

## SUPPLEMENTARY MATERIALS

### Fecundity effects on schizophrenia liability in the general population

#### DATA:

- 1- The heritability ( $h^2$ ) of liability for schizophrenia that is explained by its polygenic risk score (PRS) has been estimated as **0.05153** (Pardiñas *et al.* 2018). At the moment that study was carried out, this result was based on the largest available training sample (34,241 cases and 45,604 controls; Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014) and the largest available testing sample (5,220 cases and 18,823 controls; Pardiñas *et al.* 2018). The PRS used in the present study was produced by combining both samples, and thus this  $h^2$  value could be a slight underestimation.
- 2- The lifetime prevalence of schizophrenia is **0.0072**, which is the median of a review of 188 independent studies (McGrath *et al.* 2008). According to the authors, the median is a more appropriate estimation of the central value than the mean due to the skewed distribution of prevalences reported by different studies.
- 3- The ratio of fecundities of patients with schizophrenia to unaffected individuals is **0.35** (Power *et al.* 2013). This figure might be an underestimation as it is based on a sample of people older than 40 years of age and does not account for the reduced life expectancy seen in schizophrenia (Larsen *et al.* 2014).
- 4- In the present study, the linear regression of the number of children of unaffected individuals on the PRS gives  $r^2=0.000084$  with a 95% confidence interval  $r^2=[0.000023 - 0.000184]$ . The direction of effect shows that higher PRS leads to more children.
- 5- In the present study, the mean and variance of number of children of unaffected individuals are **1.8087** and **1.3988** respectively.

#### RESULTS:

- 1- **Genetic variance for fecundity that is explained by the liability threshold model of schizophrenia:**

The liability threshold model is responsible for a fraction of the phenotypic variance for fecundity which can be calculated from the data above. The mean fecundity in the general population (i.e. affected and unaffected individuals) explained by the liability threshold model, considering only the reduction in fecundity caused by schizophrenia, is:

$$M = (1 - 0.0072) * 1 + 0.0072 * 0.35 = 0.99532$$

After scaling for average fecundity=1, the phenotypic variance for fecundity in the general population, which is explained by the liability threshold model, is

$$V = [(1 - 0.0072) * 1^2 + 0.0072 * 0.35^2 - M^2]/M^2 = 0.0030$$

These calculations implicitly assume that the phenotypic variance is generated by the onset of schizophrenia (i.e. the disorder leads to a reduction in fecundity). Therefore, the heritability of schizophrenia equals the heritability of fecundity explained by schizophrenia. Consequently, the genetic variance for fecundity in the general population explained by variation in schizophrenia PRS under the liability threshold model is the product of the phenotypic variance for fecundity and the heritability explained by PRS:

$$V_{g\_SCZ} = 0.0030 * 0.05153 = 0.000155$$

## 2- Genetic variance for fecundity in unaffected individuals explained by variation in PRS:

The squared correlation between fecundity and PRS is the proportion of the variation in fecundity that is explained by PRS. After scaling for average fecundity=1, we get:

$$V_{g\_unaffected} = 0.000084 * \frac{1.3988}{1.8087^2} = 0.000036$$

The largest source of error in all these calculations corresponds, by far, to the estimated  $r^2$ . Using its 95% confidence interval we can get an approximation of plausible values for the genetic variance:

$$V_{g\_unaffected} = [0.000010 - 0.000079]$$

## CONCLUSION:

If we consider that fecundity is a measure of fitness, genetic variance for fecundity is the expected change of fitness by selection in a single generation (Fisher 1930, Edwards 2014). Thus, the comparison of variances gives the relative magnitude of the two selective forces:

$$V_{g\_SCZ}/V_{g\_unaffected} = 4.31$$

A range can be approximated using the 95% confidence interval of  $V_{g\_unaffected}$ :

$$V_{g\_SCZ}/V_{g\_unaffected} = [1.96 - 15.50]$$

This ratio refers to the genetic variance explained by PRS in this study. Strictly, this cannot be extended to the whole genetic system affecting schizophrenia, unless we accept that the expected fertility of unaffected individuals is a linear function of the liability score of individuals for schizophrenia. Thus, although the present study detects a selective force acting in favour of the persistence of schizophrenia risk alleles in the general population, its effect is offset by the removal of these alleles caused by the reduced fecundity of affected individuals.

## REFERENCES:

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