*Studying the effects of bipolar disorder on the microenvironment of different areas in the brain*

*Ziv Cohen <326178266>*

*Noam Barash Biram <327923595>*

*Introduction to Bioinformatics – Final Project*

***Abstract***

\*Up to 250 words.

Brief introduction on the disease:

The knowledge gaps:

The main goal of the analysis: We aim to identify how people who suffer from bipolar disorder differ from healthy people on the microenvironment level – gene expression, pathways and tissue composition.

Brief overview of your analysis:

Your key result(s):

Main conclusion(s):

***Introduction***

Bipolar disorder is a multicomponent genetic illness that involves severe mood disturbance, neuropsychological deficits, and physiological changes and it is one of the leading causes of disability globally (Rowland and Marwaha, 2018). Patients often experience extreme mood swings from manias to depressions and vice versa. In fact, the name "bipolar disorder" was adopted by the DSM (Diagnostic and Statistical Manual for Mental Disorders) in 1980 to replace the term "manic depression" (Phillips and Kupfer, 2013). The mood swings are different in different individuals and ranges from mild hypomania or depression to severe manias or depressions, sometimes accompanied by psychosis (Miklowitz, 2008; Müller-Oerlinghausen et al., 2002). We tend to classify bipolar disorder into 3 types: Bipolar Disorder I which includes manic episodes, Bipolar Disorder II which includes only hypomanic episodes and major depressive episodes and Cyclothymia which is consistent of hypomanias and minor depressions (Cerimele et al., 2014).

Bipolar disorder affects both young and adult people: recently, there have been some evidence that indicates an increase in the prevalence of bipolar disorder in young people (Moreno et al., 2007). In addition, in the United States, bipolar disorder patients make up 10% to 25% of all the geriatric patients with mood disorders (Aziz et al., 2006). When it comes to biological sex, men are affected slightly more than women in a ratio of 1.1:1 (Miller and Black, 2020). It is unclear what is the lifetime prevalence of people who are on the bipolar spectrum (suffer from one of the 3 bipolar types mentioned before) because different studies have came to very different results. In any case, all the studies have found that the patients' lifetime prevalence decreases significantly (Cerimele et al., 2014).

The mortality rate of people with bipolar disorder is quite high – around 10% to 20% of individuals with this illness has committed suicide and more than a third have attempted suicide at least once (Müller-Oerlinghausen et al., 2002).

As we have established before, the bipolar disorder portrays a threat on a variety of people in different ages, hence, it is of great importance for us to develop new ways of identifying patients before they experience an outbreak.

Write about what is still unknown, what main challenges do we face in the context of this disease? (~1 page)

In the research literature, it is apparent that diagnosing bipolar disorder is quite challenging: based on one manic episode, bipolar disorder II is diagnosed based on depressive and hypomanic episodes and cyclothymia is diagnosed based on hypomanic and depressive symptoms that do not count as depressive episodes. In addition, some other psychiatric illnesses resemble the bipolar disorder's symptoms, especially recurring unipolar depressive disorder (a disorder which is characterized by recurrent depressive episodes). The misdiagnosis between unipolar disorder and bipolar disorder is made the most when differentiating unipolar disorder and bipolar disorder type II, that's because patients who suffer from bipolar disorder type II do not experience manic episodes. However, it is difficult to differentiate bipolar patients in general because manic episodes are rarer than the depressive ones (Phillips and Kupfer, 2013).

It is still unknown

How analyzing genomic data can help to overcome those challenges? (Give examples based on results of the studies you collected) (~0.5 pages)

In the last decade, various studies have focused on the genetics of bipolar disorder and the various risk factors that can affect its development (Rowland and Marwaha, 2018). It is found that bipolar disorder has a major genetic component and it seems to be very heritable (Kim et al., 2021). The new findings shows that there are some genes that seem to be associated with bipolar disorder. Those include: SERINC2 (increases the risk of bipolar disorder in Asian population), SLC6A2 (affects the likelihood of having bipolar disorder I and its severity) (Kim et al., 2021; Yang et al., 2021).

