Applying polygenic risk scoring for psychiatric disorders to a large family with bipolar disorder and major depressive disorder

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Psychiatric disorders are thought to have a complex genetic pathology consisting of interplay of common and rare variation. Traditionally, pedigrees are used to shed light on the latter only, while here we discuss the application of polygenic risk scores to also highlight patterns of common genetic risk. We analyze polygenic risk scores for psychiatric disorders in a large pedigree (n ~ 260) in which 30% of family members suffer from major depressive disorder or bipolar disorder. Studying patterns of assortative mating and anticipation, it appears increased polygenic risk is contributed by affected individuals who married into the family, resulting in an increasing genetic risk over generations. This may explain the observation of anticipation in mood disorders, whereby onset is earlier and the severity increases over the generations of a family. Joint analyses of rare and common variation may be a powerful way to understand the familial genetics of psychiatric disorders.
The development of polygenic risk scoring (PRS) has greatly advanced the field of psychiatric genetics. This approach allows for even sub-genome-wide significant threshold results from large genome-wide meta analyses to be leveraged to explore genetic risk in smaller studies. The effect sizes at many individual single-nucleotide polymorphisms (SNPs), estimated by large genome-wide association studies (GWAS) on the disorder of interest, are used to calculate an individual level genome-wide PRS in individuals from an independent genetic dataset. The PRS based on the summary statistics of the schizophrenia (SCZ) GWAS by the Psychiatric Genomics Consortium (PGC) has proven to be most powerful in predicting not only SCZ, but also other psychiatric disorders. In addition, updated, more powerful, summary statistics from the Psychiatric Genomics Consortium from the latest GWAS for bipolar disorder (BPD) and major depressive disorder (MDD) are available via the PGC Data Access Portal (https://www.med.unc.edu/pgc/shared-methods).

Aside from increasing power in traditional case-control designs, PRS algorithms also open up new avenues for studying common variation. In this study, we consider the application of PRS within a family context. While pedigree studies have been traditionally used to explore rare genetic variation through linkage analyses, studying patterns of PRS throughout a pedigree would allow for assessment of phenomena like assortative mating and anticipation. Assortative (non-random) mating is a common phenomenon where mated pairs are more phenotypically similar for a given characteristic than would be expected by chance. Results from a recent study by Nordsletten et al. show extensive assortative mating within and across psychiatric, but not physical disorders. This could explain some of the features of the genetic phenomenon as evidenced by no significant differences in PRS as compared to the population control group (BRA; see Methods).

In the current study, we aim to discuss the application of polygenic risk scoring for SCZ, MDD, and BPD to explore patterns of common risk variation within a family context. We illustrate our discussion by investigating the relationship between PRS and apparent assortative mating, and anticipation within a complex multigenerational pedigree affected with mood disorders.

**Results**

**Study overview.** We identified a large pedigree in Brazil, the Brazilian Bipolar Family (BBF), after examination of a 45-year-old female who presented with severe Bipolar Type 1 (BPI) disorder. She stated there were dozens of cases of mood disorders in the family, most of whom lived in a small village in a rural area of a large state north of São Paulo (see Methods for details). We conducted 308 interviews using the Portuguese version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/16 for family members over the age of 16 and the Portuguese version of Kiddie-SADS-Present and Lifetime Version (K-SADS-PL) for family members aged 6–16. Following diagnostic interviews, we conducted genotype analysis of all interviewees using the illumina Illuminum PsychArray-24. Polygenic risk scores (PRS) were assigned to each family member using PRS thresholds most predictive in discriminating affected from unaffected family members (see Methods).

**Affection status.** The PRS thresholds were selected to optimally discriminate between affected (n = 78) versus unaffected (n = 147) family members with a higher score in affected for SCZ:PRS (Beta = 0.069, SE = 0.032, Z-ratio = 2.117, p = 0.035, R² = 0.021), and BPD:PRS (Beta = 0.094, SE = 0.030, Z-ratio = 3.123, p = 0.002, R² = 0.039). None of the PRS significantly discriminated between individuals having experienced a psychotic episode at some point in their lives (n = 25) versus the unaffected group (n = 147). Visualization of PRS in different diagnostic categories is shown in Supplementary Figure 1.

**Assortative mating.** Married-in individuals were defined as individuals married to a BBF member, but having no parents in the family themselves. Of the 70 married-in individuals ascertainment (irrespective of having genotype data) 19 (27%) were affected with a psychiatric disorder. This is significantly higher than the 17% population prevalence of the most common of the three disorders: MDD (Fisher’s exact p = 0.02). The unaffected married-in group does not differ from the general healthy population as evidenced by no significant differences in PRS as compared to the population control group (BRA; see Methods).

