Orchid Genetic Risk Score: Bipolar Disorder

Orchid has developed advanced genetic risk scores (GRS) for a variety of diseases. Here we present our data on our GRS of Bipolar disorder

Written by the Orchid Team

1. Bipolar Disorder

Bipolar disorder is a psychiatric disorder characterized by extreme changes in mood, energy level, and activity ranging from emotional highs (manic) to emotional lows (depression). There are two main types of bipolar disorder: bipolar I disorder and bipolar II disorder [1]. The exact cause of the disease is unknown but certain changes in the brain have been associated with it [2]. Multiple studies give an estimated range of heritability of between 79 and 93% [3]. One study, conducted on 19,124 pairs of twins from Finland, estimated bipolar I disorder to be 93% heritable [4].

2. Clinical Impact and Prevalence

Around 4.4% of U.S. adults [5] will experience bipolar disorder in their lifetime. Although it can be diagnosed at any age, bipolar disorder is typically diagnosed in the teen years through the early 20s [6]. People with bipolar disorder have a lifespan that is 8-15 years shorter than people without this disorder [7] and are more likely to have other mental health issues like anxiety, attention-deficit /hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), and substance use disorders/dual diagnosis [8]. If left untreated, there can be problems related to drug and alcohol use, suicide or suicide attempts, legal or financial problems, damaged relationships, and poor school performance [6]. An effective treatment plan for bipolar disorder usually involves medication, such as mood stabilizers, antidepressants, and antipsychotics, as well as psychotherapy [9].

3. Genetic risk score (GRS)

A genetic risk score (GRS) quantifies the degree to which an individual's genetics increases their likelihood of developing a specific disease. The GRS for bipolar disorder includes 286,021 variants and was developed based on the variants identified in a study that analyzed genomes of 51,710 individuals of European ancestry [10]. The study included 20,352 cases (individuals with bipolar disorder) and 31,358 healthy controls.

Number of variants in genetic risk score	**286,021**
Discovery GWAS(n=51,710)	Cases: 20,352 Controls: 31,358

Table 1: **Discovery cohort statistics**. Variants in GRS and sample number used in the bipolar disorder GWAS.

4. Performant bipolar disorder risk stratification

4.1. Validated using a large cohort of individuals with known disease status

Within the UK Biobank cohort, adults in the 99th percentile of genetic risk have a 1.66% absolute risk of bipolar disorder, compared to 0.45% for the baseline rate. Baseline rate is the prevalence of the disease in the entire reference population.

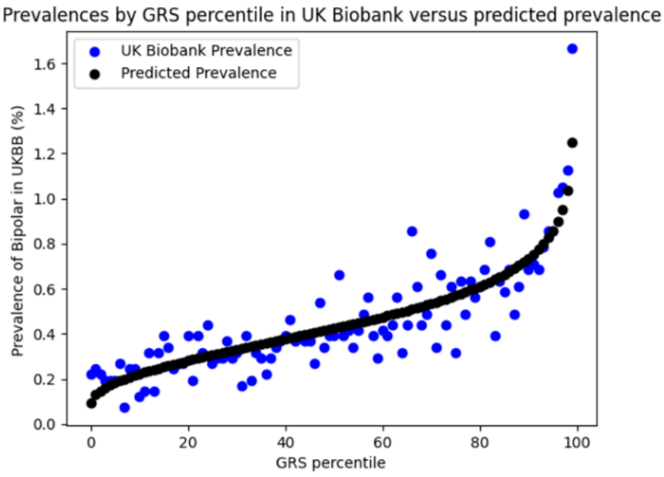

Figure 1: Risk gradient for bipolar disorder. Each blue dot represents a percentile of Genetic Risk Score, with its percent prevalence in UK Biobank self-reported White British in the y-axis. The black line represents the predicted prevalence from a logistic regression derived from the data.

In the UK Biobank, cases were identified using self-reported bipolar disorder and relevant ICD-9 and -10 diagnosis codes. See supplementary table for more details. In the validation, prevalence of the disease increased with GRS. Using our phenotype definition, in our sample of self-reported white British, there were 1855 cases of bipolar disorder and 406,665 controls (prevalence of 0.45%).

Elevated Genetic Risk Definition	Prevalence	Odds ratio
Baseline rate	0.45%	1.0
Top 5% of distribution	1.15%	2.54
Top 3% of distribution	1.28%	2.84
Top 1% of distribution	1.66%	3.71
Top 0.5% of distribution	1.86%	4.15

Table 2: **Prevalence and odds ratios of bipolar disorder in elevated genetic risk subgroups.** Adults at the tail end of GRS distribution were at an elevated risk for and had higher odds for the disease in comparison to the baseline rate of 0.45%.

4.2. Comparing Baseline and elevated risk for bipolar disorder

Adults in the 99th percentile of genetic risk have a 1.66% risk of developing bipolar disorder. The odds ratio for adults in the 99th percentile of genetic risk was 3.7.

