Hackathon Research for Team DepScreeners

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Challenge Name

Prevention of PPD

Research Inquiries

Early diagnosis of PPD using biological biomarkers and relevant data sets

Findings

Which general physiological and psychological markers are most significant for correlating with PPD?

There is ongoing research into potential biomarkers for depression generally and PPD specifically, with the hope of improving the accuracy of diagnosis and guiding treatment decisions. Some markers that have been studied include:

- Hormone levels: Changes in hormone levels, such as prolactin and cortisol, have been associated with PPD.
- Inflammatory markers: Elevated levels of inflammatory markers, such as interleukin-6 and C-reactive protein, have been linked to PPD.
- Brain activity: Abnormalities in brain activity, as measured by functional magnetic resonance imaging (fMRI), have been observed in women with PPD.

- Genetic markers: Certain genetic variants have been associated with an increased risk of PPD.

We have examined specific publications, including:

- An article[1] published in Nature molecular psychiatry in 2022 presents a novel peripheral biomarker for depression and antidepressant response. The researchers in the study found that the heterotrimeric G protein, **Gsalpha (Gsα), is mainly located in lipid rafts in subjects with major depressive disorder (MDD) resulting in impaired stimulation of adenylyl cyclase.**

  The study results showed in the article that in **a small group** of 49 subjects with MDD (HamD17 score ≥15) and 59 healthy controls, the MDD group had lower activation of adenylyl cyclase activity than controls (p = 0.02). Those results are further supported by the fact that the patients that responded to antidepressant treatment in the study arm revealed a significant increase in PGE1-stimulated adenylyl cyclase compared to non-responders (p = 0.05) with an effect size of 0.83 for the **PGE1/Gsα lipid-raft biomarker**.

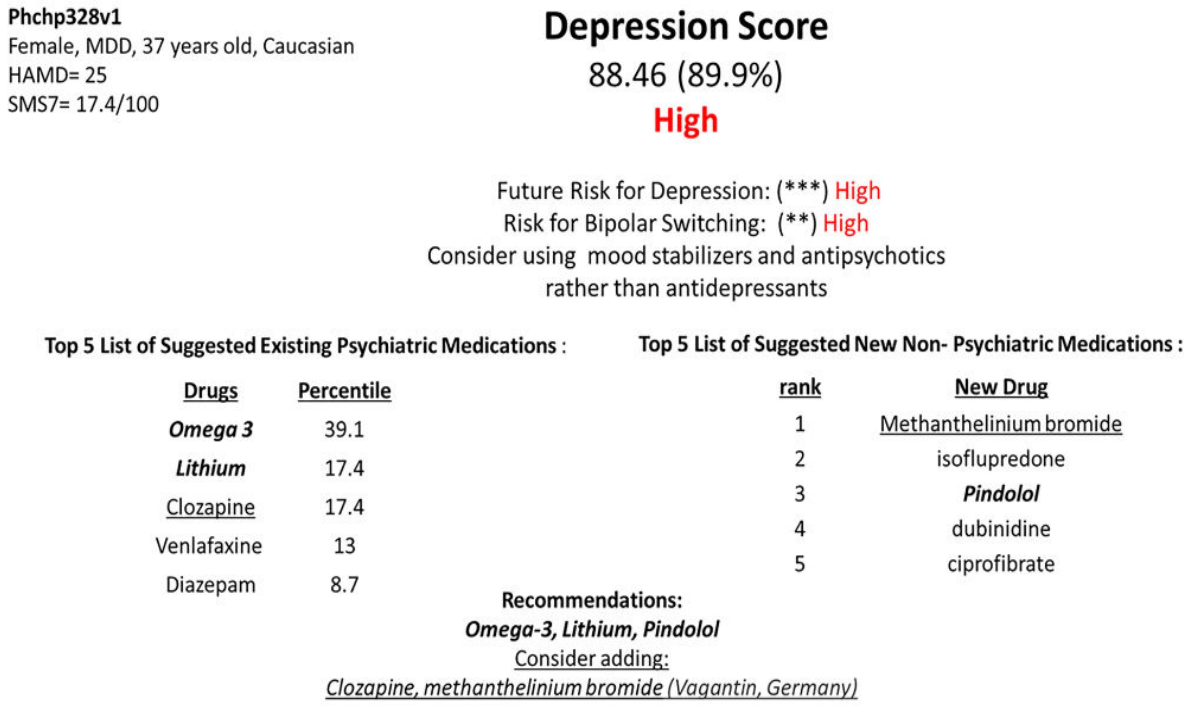
  Methodes: The writers used **AlphaScreen (PerkinElmer) assay** to measure the basal coupling of the G protein mentioned above to adenylyl cyclase and later on used **prostaglandin E1 (PGE1)**, which stimulates the coupling.