The above led us to investigate whether we can observe assortative mating on a genetic level, using PRS. In spouse pairs, we were unable to predict the PRS of the husband, using that of his wife, even when selecting concordant (both affected or both unaffected) pairs only. We considered the possibility that the married-in individuals might confer a different genetic predisposition to mood disorders to their offspring than the original family members. The number of children contributed per spouse pair to each offspring category is shown in Supplementary Table 1. Demographics of the offspring in the different offspring categories (no affected parents (n = 54); one affected family member parent (n = 69); one affected married-in parent (n = 15) and two affected parents (n = 30)) are given in Supplementary Tables 2 and 3. Indeed, we find that offspring of an affected married-in parent show increased SCZ:PRS (Beta = 0.209, SE = 0.064, Z-ratio = 3.288, p = 0.002, R² = 0.186, Fig. 1) and BPD:PRS (Beta = 0.172, SE = 0.066, Z-ratio = 2.613, p = 0.013, R² = 0.126, Fig. 1) as compared to having no affected parents.

**Anticipation.** The BBF shows patterns of anticipation, with individuals having an earlier age at onset (AAO) in later generations. For 104 individuals (irrespective of having genotype data), the average age at onset significantly decreases over generations with G2 (n = 1, AAO = 8), G3 (n = 23, AAO = 30.2 yrs ± 21.1), G4 (n = 53, AAO = 31.2 yrs ± 12.3), G5 (n = 5, AAO = 19.7 yrs ± 9.5), and G6 (n = 4, AAO = 13 yrs ± 3.6) (Supplementary Table 2) with older participants recalling their AAO directly and younger participants recalling their AAO indirectly using clinical records or parental recall (Beta = −4.549, SE = 1.793, Z-ratio = −2.537, p = 0.013, R² = 0.059). We hypothesized that this decrease in AAO would be reflected in a negative correlation with PRS, subsequently resulting in a pattern of increased PRS over generations. Because of a limited sample size of affected individuals per generation, a direct correlation of AAO and PRS does not reach significance, although the youngest generation (G5) does show trends towards negative correlations for SCZ:PRS and MDD:PRS (Supplementary Figure 3). The SCZ:PRS does show a significant increase over generations (Fig. 2) where n = 197 family members were included (46 married-in individuals were excluded from the analysis to capture inheritance patterns of SCZ:PRS) in a linear regression with generation as independent variable (Beta = 0.131, SE = 0.049, Z-ratio = 2.668, p = 0.008, R² = 0.025). The presence of such an effect when comparing generations suggests ascertainment effects such as relying on the recall of older family member with very long duration of illness in previous generations may be masking an overall effect across the entire family.

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Discussion
The current study is one of the first to study patterns of
common genetic variation within a traditional pedigree
design. While increased polygenic scores in patients as
compared to unaffected family members have been demonstrated recently17,
we aimed to illustrate the possibilities of this approach by investigating apparent assortative mating and anticipation in a
large multigenerational pedigree affected with mood disorders
through polygenic risk scores for SCZ2, MDD18, and BPD19, and thereby improve mechanistic understanding of common genetic risk for psychiatric disorders.

Highlighting the possibilities of PRS applications within a
family context, we set out to utilize patterns of common variation to
illuminate phenomena within the family that are out of reach
from traditional case/control studies. Assortative mating is one of
the features in this family, where many married-in individuals are
more affected with a mood disorder than the general population.
As opposed to the family members, the married-in individuals
were more often affected with (r)MDD instead of BP. As diagnoses
were determined after the couples were married, we cannot
rule out that this could be a result from a causal effect of a spouse’s
mental health on that of their partner. However, non-random
mating patterns have been reported in the population regarding
body type, socio-economic factors and psychiatric traits8,10. The
BFB provides a unique opportunity to look at the genetic corre-
lation between spouse pairs and the contribution of married-in individuals to overall psychiatric morbidity. A recent study has
found genetic evidence for assortative mating when studying BMI
and height in spouse pairs11. In the BFB, the affected married-in
individuals have a higher, though non-significant, polygenic score
than affected or unaffected family members but it appears that we
observe significant consequences of this in that the offspring of an
affected married-in parent collectively show significantly increased
SCZ:PRS and BPD:PRS. However, it is puzzling we do not see an
effect on offspring of two affected parents (which would include a
married-in parent), which could indicate this finding to be of
limited statistical robustness.