5. Comparison to Published Benchmarks

Orchid's model achieves comparable stratification performance with an AUC of 0.624 compared to the benchmark at 0.65.

We compared the performance of our model as validated on the UK Biobank with the performance of a similar model in Mullins et al [11]. In the first column, we give the results for our predictor with the phenotype as described above. In the second, we report the metrics for the best-performing predictor in Mullins et al using the numbers reported in their paper.

Bipolar disorder GRS	Orchid	Reference[1]
AUC	0.624	0.65

Table 3: **Accuracy metric comparison.** Our model compared to reference.

References

[1] Orchid Team. Bipolar disorder whitepaper. Available at `https://www.nimh.nih.gov/health/topics/bipolar-disorder`, 2022. [cited 2 Aug 2022].

[2] DP Hibar, Lars Tjelta Westlye, Nhat Trung Doan, Neda Jahanshad, JW Cheung, Christopher RK Ching, Amelia Versace, AC Bilderbeck, Anne Uhlmann, B Mwangi, et al. Cortical abnormalities in bipolar disorder: an mri analysis of 6503 individuals from the enigma bipolar disorder working group. *Molecular psychiatry*, 23(4):932–942, 2018.

[3] Jennifer H Barnett and Jordan W Smoller. The genetics of bipolar disorder. *Neuroscience*, 164(1):331–343, 2009.

[4] Tuula Kieseppä, Timo Partonen, Jari Haukka, Jaakko Kaprio, and Jouko Lönnqvist. High concordance of bipolar i disorder in a nationwide sample of twins. *American Journal of Psychiatry*, 161(10):1814–1821, 2004.

[5] Orchid Team. Bipolar disorder statistics. Available at `ttps://www.nimh.nih.gov/health/statistics/bipolar-disorder`, 2022. [cited 2 Aug 2022].

[6] Orchid Team. Bipolar disorder–symptoms & causes. Available at `https://www.mayoclinic.org/diseases-conditions/bipolar-disorder/symptoms-causes/syc-20355955`, 2022. [cited 2 Aug 2022].

[7] Wong C Chan J, Chen E Yung N, and Chang W. Excess mortality and life-years lost in people with bipolar disorder: An 11-year population-based cohort study. Available at `https://doi.org/10.1017/S2045796021000305`, 2021.

[8] Orchid Team. Clinic–bipolar disorder. Available at `https://my.clevelandclinic.org/health/diseases/9294-bipolar-disorder`, 2022. [cited 2 Aug 2022].

[9] Orchid Team. Bipolar disorder–treatments and therapies. Available at `https://www.nimh.nih.gov/health/topics/bipolar-disorder#part_2264`, 2022. [cited 2 Aug 2022].

[10] Eli A Stahl, Gerome Breen, Andreas J Forstner, Andrew McQuillin, Stephan Ripke, Vassily Trubetskoy, Manuel Mattheisen, Yunpeng Wang, Jonathan RI Coleman, Héléna A Gaspar, et al. Genome-wide association study identifies 30 loci associated with bipolar disorder. *Nature genetics*, 51(5):793–803, 2019.

[11] Niamh Mullins, Andreas J Forstner, Kevin S O'Connell, Brandon Coombes, Jonathan RI Coleman, Zhen Qiao, Thomas D Als, Tim B Bigdeli, Sigrid Børte, Julien Bryois, et al. Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. *Nature genetics*, 53(6):817–829, 2021.

6. Appendix

Disease case identification and number of cases in UK Biobank

Phenotype	ICD-10 Codes	Self-Report Codes	Cases in UK Biobank (white British)
Prostate cancer	C61, D075	1044	13,806
Type 2 diabetes	E11.1-9	1223	30,507
Coronary artery disease	I2104,1219,I220, I221,I228,I232 I233,I235,I236 I238,I249,I252	1075	22,451
Breast cancer	C5.0-9, D05.0, D059	1002	18,588
Inflammatory bowel disease	K51	1461,1462 ,1463	5,959
Atrial fibrillation	148.0-4,148.9	1471,1483	22,472
Schizophr enia	F20.0-9, F21, F23.0-3, F23.8	1289	1,376
Alzheimer's disease	F00.0-2, F00.9, G30.0-1,8-9.	1263	2,547
Celiac disease	K900	1456	3,253
Bipolar disease	F31	1291	1,855
Type 1 diabetes	*	*	421

Table 4: Supplementary Table: How each disease case is defined in evaluating genetic risk scores in the UK Biobank

*Type 1 diabetes was defined as a combination the following inclusion and exclusion criteria:

- Self-diagnosed diabetes (any type)
- No self-diagnosed Type 2 diabetes
- Age of diabetes onset between 0 and 20 years
- Started insulin within one year of diagnosis of diabetes