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Association between Inflammatory and Metabolic markers and the Polygenic Risk Score of Schizophrenia in First Episode Psychosis

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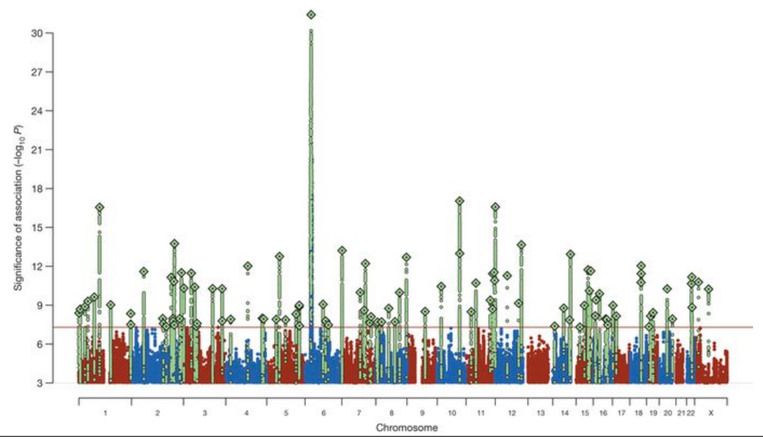
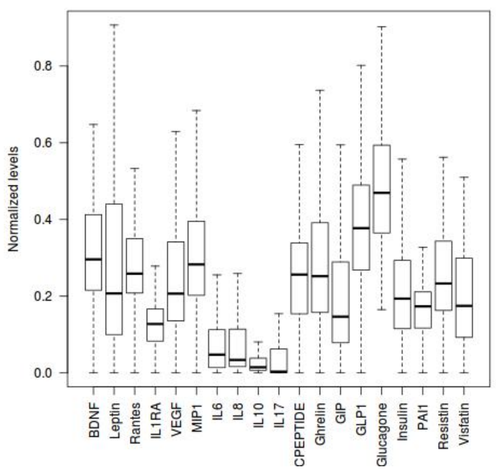
Introduction

In psychiatry, there is a strong interest for the identification of genetic and expression biomarkers supporting diagnosis and personalized treatment. In this work using a systems biology approach, we correlated the polygenic risk score for schizophrenia with serum levels of 19 different inflammatory/metabolic markers in 116 subjects including 83 patients at first episode psychosis and 33 controls. The results suggest an association between the genetic component for schizophrenia and the presence of altered biomarkers in psychosis. In particular, we identified a significant positive correlation between the polygenic risk score of schizophrenia and the levels of MIP-1b/CCL4 and negative association with ghrelin.



$$PRS = \sum_{i=1}^{n} w_i \cdot X_i$$

- X_i= effect allele
- W_i=Weight



Method

Polygenic Risk Score (PRS) for each individual has been computed according to the latest Psychiatric Genomics Consortium (PGC2) schizophrenia meta-analysis [1] as base dataset. The PRS has been computed as the weighted sum of the risk alleles (log of odd ratio as weighs). The correlation between PRS and 19 metabolic and inflammatory biomarkers have been computed (see [2] for more details about biomarkers selection). Linear regression and Spearman correlation tests were used to identify correlation between protein serum levels and PRS after outliers removal (Mahalanobis distance<3). The correlations have been tested by selecting the best fitting model considering different p-value thresholds for variant selections in PRS computation (from genome wide significant to full SNPs). Pathway specific PRS have been computed by selecting variants in gene regions of genes involved in different biological processes (i.e., 186 kegg pathways). Case-control status prediction have been tested by comparing ROC curve considering schizophrenia PRS and molecular markers differentially expressed in case/control status (in an independent sample).

