ABSTRACT BOOK 2025

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[P1] MULTIMODAL HAZARD SCORE INTEGRATES GENETICS, METABOLOMICS, AND MENTAL HEALTH-RELATED RISK FACTORS TO IMPROVE CARDIOVASCULAR DISEASE RISK PREDICTION

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Background

Severe mental disorders (SMDs), including schizophrenia, bipolar disorder, and major depression are associated with markedly reduced life expectancy, compared to the general population, largely driven by elevated risk of cardiovascular disease (CVD). Mounting evidence indicates the role of metabolic dysregulation in SMDs, consistent with abnormalities in lipid, glucose, and inflammatory profiles. Advances in high-throughput plasma metabolomics technologies, such as nuclear magnetic resonance (NMR) spectroscopy, now enable robust quantification of key metabolic biomarkers. While existing CVD risk models focus on single modalities, multimodal hazard scores (MHS) have potential to improve early detection of CVD, through integration of genetic, metabolic, and clinical risk factors, including prior SMD diagnosis and antipsychotic medication use, which may lead to tailored treatment and lifestyle interventions.

Methods

We developed a polygenic hazard score (PHS) to predict age of onset of coronary artery disease (CAD) using SNPs ($p<10^{-5}$) derived from the latest CARDIoGRAMplusC4D genome-wide association study (181,522 cases; 984,168 controls). The PHS was trained and tested (80/20%) in the UK Biobank (UKB: 41,918 CAD cases; 295,028 CAD-free controls) with genotype data, sex, and the first ten genetic principal components, using Cox proportional hazard models. External validation was performed in the independent Hordaland Health Studies (HUSK) cohort (6,249 CAD cases; 26,578 controls). We further assessed 15-year CAD risk in a UKB test set (1,391 CAD cases; 27,527 CAD-free controls), by incorporating SMD diagnosis, atypical antipsychotic use, and other risk factors from an established clinical algorithm (QRISK3). We developed a biomarker hazard score (BHS) using 249 NMR-derived plasma metabolites. We then evaluated the predictive improvement of a MHS, which integrated the PHS with the clinical risk score (QRISK3), and the BHS.

Results

The PHS, comprising 835 SNPs, was a strong predictor of CAD age of onset in the HUSK validation cohort (Hazard ratios [HR] for 80th vs. 20th percentile = 3.6; 95% confidence intervals [CIs]: 3.3–4.0). When predicting 15-year CAD risk in the UKB test set, QRISK3 alone yielded a $HR_{80}/_{20}$ of 9.3 (95% CIs: 7.4–11.7), which increased to 14.7 (95% CIs: 11.2–19.3), when combined with the PHS. A BHS, consisting of 75 plasma metabolites, yielded a $HR_{80}/_{20}$ of 16.9 95% CIs (12.3–23.2), which improved to 23.6 (95% CIs: 16.9–32.9), when combined with the PHS and QRISK3. Overall, the MHS model (PHS + QRISK3 + BHS)

demonstrated improved time-dependent risk stratification for CAD, compared to single modalities alone.

Discussion

We present the first polygenic hazard model for CAD age of onset, validated in an independent cohort. Our findings demonstrate that multimodal integration of genetic, metabolic, and clinical risk factors, including prior SMDs diagnoses, as well as psychotropic medication use, further enhances CVD risk stratification. The MHS enable identification of high risk individuals which may inform personalized prevention strategies. Future work will focus on further validation in patients with SMDs and development of decision-support tools for psychiatric care settings.

