

Genome-wide association study of a frailty Index in UK Biobank and TwinGene

Juulia Jylhävä, Karolinska Institutet, Department of Medical Epidemiology and Biostatistics; Luke Pilling, University of Exeter Medical School, Epidemiology and Public Health Group; Dylan Williams, Karolinska Institutet, Department of Medical Epidemiology and Biostatistics; Yi Lu, Karolinska Institutet, Department of Medical Epidemiology and Biostatistics; Nancy L Pedersen, Karolinska Institutet, Department of Medical Epidemiology and Biostatistics; David Melzer, University of Exeter Medical School, Epidemiology and Public Health Group; Janice Atkins, University of Exeter Medical School, Epidemiology and Public Health Group

Frailty is a common geriatric syndrome and a strong predictor of adverse outcomes, such as disability and mortality. The mechanisms of frailty are multifactorial and not well understood, but the heritability from twin studies ranges between 19 and 43%. This study was undertaken to analyze the genomic underpinnings of frailty.

We performed a genome-wide association study of the frailty index (FI) based on participants of European descent from the UK Biobank ($n = 164,610$, aged 60–70 years) and replicated the top hits using a genetic risk score for FI (GRS_{FI}) in the Swedish TwinGene study ($n = 10,616$). We also associated the FI with DNA methylation levels in those CpG sites that are genetically regulated i.e., associated with methylation quantitative trait loci (mQTL) in the Swedish Adoption/Twin Study of Aging (SATSA).

We identified 26 independent genetic signals (6150 variants total) at 24 loci associated with the FI ($p < 5 \times 10^{-8}$), including a large peak on chromosome 6, in the HLA region. Several of these signals have previously been associated cardiovascular disease, intelligence, and educational attainment, but six of the signals were novel i.e., unique to FI. The SNP-based heritability (h^2) of the FI was estimated at 0.14 ($SE = 0.0057$). The GRS_{FI} was significantly associated with FI in TwinGene ($\beta = 0.11$, 95% CI 0.02–0.20, $p = 0.018$). Nine mQTL-regulated CpG sites showed an association ($p < 0.05$) with the FI in SATSA, all but one mapping to HLA region.

Variants in the HLA region appear to be crucial for frailty. Some of the variants may express their effects through DNA methylation.

Heritability of subjective cognitive decline in older Australian twins

Vibeke Catts, Centre for Healthy Brain Ageing, University of New South Wales; Anbupalam Thalamuthu, Centre for Healthy Brain Ageing, University of New South Wales; Teresa Lee, Centre for Healthy Brain Ageing, University of New South Wales; John Crawford, Centre for Healthy Brain Ageing, University of New South Wales; Perminder Sachdev, Centre for Healthy Brain Ageing, University of New South Wales

Subjective cognitive decline (SCD) has been promoted as a preclinical stage of dementia, being pre-mild cognitive impairment (MCI). However, little or no heritability for SCD, derived from the TELE cognition screen, was found in the Swedish HARMONY twin study.

We examined the heritability of SCD in the Older Australian Twins Study. Participants completed the self-report Memory Complaint Questionnaire (MAC-Q). In parallel, participant-nominated informants completed the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE, short version). Inclusion criteria: twin pairs > 65 years. Exclusion criteria: current or recent (< 1 year) active cancer, self-report history of head trauma, diagnosis of Parkinson's disease or dementia, expert consensus diagnosis of MCI or dementia based on neuropsychological assessment.

The contributing sample consisted of 77 MZ and 57 DZ twin pairs with an average age of 71 years (range 65–90 years). The average years of education were 11 years (range: 6–22 years) and 65% of the sample were female. Genetic heritability for MACQ scores ($n = 134$ twin pairs) estimated under AE model was found to be $h^2 = 0.59$ (95% CI 0.44–0.70) and no significant effects observed for the covariates age and sex, but education had a significant effect (p -value = 0.02). The informant assessment of cognitive decline ($n = 133$ twin pairs) had no suggestion of genetic heritability ($h^2 = 0.13$, 95% CI 0–0.34).

Having established moderate genetic heritability with data from the MACQ, future work will examine heritability of SCD determined by other scales as well as the contribution of influencing factors, such as personality traits.