Results

Biomarker	PRS.R2	P	Direction
MIP1	0,11	6,84E-03	+
Ghrelin	0,10	7,86E-03	-
C-Peptide	0,04	5,75E-02	+
IL6	0,03	6,04E-02	-
Glucagone	0,07	6,32E-02	-
GLP1	0,03	6,39E-02	-
Leptin	0,03	7,22E-02	-
GIP	0,03	7,48E-02	-
VEGF	0,08	7,88E-02	+
BDNF	0,02	1,05E-01	+
Rantes	0,03	1,19E-01	+
Insulin	0,02	1,83E-01	+
PAI1	0,02	1,96E-01	-
IL17	0,01	2,09E-01	-
IL10	0,01	2,87E-01	+
IL8	0,01	3,40E-01	+
IL1RA	0,01	3,74E-01	-
Visfatin	0,01	4,10E-01	-
Resistin	0,01	4,99E-01	+

Table 1. Nagelkerke R^2 and P value of the best fitting model

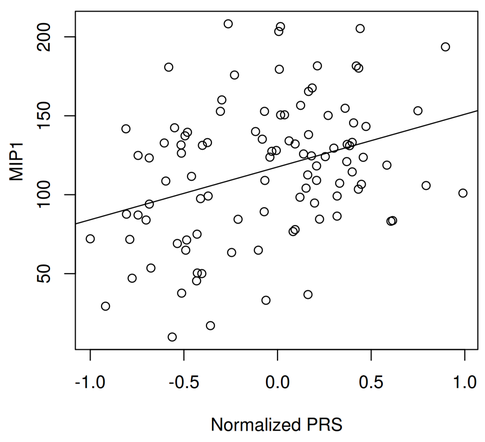


Fig. 1) Scatter plot and linear regression line between PRS and MIP1 levels (pgml)

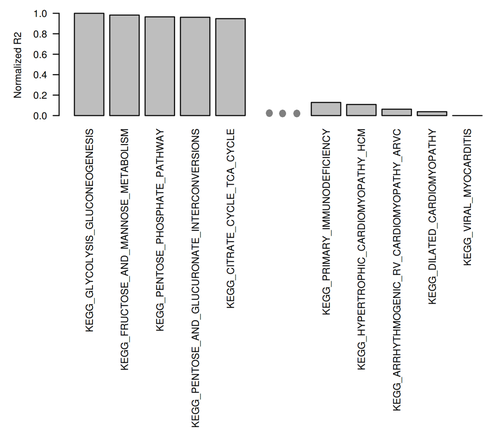


Fig. 2) Normalized R^2 of pathway specific PRS (top and bottom five for MIP1)

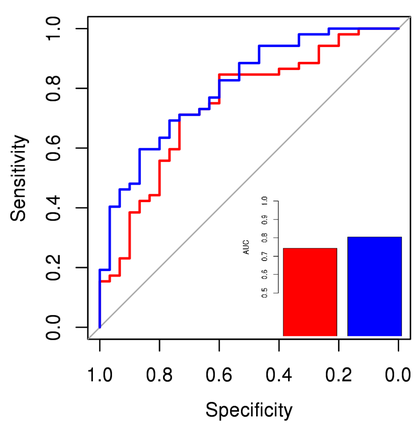


Fig. 3) ROC and AUC for: Biomarkers (red), schizophrenia PRS+ Biomarkers (blue)

Schizophrenia PRS analysis identified a significant positive association with the inflammatory biomarkers MIP1/CLL4 (Fig.1) and a significant negative association with the hormone ghrelin (Table 1). Noteworthy, in the analyzed cohort MIP1 levels were increased in patients compared to controls, while ghrelin levels were decreased (data not shown, see [2]). Interestingly, pathway specific PRS analysis showed that genes involved in different pivotal metabolic pathways (e.g., related to amino acids and nucleotides synthesis/degradation) are the ones leading the associations for both MIP1 (data not shown) and ghrelin (Fig.2). The inclusion of schizophrenia PRS in the logistic prediction models of case/control status based on biomarkers levels improved AUC from 0.74 to 0.80 (Fig.3).

Conclusion

In this study,we show that there are correlations between schizophrenia PRS and the level of inflammatory/metabolic biomarkers at first episode psychosis. Noteworthy, pathway specific PRS shows that associations are not uniformly distributed among the genome but are mainly due to genes involved in inflammatory and metabolic pathways supporting the presence of a correlation between the genetic susceptibility for schizophrenia and biological processes involved inflammation and metabolism regulation. The analysis of the performance of prediction models including schizophrenia PRS and biomarkers levels suggest that integrated approaches evaluating multi-levels omics could provide better phenotype classification.

References

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2) Immune and metabolic alterations in first episode psychosis (FEP) patients. Bocchio-Chiavetto et al. Brain, Behavior, and ImmunityVolume 70, May 2018, Pages 315-324.