Orchid Genetic Risk Score: Schizophrenia

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

Written by the Orchid Team

1. Schizophrenia

Schizophrenia is a severe and often debilitating long-term psychiatric condition, characterized by persistent cognitive deficits, frequent hallucinations and/or delusions, and social withdrawal [1]. The exact cause of the disease is unknown [2] but a study conducted on 31,524 twin pairs estimated the disease to be about 65.1 to 88.2% heritable [3].

2. Clinical Impact and Prevalence

About 1.5 million Americans (or 0.45% of the population) currently live with schizophrenia, and the disease is typically diagnosed in the early-mid 20s for males, and the early-mid 30s for females [4], [5]. The NIH has established three categories of symptoms for schizophrenia: psychotic symptoms, including delusions and hallucinations, negative symptoms, including reduced motivation and anhedonia, and cognitive symptoms, including problems with focusing or retaining information [4]. People with schizophrenia have an average lifespan that is 10 years shorter, mostly through higher suicide rates [6]. Like many psychiatric disorders, schizophrenia is very expensive for health systems and in 2001, was the 8th leading cause of DALY’s (a measure of disability that quantifies the years of healthy life lost) for young adults (15-44 years) [7]. Treatment of schizophrenia is through antipsychotic drugs, ideally with substantial social support [1], though patients tend to have residual symptoms and deficits [8].

3. Genetic risk score (GRS)

A genetic risk score quantifies the degree to which an individual’s genetics increases their likelihood of developing a specific disease. The GRS for schizophrenia includes 28,207 variants and was developed based on the variants identified in a study that analyzed genomes of 150,064 individuals of European ancestry [9]. The study included 36,989 cases (individuals with schizophrenia) and 113,075 healthy controls [9].

| Number of variants in genetic risk score | 28,207 |
|----------------------------------------|--------|
| Discovery GWAS(n=150,064)              |        |

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

4. Performant schizophrenia 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 1.44% absolute risk of schizophrenia, compared to 0.34% for the baseline rate. Baseline rate is the prevalence of the disease in the entire reference population.

In the UK Biobank, cases were identified using self-reported schizophrenia (UK Biobank field 20002, code 1289) relevant ICD-9 and -10 diagnosis codes. See our supplementary table for full 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 1,386 cases of schizophrenia and 407,144 controls (prevalence of 0.34%).

| Elevated Genetic Risk Definition | Prevalence | Odds ratio |
|----------------------------------|------------|------------|
| Baseline Prevalence              | 0.34%      | 1          |
| Top 5% of distribution           | 0.86%      | 2.57       |
| Top 3% of distribution           | 0.92%      | 3.44       |
| Top 1% of distribution           | 1.44%      | 4.34       |
| Top 0.5% of distribution         | 1.71%      | 5.16       |

Table 2: Prevalence and odds ratios of schizophrenia in elevated genetic risk subgroups.
4.2. Comparing baseline and elevated risk for schizophrenia

Adults in the 99th percentile of genetic risk develop schizophrenia at 4.24 times the baseline rate, with an odds ratio of 4.34.

5. Comparison to Published Benchmarks

We compared the performance of our model as validated on the UK Biobank with the performance of a similar model in Zhang et al [10]. To make a comparison of models, we restricted our validation sample to those in Phase II of the UK Biobank release, as in Zhang et. al. 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 Zhang et. al using the numbers reported in their paper.

| 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 | I210, I219, 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 | I48.0-4, I48.9 | 1471, 1483 | 22,472 |
| Schizophrenia      | 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                             |

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

6. Appendix

Disease case identification and number of cases in UK Biobank

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

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