You are only as old as you feel

Catalina Zavala, University of Southern California; Thalida Arpawong, University of Southern California; Carol Prescott, University of Southern California

As we grow older, the experience of aging is often increasingly subjective. Assessing self-rated health (SRH) and subjective age provides intuitive, albeit enigmatic, input regarding how an individual is feeling about their overall health and aging. Longitudinal studies suggest that both measures predict mortality in older adults. To what extent are SRH and subjective age tapping into the same underlying mechanisms? We evaluated biometric twin models to determine the degree to which SRH and subjective age may have common genetic and environmental sources of covariation. Analyses are based on 1400 twin pairs from the Project Talent Twin and Sibling (PTTS) Study, including 710 pairs with complete data for the full bivariate model (MZ = 280; DZ = 430). Participants were, on average, 70 years old when interviewed in 2014. Individuals reporting their SRH as 'good' or 'very good' also tended to endorse feeling younger than their age ($r = 0.52$). Univariate twin modeling indicated that about a third of the variance in SRH was attributed to additive (A) genetic influences, with little familial (C) environmental influences, and remaining variance attributed to individual (E) environmental influences. Similar ACE results were found for the univariate twin model for subjective age. The bivariate twin model attributed covariation between SRH and subjective age to the genetic (A) component, with much of the remaining residual variance in subjective age due to (E) environment. Current results suggest (1) common genes may be responsible for associations between SRH and subjective age and (2) each measure retained unique variation due to individual-specific environmental influences.

Does genetic risk of insomnia influence aggression?

Reece Lavender, Queensland Institute of Medical Research & University of New England; Andrea Allegrini, King's College London; Koen Bolhuis, Erasmus University Rotterdam; Fiona Hagenbeek, Vrije Universiteit Amsterdam; Teemu Palviainen, Institute for Molecular Medicine Finland; Meike Bartels, Vrije Universiteit Amsterdam; Dorret Boomsma, Vrije Universiteit Amsterdam; Iryna Fedko, Vrije Universiteit Amsterdam; Jouke-Jan Hottenga, Vrije Universiteit Amsterdam; Jaakko Kaprio, Institute for Molecular Medicine Finland, University of Helsinki; Maria Elisabeth Koopman-Verhoeff, Erasmus University Rotterdam; Tellervo Korhonen, Institute for Molecular Medicine Finland, University of Helsinki; Sander Lamballais, Erasmus University

Rotterdam; Lannie Ligthart, Vrije Universiteit Amsterdam; Kaili Rimfeld, King's College London; Henning Tiemeier, Erasmus University Rotterdam; Toos van Beijsterveldt, Vrije Universiteit Amsterdam; Eero Vuoksimaa, Institute for Molecular Medicine Finland, University of Helsinki; Alyce Whipp, Institute for Molecular Medicine Finland, University of Helsinki; Nicholas Martin, QIMR Berghofer Medical Research Institute; Lucía Colodro-Conde, QIMR Berghofer Medical Research Institute; Sarah Medland, QIMR Berghofer Medical Research Institute

Insomnia is linked to emotional and behavioral difficulties particularly in young people. Insufficient sleep, overtiredness and insomnia have been found to predict externalizing behaviors including aggression. Whilst associations between sleep quality and emotional and behavioral difficulties have been found in young people, the extent to which genetic liability for insomnia can predict aggression is unknown.

This is a collaborative project involving ~ 14,000 participants across 5 cohorts from the ACTION Consortium. Using data collected from QIMR participants we assessed insomnia and aggression from the Buss-Perry Aggression Scale, we replicated our findings with data from four additional cohorts from Finland, The Netherlands, and the UK. We used polygenic risk scores from the Jansen et al. (2018) GWAS of insomnia to test whether genetic risk for insomnia predicted aggression or any of its components. Data were analysed using linear mixed models including the effects of age, sex, their interaction, genetic principal components, and a genetic relationship matrix to account for relatedness.

Insomnia polygenic risk scores predicted aggression traits in the QIMR sample (total aggression score, physical aggression, anger, hostility; but not verbal aggression). The results were replicated at a nominal level within all cohorts.

These results suggest that genetic vulnerability to insomnia may be a useful predictor of aggression. Prevention and early treatment interventions remain important to treat the behavioral manifestations arising from insomnia, such as emotion dysregulation and distress intolerance, which are associated with aggressive behaviors.