- An article[2] published in Nature molecular psychiatry in 2021 reviews the latest updates in precision medicine for mood disorders, including the potential blood & genomic markers for diagnosis and pharmacogenomics. The researchers found **a list of 12 biomarkers (genes) for low mood/depression: SLC6A4, SMAD7, OLFM1, CD47, HNRNPDL, FANCF, GLO1, TMEM161B, PRPS1, GLS, DOCK10, and NRG1.**

  In relation to diagnostic purposes, the researchers mention that **these**

biomarkers should be tested individually as well as tested as polygenic panels of biomarkers in future clinical studies and practical clinical applications in the field. They may permit to distinguish, upon an initial clinical presentation of depression, whether the person is in fact bipolar

Methods: a computerized CFG (Convergent functional evidence) Wizard to automate and score in bulk large lists of genes by integrating evidence from these large databases (based on 1600 papers), checked against manual scoring. They also suggest a futuristic patient precision page, based on the analysis of their chosen markers:



Phchp328v1
Female, MDD, 37 years old, Caucasian
HAMD= 25
SMS7= 17.4/100

Depression Score
88.46 (89.9%)
High

Future Risk for Depression: (***) High
Risk for Bipolar Switching: (**) High
Consider using mood stabilizers and antipsychotics rather than antidepressants

Top 5 List of Suggested Existing Psychiatric Medications :

Drugs	Percentile
Omega 3	39.1
Lithium	17.4
Clozapine	17.4
Venlafaxine	13
Diazepam	8.7

Top 5 List of Suggested New Non- Psychiatric Medications :

rank	New Drug
1	Methanthelinium bromide
2	isoflupredone
3	***Pindolol***
4	dubinidine
5	ciprofibrate

Recommendations:
Omega-3, Lithium, Pindolol
Consider adding:
Clozapine, methanthelinium bromide (Vagantin, Germany)

The research mentioned above is based on another article[3] by this study group that was published in Nature molecular psychiatry in 2016. This article presents a model that is trying to predict suicidality in women based on biomarkers and clinical risk assessment. The analysis was based on data taken from **blood tests** of 51 women psychiatric participants followed longitudinally, with diagnoses of bipolar disorder, depression, schizoaffective disorder, and schizophrenia. This

research presents more biomarkers that can be relevant to suicidality, such as **BCL2, PIK3C3, GSK3B, PER1, and CSNK1A1**. They also created a **panel of 50 validated biomarkers (BioM-50)**.

- A research[4] published in Frontiers in Neuroscience journal in 2021 presented a potential Major Depressive Disorder diagnostic markers using machine learning models. The analysis result revealed six differentially expressed genes (**AKR1C3, ARG1, KLRB1, MAFG, TPST1, and WWC3**) with a false discovery rate (FDR) < 0.05 between MDD patients and control subjects. Their final SVM model was based on 70 genes (that included the ones mentioned above). Using the model verification on an independent dataset exhibited an AUC of 0.78 and an accuracy of 0.67. Methods: The writers collected nine RNA expression datasets for MDD patients from six studies and healthy samples from the Gene Expression Omnibus database. To create the ML model, they used the R package "MetaOmics", support vector machine (SVM), random forest (RF), k-nearest neighbors (kNN), and naive Bayesian (NB) tools.

- An article[5] published in Biological Psychiatry in 2020 presented a Genome-wide Association Analysis of more than 185,000 cases of Mood Disorder and 439,000 controls. The article mainly identified significant genomic loci that are related to mood disorders.

  Methods: meta-analyzed data from the latest Psychiatric Genomics Consortium genome-wide association studies of major depression (including data from 23andMe) and bipolar disorder, and an additional major depressive disorder cohort from UK Biobank.

- For further information, we collected more research data:
  - A research[6] published in Nature Neuroscience in 2019 that presents a Genome-wide meta-analysis of depression identifies 102 independent variants.

- A systematic review and meta-analysis[7] about prospective biomarkers of major depressive disorder, published in Nature molecular psychiatry in 2019.
- A review[8] published in the Journal of Clinical Medicine in 2021 presents the Biomarkers of Post-COVID Depression, with a focus on inflammatory factors.
- A review[9] published in Psychopharmacology in 2019 presents the Social Signal Transduction Theory of Depression and connects it to stress hormones, sex hormones, and inflammatory factors.
- An article[10] published in Frontiers in Psychiatry journal in 2021 presents the metabolic profile of Maternal Postpartum Depressive patients.
- A systematic[11] review published in the Journal of Affective Disorders in 2016 presents a more specific point of view about Perinatal Major Depression Biomarkers.

This is preliminary literature research, guided by the provided research question. We recommend further reading and validation of the results presented here, as there is a vast amount of literature regarding the topic, with no real implications in real clinical practice - these markers are not currently used as routine tests for the diagnosis or treatment of Major depressive disorder or PPD. Our main conclusion from the research process suggests that **a multi-factorial model will be better than relying on a few genes\hormones in the process of MDD\PDD diagnosis.**

Are there any publically available datasets which can be accessed immediately that contain physiological and psychological markers for PPD/depression?

Within this research timeframe, we recognizes these datasets that are available for immediate access:

- The National Survey of Children's Health (NSCH): The NSCH is a nationally representative survey that collects information on the health and well-being of children and their families in the USA[12], including data on maternal mental health as seen in their "variable list"[13]. Users can browse the data via the tools on the website, request NSCH Datasets at[14], or download readily available datasets from their website[15].

There are search engines dedicated for dataset search, where smaller datasets can be found. The most relevant search engines are "google dataset search"[16], "Kaggle"[17], and "data.gov"[18].

- Note the dataset called "Prevalence and risk factors of postpartum depression within one year after birth in urban slums of Dhaka, Bangladesh"[19], which is available in the .dta format (open with Stata software).
- There is also "The depression dataset"[20], which is not specific to PPD but might be useful. It contains motor activity of patients as recorded by a sensor on a wearable watch. Note that an account on the Kaggle website is required for access.

Please note that due to the limited time that was allocated to each group in the hackathon, in-depth characterization of each dataset and its content was not included in this report.

References:

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