[P2] GENOMIC AND PROTEOMIC SIGNATURES HIGHLIGHT DIVERSE PATHWAYS BETWEEN OBESITY AND TYPE-2 DIABETES

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Obesity is a significant risk factor for Type 2 diabetes (T2D), a disease that affects about 10% of the global population. Obesity is also a heterogeneous condition, and the molecular mechanisms linking it to T2D are not yet fully understood. The aim of this study was to elucidate causal pathways between obesity and T2D and to characterize their molecular signatures using an innovative multi-omics approach, thereby highlighting why some, but not all, obese individuals develop T2D. We identified 513 independent obesity-associated SNPs by meta-analysing genome-wide association study data from FinnGen and GIANT (N=699,431). Clustering of Mendelian randomization (MR) estimates, computed using T2D data from DIAGRAM (74,124 cases and 824,006 controls), identified four clusters of SNPs. These clusters, all associated with increased body mass index (BMI), showed differential effects on T2D risk, ranging from harmful to protective. Cluster-specific MR analyses identified 212, out of 2922 protein measurements from the UK Biobank (N=54,219), to be causally affected by any of the clusters. Among these, eight proteins were significantly associated with T2D in downstream MR analyses, representing potential pathways responsible for the heterogeneous link between obesity and T2D. These proteins include, for example, SNAP25, PAM, and FSTL3, suggesting that one of the underlying molecular pathways is tightly linked to insulin synthesis and secretion.

[P3] GENETIC ARCHITECTURE OF ANOREXIA NERVOSA SEVERITY: A CROSS-NATIONAL REGISTER-BASED STUDY

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Background

Anorexia nervosa (AN) is a complex psychiatric disorder with one of the highest mortality rates among psychiatric illnesses. The most recent and largest genome-wide association study (GWAS) of AN has identified two new risk loci and six previously indicated loci, suggesting the complex aetiology of AN. However, the unique genetic architecture underlying severe AN remains unexplored. Binary case-control studies by design may have a limited ability to differentiate individuals with mild symptoms from those with severe symptoms. Meanwhile, GWAS of quantitative trait provide greater statistical power and to date have revealed insights into the severity-specific genetic architectures of other psychiatric disorders (e.g., major depressive disorder, schizophrenia). In light of these findings, this study aims to explore the severity-specific genetic architecture of AN, defined both a continuous and a binary phenotype (severe vs. less-severe AN).

Methods

We used the Anorexia Nervosa Genetics Initiative – Denmark and Sweden datasets. Illness severity was evaluated using the Anorexia Nervosa Register-based Severity Index, a measure comprising inpatient admissions, outpatient treatment episodes, early/late onset, illness duration, and treatment length to quantify severity 5 years after AN diagnosis. Individuals scoring in the top 20th percentile were classified as having severe AN, and the remaining individuals were classified as less severe. We conducted separate GWASs for the continuous severity trait and the binary severe AN classification in the Danish ($n \approx 6{,}000$) and the Swedish cohorts ($n \approx 2{,}400$), adjusting for the first five principal components and batch effects. The meta-analysis of both cohorts using fixed-effects models is currently underway, and polygenic risk scores will be generated to examine prediction capabilities.

Expected Outcomes

Although final results are pending, preliminary analyses suggest the presence of specific loci associated with AN severity, supporting the potential utility of our severity-based approach to increase statistical power. Our project will provide the first comprehensive characterization of the genetic architecture underlying AN severity through two aspects: identifying novel genetic variants associated with AN severity and binary severe AN classification; and determining whether severe AN genetically differs from broadly defined AN. This approach has the potential to reveal biological pathways specific to disease severity and contribute important knowledge for the development of precision medicine strategies for AN in the future.

[P4] STRUCTURAL AND FUNCTIONAL CHARACTERIZATION OF GLP1 VARIANTS: FROM IN SILICO TO IN VIVO

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GLP-1, a critical hormone encoded by the GCG gene, regulates glucose metabolism and is central to metabolic disease therapeutics. While GLP1R and GIPR variants have been studied extensively, naturally occurring missense variants in GLP-1 itself remain largely unexplored.

We characterize 22 GLP-1 peptide variants identified in 500,000 UK Biobank participants through a multi-modal framework integrating structural modeling (in silico), cellular signaling assays (in vitro), glucose tolerance tests in mice (in vivo), and human phenotype associations (in cohort). Peptide-receptor interface metrics predicted altered signaling profiles, confirmed via fluorescence-based screening and Bayesian random-effects modeling. Variants with impaired in vitro signaling corresponded to reduced glucose-lowering capacity in vivo.

Our findings demonstrate that naturally occurring GLP-1 variants can affect physiological function, with implications for understanding individual variability in drug response. This integrative approach can be extended to other peptides to understand their clinical relevance and therapeutic applications.

