Results: In the discovery step, one of the biomarkers decreased in expression in blood in high mood states was SLC6A4 (the serotonin transporter, target of SSRIs), which is reassuring and serves as a de facto positive control. For predictions in independent cohorts, we show increased accuracy with the personalized approach, particularly in women. We also reproduced our earlier finding (Le-Niculescu et al. Molecular Psychiatry 2009) of FGFR1 as a biomarker tracking and predicting mood. Furthermore, we evaluated the evidence for our top biomarkers being targets of existing psychiatric drugs, which opens the door to pharmacogenomic targeted treatments and to measuring of response to treatment. We also used the biomarker signatures to bioinformatically identify new/repurposed candidate drugs.
Discussion: Overall, our studies provide leads for new objective assessments and targeted therapeutics that enable precision medicine for mood disorders.

Disclosure: MindX Sciences - Stock / Equity, Self

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M8
PROXY-PHENOTYPING OF ANXIETY AND DEPRESSION USING SELF-REPORTED MEDICATION DATA

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Background: Anxiety and depressive disorders are the most prevalent mental health conditions and are leading causes of disability worldwide. These internalising disorders are highly comorbid, are associated with similar risk factors and follow the same treatment recommendations (e.g. selective serotonin reuptake inhibitors as first-line medication). Furthermore, these disorders are moderately heritable and highly polygenic, with a high degree of genetic overlap. Genomic studies of anxiety and depressive disorders have been hindered by sample sizes smaller than are necessary to detect the individual genetic effects at play. High-quality diagnostic information is rarely readily available and is resource intensive to produce. Several genetic studies have used alternative, less-specific, methods of determining probable diagnostic cases in order to increase sample size and thus power. These 'broad' phenotype definitions include self-reported diagnosis and treatment-seeking. Medication data could serve as an additional method for identifying cases for genetic studies of internalising disorders, particularly when working with electronic health records and other sources of information are not available.
Method: We performed a genome-wide association study (GWAS) with individuals from the UKBiobank who reported current antidepressant or anxiolytic medication use (n = 30,488) and screened controls (n = 141,867). We also examined the degree of phenotypic overlap between these medication 'proxy cases' and cases identified by previously used definitions, including structured diagnostic questionnaires. To determine genetic overlap and the quality of the proxy phenotype, genetic correlations were computed with previous GWASs of anxiety and depression.
Results: Preliminary analyses indicate that the liability scale heritability estimate for self-reported antidepressant or anxiolytic medication use is between 7% and 15%. This phenotype has significant genetic correlations with anxiety and depression under existing definitions in psychiatric genetic literature (rG .74 - .87). Of note, ~3,000 individuals who reported using antidepressant or anxiolytic medication were not identified as anxiety or depression cases through broad or structured diagnostic phenotyping.
Discussion: Our initial results support the use of self-reported antidepressant or anxiolytic medication use for identifying probable anxiety or depression cases. We are currently further investigating to what extent this proxy phenotype captures shared common genetic variation with an internalising diagnosis, as opposed to increasing heterogeneity and resultant noise. We are using polygenic risk scores to examine the shared genetic architecture between these different methods of identifying individuals with probable anxiety or depression. From the present findings, we conclude that medication status could be used as a proxy phenotype in genetic studies of internalising disorders when it is the only available indicator of mental health status.

Disclosure: Nothing to disclose.

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M9
EXPLORING THE HETEROGENEITY OF DEPRESSION: STRESSFUL LIFE EVENTS AND DEPRESSIVE SYMPTOMS

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Background: The heterogeneity of the combination of symptoms that fall under the umbrella of major depressive disorder (MDD) is striking - there are 227 possible ways to meet the symptom criteria.

The origins of MDD are usually explained as the result of the interaction of a diathesis or vulnerability (genetic risk) and the occurrence of stressful life events. Previous research has suggested that the presentation of certain symptoms of MDD and not others is associated with the occurrence of specific stressful life events.

In this study, we aim to identify differential profiles in the presentation of MDD symptoms, genetic vulnerability for the disorder, and stressful life events.