Testing structural models of psychopathology at the genomic level

Irwin Waldman, Emory University

Recent Genome-wide Association Studies (GWAS) have revealed hundreds of genetic loci that underlie major psychiatric disorders. Post-GWAS analyses have also revealed substantial genetic correlations among various psychiatric disorders. This suggests these disorders share common genetic causes, implying the presence of a higher-order structure of psychopathology, although the exact nature of this structure is unknown. Herein we test multiple structural models of psychopathology at the genomic level using the genetic correlations among fourteen psychiatric disorders and related traits. We show that the best-fitting model contains three correlated factors, Externalizing, Internalizing, and Thought Problems—and an uncorrelated Neurodevelopmental Disorders factor, but no General Psychopathology factor. These factors show distinct patterns of genetic correlations with relevant traits and account for substantial genetic variance in their constituent disorders. These findings also suggest a similar structure of psychopathology at the genomic and phenotypic levels. Such higher-order psychopathology factors are potentially better targets for GWAS than individual disorders and are more predictive of external criterion variables.

Dissecting the genetic architecture of chronic pain using CTG-VL: complex-traits genetics virtual lab

Mischa Lundberg, University of Queensland Diamantina Institute; Adrian Campos, QIMR Berghofer Medical Research Institute; Miguel Renteria, QIMR Berghofer Medical Research Institute; Trung Ngo, University of Queensland Diamantina Institute; Gabriel Cuellar Partida, University of Queensland Diamantina Institute

Chronic pain (CP) affects 30–50% of the population and is one of the leading causes of disability worldwide. Observational studies show that CP increases the risk of opioid use disorder, illicit drug use and depression. Despite these major public health issues, research into the underlying genetics of CP is limited compared with other common chronic disorders.

Here, we present a genome-wide association study (GWAS) of CP using UK Biobank data (controls $N = 78,691$; cases $N = 209,426$). CP was modeled as a binary trait and assessed by participants' survey responses to pain occurring in any body region for ≥ 3 months. Two genome-wide significant associations ($P < 5 \times 10^{-8}$) were identified which mapped to genes ADAMTS6 (a risk locus for inguinal hernia) and LEMD2 (required for embryonic development).

Furthermore, we present CTG-VL (<https://genoma.io>) which is a new freely available online platform that integrates an extensive suite of post-GWAS analysis tools and results from > 1500 complex traits. Genetic correlation analyses using the platform revealed a strong association of CP with smoking ($rG = 0.4264$, $P = 2.6688 \times 10^{-24}$) and other compulsive behaviors or addictions to any substances ($rG = 0.2928$, $P = 0.0024$).

In conclusion, we identified two novel genome-wide significant associations, ADAMTS6 and LEMD2. A gene-based test ($P < 5 \times 10^{-5}$) also revealed genes in the 17q21.31 locus (DCAKD and NMT1) associated with CP using the CTG-VL.

Children's emotionality in context: family to school spillover

Elizabeth Shewark, Pennsylvania State University; Jenae Neiderhiser, Pennsylvania State University; Jody Ganiban, George Washington University; Daniel Shaw, University of Pittsburgh; David Reiss, Yale University; Misaki Natsuaki, University of California, Riverside; Leslie Leve, University of Oregon

Parent–child and teacher–child relationships are critical for child behavioral adjustment, yet we know little about the role of the child and how their relationships with parents influence relationships with teachers. We examined how child's inherited negative emotionality may evoke close or conflictual relationships with their parents (via evocative rGE), and how this association impacted the child's later relationships with their teachers.

Using data from the longitudinal adoption Early Growth and Development Study ($N = 561$) we examined how genetic influences on child sadness and anger (inferred from latent factors of birth parents' negative emotionality and behavioral activation), and parent–child relationships (parent–child closeness and conflict at age 6) affect teacher–child closeness and conflict (age 7).

Results of the structural equation model. Mother–child closeness was associated with low conflict between children and their teacher a year later ($b = -0.20$, $p < 0.05$). Of interest, inherited child anger played a significant role in impairing the child's closeness to mother ($b = -0.02$, $p < 0.05$) but not to father. In comparison, inherited child anger evoked more conflictual relationships with mother ($b = 0.03$, $p < 0.01$) and father ($b = 0.02$, $p < 0.01$). Revealed here is an unanticipated role of children's ability to regulate their own anger