[P6] BEYOND DIAGNOSTICS: A DIMENSIONAL APPROACH TO MENTAL PROFILING

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Mental health extends beyond the absence of mental illness (MDx). It arises from a complex interplay between hereditary factors and exposures, encompassing emotional, psychological, and social dimensions. However, ambiguity between pathological and non-pathological states challenges traditional diagnostic classifications, necessitating a dimensional approach for precision psychiatry. This study aimed to explore data-driven methods for stratifying mental health risk based on psychometric and biological markers.

Here we analyze data from a large, young, representative and deep-phenotyped European sample. Data included psychometric assessments (e.g., personality, cognition, emotional regulation), brain-imaging, circulatory OMICs markers, and polygenic scores (PGSs) for a wide range of of psychiatry-related traits. Archetypal (soft-clustering) analyses was applied to psychometrics and PGSs to display participants on the phenotype spectrum as convex combinations of extreme observations. Associations between archetype scores, OMICs and imaging were assessed using standard statistical tests.

Deep psychometric archetypal profiling effectively stratified participants into risk clusters defined by personal and familial MDx history. Highlighting their biological basis, clusters exhibited distinct biological features, with individual PGSs (e.g., well-being, MDx, and brain MRI measures) predicting liability to psychometry-based archetypes. Intriguingly, psychometric and PGS-based archetypes significantly overlapped, identifying high-risk subsets with multiple MDx diagnoses and elevated genetic risk.

Our findings demonstrate the feasibility of data-driven risk stratification of the general population the relevance of multimodal archetypal analyses for uncovering latent psychopathology structures. By integrating psychometric and biological data, we refine risk stratification and trait specification, revealing biosignatures associated with particular mental health traits. While replication in larger, longitudinal cohorts is warranted, our study advances the understanding of mental health by embracing a dimensional perspective, laying the foundation for personalized mental health care strategies.

[P7] IDENTIFICATION OF RARE NONSENSE HOMOZYGOUS VARIANT IN VLDLR GENE CAUSING DYSEQUILIBRIUM SYNDROME IN A CONSANGUINEOUS PAKISTANI FAMILY

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Background

Dysequilibrium syndrome (DES, OMIM 224050) is a rare genetically heterogeneous group of disorders characterized by a non-progressive cerebral ataxia with intellectual disability having autosomal recessive inheritance. Cerebellar hypoplasia is the most common among brain abnormalities, occurring in almost 50% of the cases and associated with non-progressive cerebral ataxia. The affected individuals may exhibit either bipedal or quadrupedal ambulation.

Methods

A large Pakistani family comprises of 3 affected and 2 normal individuals along with their phenotypically healthy parents were analysed using whole exome sequencing (WES). The data obtained were filtered against control data bases to remove the polymorphism. Similarly only those recessive variants were selected which were shared among the affected individuals. The prioritized variants were Sanger sequenced in all the individuals of the family.

Results

All the affected individuals were segregating cerebral ataxia, intellectual disability and dysarthria. The patients were able to walk with support having bipedal and broad based gait. One of the three affected individuals was diagnosed with left eye strabismus. There was no history of seizures or epilepsy in any of the affected individuals. Whole exome sequencing (WES) was used to elucidate the genetic basis of the disease. Data analysis from WES revealed a nonsense c.2027C>A, p.(Ser676*) variant in VLDLR gene (NM_003383). Absence of any other candidate variant strongly support for the VLDLR variant (c.2027C>A) being the true causative variant. Segregation of the VLDLR nonsense variant c.2027C>A p. (Ser676*) was confirmed by bidirectional Sanger sequencing. The affected individuals were homozygous for the mutant allele while the phenotypically healthy parents and their normal siblings were heterozygous for the mutation. The variant is Located in the exon 14 of VLDLR gene and creates a premature stop codon and expected to result in truncated protein.

Conclusions

The current study not only adds to the evidence that a deficiency of the VLDLR gene can cause the human DES phenotype, but it also expands the genetic variability associated with the VLDLR gene.

