twins

Self-rated health (SRH) has been shown to be predictive of morbidity and mortality, above and beyond socio-demographic characters and objective, clinical ratings of health. Two research streams suggest that this relationship could have bases in both: a) family background and b) genetics. First, childhood health and family environment are known to have long-term implications for health and wellbeing. Second, SRH has been shown to be highly heritable ($h2 \leq 0.60$). These two sets of findings argue that at least some of the relationship

between self-rated health and mortality may have roots in childhood and inherited genes. This study uses twin-differencing approaches (MZ/DZ) and controls for genetics using MZ twin-pairs and finds that a substantial portion of the SRH/mortality gradient is due to family background. While genetics are further implicated in this relationship, they do not fully account for it, suggesting the continued utility of SRH for population-based health research.
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Multi-polygenic Prediction of Frailty

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Keywords: GWAS-PGS, Frailty, Ageing

Frailty is a complex trait. Twin studies and a recent Genome Wide Association Study have demonstrated a strong genetic basis of frailty but there remains a lack of genetic studies exploring Frailty. Previous work has shown that a single polygenic predictor – represented by a Frailty polygenic score—can predict Frailty in independent samples within the United Kingdom. We extended on this work, using a multi-polygenic score (MPS) approach to increase predictive power. Predictor variables, multiple polygenic scores, were based on statistical power with the outcome of Frailty (measured via the Frailty Index). 26 Polygenic scores were modelled in regularised net elastic regression models, with repeated cross-validation, to estimate the joint prediction of the polygenic scores and order the predictions by their contributing strength to Frailty in 5959 individuals in the English Longitudinal Study of Ageing aged 65 + . Results showed that the MPS model predicted 1.2% more variance than the strongest PGS single-model prediction model for Frailty—MPS explained 3.6% of variance and single-score prediction explained 2.4% of variance. With the strongest prediction coming from PGS for Chronic Pain, Depressive Symptoms, Parental Death, Waist Circumference and Educational Attainment. Results from the predictors that remained in the final model were then validated with PGS scores made from the same GWAS summary statistics in 1005 individuals the Lothian Birth Cohort 1936 cohort. This MPS approach provides new evidence for the genetic contributions to frailty in later life and sheds light on the complex structure of the Frailty Index measurement.
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Uncovering the Multivariate Genetic Architecture of Frailty Using Genomic Structural Equation Modelling

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Keywords: Frailty, aging, genomic SEM, multivariate GWAS, shared genetics

Frailty is a multifactorial syndrome that is associated with poor health outcomes and earlier mortality in older adults. Clinically, it is often measured using the Frailty Index, which creates a frailty score based on the number of deficits that co-occur within an individual. We currently lack a genetic phenotype for frailty that accounts for the complex relationships between the numerous traits that define it. This undermines our ability to assess how frailty might interact on a genetic level with other complex traits associated with aging, such as dementia. We used Genomic Structural Equation Modelling (Genomic SEM) to define the shared and trait-specific genetic architecture for 30 traits from the Frailty Index using well-powered GWAS summary statistics for each trait. We found that the genetic overlap between these traits can be captured by 6 latent factors, providing novel insights into distinct mechanistic groupings that underlie frailty pathogenesis. These latent genomic factors included those defined by a broad-spectrum of traits linked to generally poor health and unhealthy lifestyle behaviors, as well as factors defined by more specific groupings of items such as cardiometabolic and psychiatric indicators. We will apply Stratified Genomic SEM to assess whether the genetic signal for these genomic frailty factors is enriched for functional annotations (i.e., groupings of genetic variants) that index different brain regions and cell types associated with cognitive aging. Our findings reflect the first multivariate genomic analyses of frailty and provide a framework for analyzing the shared and unique pathways that commonly occur during aging.
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Pathways From Parental Predisposing Factors to Child Attention Deficit Hyperactivity Disorder Traits via DNA Methylation—A Genetically Informed Mediation Analysis

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