A contribution of the married-in parents to a genetic driven
anticipation in age of onset is supported by the increase in SCZ:
PRS over generations, although our cross sectional study dataset
was less well powered to find an association with age at onset
within affected family members. We did observe a trend for
association between age at onset and PRS in the youngest
generation in this study but not when combining sample across
generations. Age at onset can be considered a proxy for
severity20,21 and has been previously associated with genetic risk
in MDD13,14. However, this variable needs to be interpreted with
cautions, especially when analyzing patterns over time since it is
dependent on context and memory22. Ascertainment bias can be
a confounding factor in studies of psychiatric traits, with older
generations having less access to psychiatric care and possibly
misremembering the onset or nature of their first episode. In
addition, although currently classified as “unaffected” or
“unknown”, members of the youngest generations can still
develop a psychiatric disorder in the future.

Finally, we explored the balance of common and rare risk
variation through combining our current PRS results with
previously performed linkage analyses. We did not find a decrease in potential rare risk allele genotypes over generations contrasting the increase in SCZ:PRS, and PRS profiles for individuals carrying rare risk genotypes are not significantly different. This indicates that these factors separately confound independent disease risk. We recognize the limitations in sample size of our pedigree and therefore the power to draw statistically robust conclusions, especially in the offspring and combined linkage and PRS analyses. Even though the BBF might not be sufficiently powered, our point is to use this dataset to illustrate our approach and emphasize the unique nature of the family enabling the study of patterns of PRS and the balance of common and rare genetic risk for psychiatric disorders conferred within families. We encourage replication in similar pedigrees including affected married-in individuals when available to fully utilize the potential of PRS in this setting.

In conclusion, our study is an exploration of PRS as a tool for investigating patterns of common genetic risk in a traditional pedigree context. The SCZ and BPD scores appear best suited in investigating patterns of common genetic risk in a traditional setting. The SCZ and BPD scores appear best suited in investigating patterns of common genetic risk in a traditional setting. This setting.

### Methods

#### Subject description

The Brazilian bipolar family (BBF) was ascertained via a 45-year-old female proband who presented with severe Bipolar Type 1 (BPI) disorder during their lifetime. Historically, the entire BBF consists of 960 individuals (197 family members and 46 married-in individuals) and 57 BRA controls. The BBF and the BRA control dataset at the in-house BRC BioResource Illumina core lab according to manufacturers protocol. Samples were excluded when average call rate was <89%, missingness >1% with additional check for excess heterozygosity, sex, family relationships and concordance rates with previous genotyping assays. SNPs were excluded when missingness >1%, MAF <0.01 or HWE <0.00001 and if showing Plink v1.07 or Merlin v1.1.29. The BBF and BRA control datasets were QC separately and then merged, applying the same SNP QC thresholds to the merged dataset as well. This quality control procedure resulted in a dataset of 225,235 SNPs for 243 BBF individuals (197 family members and 46 married-in individuals) and 57 BRA controls. Eigensort v4.20 was used to check for population differences between the BBF family members, married-in individuals and BRA control sets. The BBF members self-reported mixed Southern European ancestry, confirmed by genome-wide principal components analysis showing that family members clustered closely with the Northern and Western European and Tuscan Italian populations in Hapmap3, with a relative lack of African or Native American ancestry (Supplementary Figure 6). The principal components appear to represent within-family structure, with most PCs seemingly separating subfamilies (Supplementary Figures 7 and 8). PRS analyses as described below were also performed to include subfamily as a fixed effect, controlling for household effects (Supplementary Table 3). PC1 and PC2 are significantly correlated to the SCZ:PRS (PC1 r = −0.131, p = 0.023; PC2 r = −0.268, p = 2.61 × 10−5), PC1 to MDD:PRS (PC1 r = −0.251, p = 1.11 × 10−5), and PC1 and PC2 to BPD:PRS (PC1 r = 0.189, p = 9.71 × 10−4, PC2 r = −0.123, p = 0.033). The principal components were not used in subsequent analyses.

### Polymorphic risk scores

Polymorphic risk scores for each family member (n = 243) and population control (n = 57) were generated in the same run using the PRSice v1.25 software31 with the publicly available PGC schizophrenia GWAS3 as a base dataset (36,989 SCZ cases, 113,075 controls), in addition to MDD (51,865 MDD cases, 112,200 controls, not including index individuals) and BPD (20,352 BPD cases, 31,358 controls) summary statistics from the latest PGC meta analyses (unpublished data32). We performed p-value-informed clamping on the genotype data with a cut-off of r2 = 0.25 within a 200-kb window, excluding the MHC region on chromosome 6 because of its complex linkage disequilibrium structure. Acknowledging the possibility of over-fitting, we selected the PRS thresholds most predictive in discriminating affected from unaffected family members through linear regression in PRSice for SCZ:PRS (p < 0.00055, 1218 SNPs), MDD:PRS (p <


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Additional information

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