[P8] GENETIC INFLUENCES ON ANTIDEPRESSANT SIDE EFFECTS: A CYP2C19 GENE VARIATION AND POLYGENIC RISK STUDY IN THE ESTONIAN BIOBANK

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Introduction

Antidepressant side effects are prevalent, leading to significant treatment discontinuity among patients [1]. A deeper understanding of the underlying mechanisms could help identify individuals at risk of side effects and improve treatment outcomes.

We aim to investigate the role of genetic variation in CYP2C19 and polygenic scores (PGS) for psychiatric and side effect-related traits in the occurrence of side effects from antidepressant use.

Methods

We pooled Estonian Biobank data layers from the Mental Health online Survey (N=86,244), the Adverse Drug Events Questionnaire (N=49,366) and from unstructured electronic health records using natural language processing (N=206,066) covering 25 common side effects to 16 most prescribed antidepressants. The side effects cover several symptom domains: general, cardiometabolic, neurological, psychological, gastrointestinal and allergic. Metaboliser phenotypes were determined based on CYP2C19 star alleles, including copy number variation, for individuals taking CYP2C19-metabolised antidepressants. Associations between side effects and CYP2C19 metaboliser phenotype or 19 PGSs (including 8 psychiatric and 12 trait-specific PGS) were assessed using logistic regression. The models were adjusted for birth year, sex, and 10 principal components, with multiple testing correction applied via Benjamini–Hochberg FDR. A meta-analysis was carried out using previously published results from the Australian Genetics of Depression Study [2].

Results and discussion

Among 13,729 antidepressant users in our analytical sample, 52.0% reported side effects. In a subgroup of 9,563 individuals taking antidepressants metabolised by CYP2C19, poor metabolisers had 49% higher odds of experiencing a side effect (OR=1.49, 95%CI=1.09-2.04), while ultrarapid metabolisers had 17% lower odds compared to normal metabolisers (OR=0.83, 95%CI=0.70-0.99). The PGSs for schizophrenia and depression showed the most associations with overall as well as with specific side effect reporting among all pooled antidepressants users, with significant correlations also observed among individuals taking either selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors and atypical antidepressants, and tricyclic antidepressants. PGSs for higher body mass index (BMI), anxiety, and systolic blood pressure were significantly associated with respective side effects among any antidepressant and SSRI users. Meta-analysis showed that a higher PGS for BMI was associated with higher weight gain in all nine examined antidepressants and the PGS for headache was linked to the headache side effect among individuals taking sertraline.

Conclusion

Our findings underscore the role of genetic factors in experiencing antidepressant side effects and have potential implications for personalised medicine approaches to improve antidepressant treatment outcomes.

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[P9] MIGRAINE, HEADACHE AND ADHD-SYMPTOMS

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Migraine and Attention Deficiency Hyperactivity Disorders (ADHD) are both common brain disorders with a considerable genetic component, and both have a disproportional sex distribution, with migraine affecting more females and ADHD affecting more males. ADHD is classified as a neurodevelopmental disorder, with its incidence peaking in childhood and adolescence, while migraine is defined as a heterogeneous neurovascular disorder, with incidence peaking during reproductive age. Despite their distinct characteristics, migraine and ADHD show a significant genetic correlation and a notable co-occurrence.

Using a population cohort with validated migraine diagnoses and who has answered the Adult ADHD Self-Report Scale (ASRS v1.1), (N = 29.999), we examine the endophenotypes correlation and impact of polygenetic risk for ADHD and Migraine subtypes.

Sex-stratified analysis of migraine with and without aura, frequent headache, and visual disturbances accompanied with headache, was all associated with increase ASRS-score. Dichotomizing on ASRS>=37, resembling clinical relevance level, females had a significant higher odds ratio for being above the threshold for all subtypes. However, for males only frequent headache was associated, with higher odds ratio then females. Notably, these association was unaffected by the polygenetic risk of migraine subtypes.

[P10] GENOME-WIDE COPY NUMBER VARIATION ASSOCIATION STUDY IN SCHIZOPHRENIA

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Background

Copy number variations (CNVs) are a class of structural variations that have been linked to a number of psychiatric disorders, including schizophrenia spectrum disorder (SSD). Although genomic studies have successfully identified (common) risk variants in SSD, the rarity of CNVs in the general population, the complexity of CNV detection, and the focus on a limited number of known and well-studied CNVs have limited the scope of previous studies and restricted more comprehensive analysis of CNVs in SSD.