One of the popular approaches in order to better understand the genetics of bipolar disorder, is to perform GWAS (Genome-Wide Association Study) which helps identifying significant SNPs (Single Nucleotide Polymorphisms) that are associated with this illness. It is also common to use PRS (polygenic risk scores) – in general, those scores are the summation of all the individual's alleles which are associated with the phenotype (in this context, the phenotype is bipolar disorder) weighted by the size of their effect on it – which provides a way to approximate how well a patient will respond to a clinical treatment. Another useful method is WES (whole-exome sequencing) which helps identifying rare variants in genes and brain-related pathways. Finally, there is WGS (whole-genome sequencing) which is the most extensive yet most expensive and technically challenging method (Oraki Kohshour et al., 2022).

Finish by writing about the biological question you are about to address. What are you looking for? How is it going to help address those challenges? (~0.5 pages)

***Results***

The brain's Dorsolateral prefrontal cortex is equivalent the 9th and 46th areas of the brain according to the Brodmann areas system (Horn and Leigh, 2011).

***Discussion***

What conclusions have you drawn from the analysis? Do they provide any insight into the biological question?

Mention the limitations of your analysis.

What would you do next? Are there any ways to overcome those limitations? What future experiment can you suggest answering your biological question that will address what is still unknown?

***References***

Aziz, R., Lorberg, B., and Tampi, R.R. (2006). Treatments for late-life bipolar disorder. The American Journal of Geriatric Pharmacotherapy *4*, 347–364.

Cerimele, J.M., Chwastiak, L.A., Dodson, S., and Katon, W.J. (2014). The prevalence of bipolar disorder in general primary care samples: a systematic review. General Hospital Psychiatry *36*, 19–25.

Horn, A.K.E., and Leigh, R.J. (2011). Chapter 2 - The anatomy and physiology of the ocular motor system. In Handbook of Clinical Neurology, C. Kennard, and R.J. Leigh, eds. (Elsevier), pp. 21–69.

Kim, S.Y., Kim, H.N., Jeon, S.W., Lim, W.J., Kim, S.I., Lee, Y.J., Kim, S.Y., and Kim, Y.K. (2021). Association between genetic variants of the norepinephrine transporter gene (SLC6A2) and bipolar I disorder. Progress in Neuro-Psychopharmacology and Biological Psychiatry *107*.

Miklowitz, D.J. (2008). Bipolar disorder : a family-focused treatment approach (Guilford Press).

Miller, J., and Black, D. (2020). Bipolar Disorder and Suicide: a Review. Current Psychiatry Reports *22*.

Moreno, C., Laje, G., Blanco, C., Jiang, H., Schmidt, A.B., and Olfson, M. (2007). National Trends in the Outpatient Diagnosis and Treatment of Bipolar Disorder in Youth. Archives of General Psychiatry *64*, 1032–1039.

Müller-Oerlinghausen, B., Berghöfer, A., and Bauer, M. (2002). Bipolar disorder. The Lancet *359*, 241–247.

Oraki Kohshour, M., Papiol, S., Ching, C.R.K., and Schulze, T.G. (2022). Genomic and neuroimaging approaches to bipolar disorder. BJPsych Open *8*, e36.

Phillips, M.L., and Kupfer, D.J. (2013). Bipolar disorder diagnosis: challenges and future directions. The Lancet *381*, 1663–1671.

Rowland, T.A., and Marwaha, S. (2018). Epidemiology and risk factors for bipolar disorder. Therapeutic Advances in Psychopharmacology *8*, 251–269.

Yang, D., Chen, J., Cheng, X., Cao, B., Chang, H., Li, X., Yang, C., Wu, Q., Sun, J., Manry, D., et al. (2021). SERINC2 increases the risk of bipolar disorder in the Chinese population. Depression and Anxiety *38*, 985–995.