Methods: A total of 1,480 genotyped participants from the Australian Genetics of Depression Study at QIMRB (AGDS; 74% female, age mean = 37, SD = 14, range 18-78) reported the stressful life events they had experienced in the last 12 months and the symptoms of their worst depression episode (only participants reporting their worst episode in the last year were selected for this project). Questions were adapted from the composite international diagnostic interview (CIDI) and the List of threatening experiences. Genetic risk was operationalised as the polygenic risk scores (PRS) of depression. PRS were derived from the QIMRB and 23andMe leave-one-out results from the latest GWAS meta-analysis (Howard et al 2018; PRS p-value threshold of 0.05). Symptoms were collected as separate items were possible (e.g. weight gain, weight loss, and appetite changes). Some stressful life events were grouped (e.g. broken romantic relationships) and others (e.g. burgled or robbed) were eliminated due to lack of variability.

Two logistic regressions were conducted on each of the symptoms of depression. The first included age, sex, stressful life events, PRS, principal components of genetic ancestry; the second included also the interactions between PRS with the stressful life events. Significant predictors were identified and the improvement in the model fit was assessed.

Results: Only the experience of a romantic breakup (including divorce, marital separation, broken engagement or steady relationship) in the last 12 months was associated with weight loss in the concomitant MDD episode; financial problems were associated with hypersomnia. Although the genetic risk for MDD predicted guilt or worthlessness, diminished ability to think, concentrate, or make decisions, and thoughts of death or suicide, it did not remain significant when the stressful life events were incorporated in the models. Similarly, the inclusion of the interaction between the PRS and the stressful life events did not improve the model fit.

Discussion: The present study identifies the association between romantic breakups and the presentation of specific depressive symptoms. This association is far from suggesting any causality but a close presentation in time.

The participants in this study were recruited mainly through media campaign and they tended to present with severe, recurrent, and early-onset MDD. The severe clinical presentations of depression reported as their worst episode limited the possibility of analyses due to lack of variability in the data.

This study will be completed with data collected within the context of community-based recruitment from ~8,000 participants in other QIMRB projects. The increase in statistical power and the variability in symptom presentation will add information on the heterogeneous presentation of depression and stressful life events.

Disclosure: Nothing to disclose.

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M10
STUDYING DIFFERENCES IN CELLULAR FUNCTIONS BETWEEN SUBJECTS WITH BIPOLAR DISORDER AND HEALTHY INDIVIDUALS IN A CELL-BASED MODEL SYSTEM: ARE THERE SPECIFIC PREDICTORS OF LITHIUM RESPONSE?

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Background: Lithium and valproate are the mainstay of treatment for Bipolar disorder (BD). Though prescribed very commonly, they are not always effective, and the reasons for such discrepancies are not known. To this end, we used patient IPSC-derived neural precursor cells (NPCs) and lymphoblastoid cell lines (LCLs) to examine specific cellular phenotypes related to BD and lithium treatment response.

Methods: BD subjects (DSM-IV) attending the outpatient services of National Institute of Mental Health and Neurosciences, Bangalore, India were recruited after informed consent. Treatment response was assessed by using the Alda scale and "NIMH Retrospective Life chart method". The controls were consenting, ethnically matched healthy subjects with no family history of neuro-psychiatric illness. NPCs from two BD patients (from a multiple affected family), who clearly differed in their clinical response to lithium were chosen and compared to those from healthy population controls. A hypothesis-free approach using RNAseq analysis was performed in NPCs, with and without in vitro lithium exposure (1mM for 7 days). In addition, mitochondrial membrane potential (MMP), cell viability and cell proliferation were examined. Experiments were also carried out in 25 LCLs from BD patients characterized for lithium response (16 responders and 9 non-responders) and 12 healthy controls, to establish them as amenable to clinical translation.

Results: Whole transcriptome analysis did not reveal differences in NPCs with and without in vitro lithium treatment. MMP was lower in BD, both in NPCs and LCLs; reversal with in vitro lithium happened only in LCLs, and was unrelated to lithium response. Cell proliferation was increased in BD, both in NPCs and LCLs; reversal with in vitro lithium happened only in LCLs, and unrelated to lithium response. Cell viability assays indicated greater cell death in BD, both in NPCs and LCLs; reversal with in vitro lithium happens only in LCLs, but specifically in lithium responders. The latter finding was associated with enhanced BCL2, NR1D1 and GSK3B expression in the LCLs of the lithium responder group

Discussion: This study used NPCs and LCLs from BD patients who are well characterized for lithium response, to interrogate cellular phenotypes related to disease and lithium treatment response. Overall, study findings report that there are common cellular phenotypes related to disease (mitochondrial potential, cell proliferation) in NPCs and LCLs; and lithium treatment response related phenotypes (cell viability, BCL2/ GSK3B expression) in LCLs. The