Material and Methods

This study aims to perform a comprehensive genome-wide CNV enrichment analysis, utilising microarray data from the iPSYCH2015 case-cohort sample, which includes 13,147 SSD cases and 43,177 population controls. Specifically, the genome-wide burden of recurrent and non-recurrent CNVs in SSD will be assessed, as well as the overall CNV heritability. Furthermore, we will investigate the genome-wide association of CNVs in SSD in the Danish population and examine CNV enrichment in defined brain-expressed gene sets to provide functional insights.

Results

Preliminary results suggest a higher overall burden of CNVs in brain-expressed genes among individuals with SSD compared to population controls, and that their aggregation in specific gene networks may provide insights into the genetic etiology of SSD.

Conclusion

Our findings will enhance the understanding of the contribution of CNVs to SSD, leading to better estimates of individual risk and establishing a foundation of future studies.

[P11] RECURRENT COPY NUMBER VARIANTS AND POLYGENIC SCORES JOINTLY INFLUENCE THE RISK OF PSYCHIATRIC DISORDERS IN THE IPSYCH2015 CASE-COHORT SAMPLE

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Background

While both recurrent copy number variants (rCNVs) and common SNP variants are known to influence the risk of psychiatric disorders, their joint effect remains underexplored. Using the population-based iPSYCH2015 case-cohort, we investigated the combined effect of rCNVs and polygenic scores (PGS) on major psychiatric disorders.

Methods

The iPSYCH2015 case-cohort includes all individuals diagnosed with major psychiatric disorders (n=82,626) and a random population-based sample (n=41,346) from a Danish birth cohort (1981 to 2008). We identified rCNVs at 27 genomic loci using PennCNV and grouped them according to their gene constraint. PGSs were derived from external genome-wide association studies, with SNP effect sizes rescaled using SBayesR. Survival models, incorporating inverse probability weights, were used to estimate absolute risks, while generalized linear models were employed to evaluate additive and interactive effects between rCNVs and PGSs, as well as differences in PGS distributions between rCNV carriers and non-carriers.

Results

Higher PGS and gene-constrained rCNVs were associated with increased absolute risk for autism, ADHD, and schizophrenia, but not major depressive disorder. For ADHD and Schizophrenia, more individuals at similar risk levels attributed to rCNV groups were identified through PGSs. We observed additive, but not multiplicative, effects of rCNVs and PGSs on ADHD, ASD, and schizophrenia. PGS profiles for psychiatric and several non-psychiatric traits did not differ significantly between rCNV carriers and non-carriers.

Conclusion

Joint assessment of rCNVs and PGSs in a population-based iPSYCH2015 case-cohort highlights their additive contributions to psychiatric risk and supports integrated genetic profiling as a tool for precision psychiatry.

[P12] ASSORTATIVE MATING PATTERNS IN PSYCHIATRIC DISORDERS ARE PARTIALLY EXPLAINED BY SOCIOECONOMIC STATUS

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Partner selection is a key force shaping both social structure and the genetic architecture of human traits. In this study, we use Danish nationwide registry data covering over 700,000 couples born between 1969 and 2022 to quantify assortative mating (AM) across ten major psychiatric disorders and assess the role of AM on socioeconomic status (SES, measured by education and income) herein. We assess how these domains intersect by adjusting for their mutual influence.

We find strong spousal correlation for education ($r \approx 0.58$) and moderate AM for income ($r \approx 0.32$), confirming SES—particularly education—as a central dimension of partner similarity. Psychiatric disorders also show notable spousal correlation, albeit weaker than SES, with the highest within-disorder observed for schizophrenia, ADHD, autism spectrum disorder, and substance use disorder ($r = 0.27–0.32$). Cross-disorder psychiatric correlation was widespread but generally weaker.

Spousal correlations between SES and psychiatric disorders were consistently negative, indicating that individuals with higher SES are less likely to partner with someone diagnosed with a psychiatric condition. Adjustment analyses revealed that SES explains a substantial share of psychiatric AM—up to 29% within disorders and up to 70% across disorders—while psychiatric traits had minimal impact on SES-based AM.

These findings highlight the dual but unequal roles of SES and mental health in assortative mating, with SES emerging as the dominant driver. The results emphasize the powerful influence of social stratification on mating patterns and its implications for the intergenerational transmission of social and mental health inequalities.

[P13] RECREATIONAL SCREEN USE AND INTERNALIZING PROBLEMS FROM PREADOLESCENCE TO YOUNG ADULTHOOD: A POPULATION-BASED COHORT AND CO-TWIN CONTROL STUDY

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Importance
The mental health impact of recreational screen use among youth remains inconclusive, due to challenges in addressing reverse causality and unmeasured familial confounding.

Objective
To investigate the longitudinal and bidirectional associations between recreational screen use and internalizing problems from preadolescence to young adulthood, while accounting for shared familial influences.

Design, Setting, and Participants
This cohort and co-twin control study included participants from the Child and Adolescent Twin Study in Sweden (n=21797). Twins were assessed at age 9 (via parent-report), 15, 18, and 24 (self-report), with linkage to national registers for diagnoses and dispensed prescriptions.

Exposures
Frequencies (times/week, and hours/day) on recreational screen use (interactive activities including playing games/browsing internet/chatting and passive activities including watching TV/DVD/videos) reported at age 9 on weekly basis, and at ages 15 and 18 during weekdays and weekend.

Main Outcomes and Measures
1) Depressive and/or anxiety symptoms from validated questionnaires; 2) Register-based measures of depressive and/or anxiety disorders from subsequent diagnoses from secondary and tertiary care and/or antidepressant dispensing at pharmacy.

Results
Of 21,797 twins at age 9, 16,027 (73%) participated at age 15, 13,050 (60%) at 18, and 5,772 (27%) at 24. Cross-sectional associations showed that heavier screen use—especially interactive activities—was linked to more internalizing symptoms, with stronger effects in girls. Co-twin control analyses indicated that these associations were partly—but not fully—explained by shared familial factors, along with prior symptom levels. Cross-age analyses suggested a bidirectional relationship: prior screen use predicted later internalizing symptoms, and vice versa, but with weaker reverse associations. Persistently heavy (>6 hours/day) at ages 15 and 18 or increasing screen use (from >4 hours/day) was associated with more

symptoms at age 18 and 24. Furthermore, daily screen use at age 9 and heavy use at age 15 were associated with subsequently increased risks of clinically ascertained depression or anxiety (adjusted hazard ratios up to 1.86).

Conclusions and Relevance

Recreational screen use—particularly heavy interactive screen activities—was consistently associated with internalizing problems from preadolescence to young adulthood. Associations persisted after adjustment for prior symptoms and shared familial factors, suggesting potential causal links. These findings highlight the importance of monitoring screen use and provide evidence to inform guidelines for healthier digital media use in youth.

[P14] GENE NETWORK-BASED PARTITIONED POLYGENIC RISK SCORES REVEAL CLINICAL INSIGHTS INTO SCHIZOPHRENIA

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Background

Schizophrenia is a severe mental disorder. Many genetic variants have been identified as risk factors for developing the condition. Translating these insights into actionable biological mechanisms remains a challenge. Gene networks defined by cell type-specific protein-protein interaction partners of high-risk schizophrenia variants have been proposed to be enriched in biologically relevant pathways related to schizophrenia. In this study, we develop and test a novel framework to prioritize genetic risk variants of schizophrenia by assessing whether polygenic risk scores (PRS) partitioned to genetic variants in such networks are associated with clinical features of schizophrenia.

Methods

We calculate PRS partitioned to gene networks using genotypes from 10650 individuals with a schizophrenia spectrum disorder diagnosis in the Danish iPSYCH cohort, in combination with allelic effects from recent genome-wide association studies of schizophrenia and related traits. We then investigate the pairwise associations between these partitioned PRS and relevant clinical endophenotypes from the Danish national health registers. We interpret significant associations as functional signatures of gene networks that could point toward novel schizophrenia-related biological mechanisms.

Results

Preliminary findings indicate that the PRS for schizophrenia, partitioned to gene networks characterized by Neural Progenitor Cell expression are significantly associated with an ADHD diagnosis in individuals with schizophrenia spectrum disorders, but not in those without. This suggests the possible functional relevance of these gene networks in specific clinical manifestations.

Conclusion

Partitioned PRS provide a promising framework for studying pathways involved in polygenic disorders such as schizophrenia. This approach may, in time, help provide insight into the identification of actionable biological mechanisms of schizophrenia.

[P15] DEMENTIA AGE-OF-ONSET PREDICTION IN THE NORWEGIAN HUSK COHORT – A PILOT STUDY

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Dementia accounts for the highest spending by GDP in the Norwegian healthcare system, increasing significantly by 2050 as the population ages [1]. The 2024 Lancet Standing Commission report on dementia [2] reviewed modifiable lifestyle- and environmental risk factors associated with dementia (e.g., education level, hypertension, cholesterol level, smoking, obesity, depression, physical activity, diabetes, alcohol use, social isolation). Individuals may be genetically predisposed, as Apolipoprotein E4 and other variants increase dementia risk [2]. ¬

Norwegian population cohorts and biobanks (Tromsø Study, https://uit.no/research/tromsostudy; HUNT Study, https://www.ntnu.edu/hunt; HUSK Study https://husk-en.w.uib.no) provide unique opportunities to study interactions between lifestyle- and environmental risk factors and genetics through biological samples and phenotypic information from questionnaire data, clinical assessments, health records data (Norwegian Patient Registry, Cause of Death Registry). Here, we employ polygenic scores and polygenic hazard score predictions [3] with lifestyle risk factors using Cox proportional hazards models [4] to investigate survival probabilities as a function of age for Alzheimer's disease and related dementias in the HUSK cohort (n=34.4K; born 1925-1956), accounting for risk factors listed. The model improves predictive performance over established approaches accounting only for genetics [3]. We aim to extend the investigation to the HUNT and Tromsø studies.

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[P16] VARIATIONAL AUTOENCODERS IN MS GENETIC CLUSTERING: ENHANCED DETECTION OF SNP-BASED SUSCEPTIBILITY SIGNATURES

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Introduction

Identifying genetic predispositions to multiple sclerosis (MS) is crucial for understanding disease aetiology and improving predictive models. While traditional genome-wide association tests and dimensionality reduction techniques like principal component analysis (PCA) have inherent limitations when applied to high-dimensional genomic data, emerging applications of variational autoencoders (VAEs) to the analysis of genome-wide human single nucleotide polymorphism (SNP) data suggest VAEs may hold an advantage in dealing with complex non-linear relationships in these datasets.

Objectives/Aims

To compare the effectiveness of variational autoencoders (VAEs) with PCA in clustering genome-wide single nucleotide polymorphisms (SNPs) for studying heterogeneity of genetic susceptibility to MS.

Methods

We analysed the pruned set of over 160,000 autosomal SNPs from equal numbers of MS patients and healthy controls (HC) from Sweden, incrementally increasing sample sizes across three comparisons—500HC vs 500MS, 1500HC vs 1500MS, and 2500HC vs 2500MS. VAEs were employed alongside Uniform Manifold Approximation and Projection (UMAP) for exploratory analysis and visualisation of genotype clusters. The VAE was trained on normalised SNP data over 40 epochs with a batch size of 124 samples per batch while shuffling instances between epochs. The input layer matched the number of SNPs in our dataset and was followed by an encoding layer with 16 neurons representing the reduced dimensional space. K-means clustering was used to partition VAE+UMAP and PCA-reduced data into two expected clusters, with averaged silhouette scores (ranging -1 to +1) representing cluster cohesion for each method.

Results

Our findings indicate that VAEs outperform PCA in distinguishing between MS patients and HCs as sample size increases. Specifically, a distinct cluster characterised by a higher density of MS individuals emerged more prominently using VAEs compared to PCA at larger sample sizes. The average silhouette score—a measure of cluster quality—for UMAP-enhanced VAE clusters was significantly higher at 0.7556 than for PCA clusters at 0.6175 when analysing the largest cohort comparison.

Conclusion

Our study suggests that VAEs offer superior performance over PCA in identifying subgroups within MS patients based on genetic profiles from large datasets, potentially providing more accurate ways of identifying genetically susceptible subpopulations. These results underscore the importance of considering genetic heterogeneity among MS patients when predicting disease risk and severity.

[P17] HOW MUCH CAN DIAGNOSES IN RELATIVES TELL US ABOUT RISK OF NEURO-PSYCHIATRIC DISORDERS?

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Background

State-of-the-field complex disorder genetics leverages population-scale biobanks with broad demographic, health, survey, and genetic data. This presents an opportunity for Major Depressive Disorder (MDD), where genetic predictors underperform, clinical heterogeneity is etiologically enigmatic, and missing heritability persists. Combining genotypes, family history, and adjacent phenotypes in large data can advance each aim, but requires new approaches.

Methods

We introduce Pearson-Aitken framework for Family Genetic Risk Scores (PA-FGRS) to estimate individual liability scores from complex pedigrees of individuals in the iPSYCH2015 case-cohort. [1] We compute multiple psychiatric PA-FGRS and polygenic scores (PGS) for N=37,555 MDD cases and 49,303 controls. We test discriminative utility of PA-FGRS and PGS with regression, compare GWAS on diagnoses and PA-FGRS, and compare multivariate PA-FGRS+PGS profiles of MDD cases with different clinical outcomes using multinomial logistic regression.

Results

We construct genealogies including >2,000,000 relatives of the 141,265 individuals included in iPSYCH2015. We show that PA-FGRS out-performs five published methods for estimating genetic liabilities in simulated complex pedigrees. Combining PA-FGRS with PGS explains as much additional variance in MDD as PGS alone (~3%). Clinical heterogeneity is widely associated with variability in genetic profiles, e.g., recurrent MDD increased PA-FGRS and PGS for MDD and bipolar.

[P18] SHARED GENETIC PATHWAYS UNDERLYING BIPOLAR DISORDER, SUBSTANCE USE DISORDERS AND SUBSTANCE USE

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Background
Bipolar disorder (BIP) is commonly comorbid with substance use disorders (SUDs). This co-occurrence is associated with increased mortality and morbidity for individuals with BIP. Furthermore, non-clinical substance use (SU) seems to have distinct genetic risk compared to SUDs. This project aims to characterise the underlying molecular mechanisms common to the development of SUD, SU and BIP.

Methods
The genetic architecture of the traits was explored using the most recent large-scale genome-wide association studies (GWAS) of alcohol, cannabis, opioid and tobacco use disorders. Additionally, drinks per week, lifetime cannabis use, prescription opioid use and smoking initiation were included as broader substance use traits. Polygenic overlap and genetic architecture were assessed with trivariate MiXeR and GenomicSEM. Discovery of pleiotropic loci was done using conjunctional FDR and CPASSOC. Pleiotropic loci were annotated to genes and gene sets using the OpenTargets platform, MAGMA and GSA-MiXeR. Pleiotropic loci were validated using polygenic prediction into the Norwegian Mother, Father and Child Cohort study (MoBa), and by analyzing RNA-Seq data in the Thematically Organized Psychosis (TOP) study.

Results
Trivariate MiXeR showed that a majority of trait-influencing variants are shared between BIP and SUD/SU. A multi-method approach for gene prioritization found 65 shared genes, enriched for brain and neural tissue. Polygenic prediction showed a BIP/SUD common factor as most predictive of BIP/SUD comorbidity. Differential gene expression of a subset of the prioritized genes was confirmed in bipolar cases in an independent clinical sample.

Conclusion
There is extensive pleiotropy in BIP/SUD genetic architecture, with functional genomic analyses implicating GABAergic neurons in the midbrain and medium spiny neurons in the striatum.

Conclusion

Approaches that integrate multiple data types in population biobanks give important new perspectives on genetic architectures of complex disorders like MDD. Clinical and research aims could be more data integrative and better attend to heterogeneity.