Identification of immune-related serum proteins associated with genetic risk of bipolar disorder

Mojtaba Oraki Kohshour[1, 2], Sergi Papiol[1,3], David Just[4], Nirmal R. Kannaiyan[5], Monika Budde[1], Urs Heilbronner[1], Janos L. Kalman[1,3], Eva C. Schulte[1,3], Marcella Rietschel[6], Markus M. Nöthen[7], Thorsten Müller[1], Moritz J. Rossner[5], Peter Falkai[3], Peter Nilsson[4], Thomas G. Schulze[1,8]

(1)Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Munich, Germany (2) Department of Immunology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (3) Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany (4) Department of Protein Science, SciLifeLab, KTH Royal Institute of Technology, Stockholm, Sweden (5) Molecular and Behavioral Neurobiology, Department of Psychiatry, Medical Center of the University of Munich, Germany (6) Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany (7) Institute of Human Genetics, University of Bonn, School of Medicine & University Hospital Bonn, Bonn, Germany (8) Department of Psychiatry and Behavioral Sciences, SUNY Upstate Medical University, Syracuse, NY, United States

INTRODUCTION

The diagnostic criteria for bipolar disorder (BD) and schizophrenia (SCZ) have not significantly changed over the last decades and are still based on clinical assessments of symptoms and signs. Sensitive and valid biomarkers for diagnosis and prognosis have not yet been identified, in part due to the difficulties to access the brain. Within the framework of personalized medicine, many efforts have been made to identify biomarkers in blood using state-of-the-art molecular techniques for improving the diagnosis and predicting the prognosis of these disorders. In this pilot study, we applied high-throughput antibody-based protein profiling in the serum of BD and SCZ patients with the aim of investigating the effects of polygenic risk burden on the quantitative level of patient serum proteins.

METHODS

113 schizophrenia and 125 bipolar patients belonging to the German KFO241/PsyCourse cohort(www.kfo241.de; www.PsyCourse.de) were included in this study. Analysis of a selected panel of 95 serum proteins (Table 1) was performed using a set of 155 antibodies in a high-throughput antibody-based assay. Log-transformation and standardization were done for median fluorescent intensities to consider in downstream analyses. Genotyping(Infinium PsychArray) and imputation (1000 Genomes Phase 3 reference panel) were performed for DNA samples and PRS were calculated by summing up the weighted effect of each SNP contributing to the PRS to obtain an individual estimate of SCZ and BD genetic risk burden. Age, sex, duration of illness and principal component ancestry were considered as covariates. Linear regression model in R program were applied to the correlation analysis between schizophrenia and bipolar PRS (PRS-CS method, auto settings) and the measured proteins levels.

RESULTS

After data cleaning, applying log-transformation and standardization and removing outliers, 208 cases remained. Related demographic and psychopathological data of these 208 patients is presented in Table 2. Our analyses showed an association of six proteins with the SCZ-PRS with a p-value < 0.05 (i.e. APOL1 [p-value=0.018], CEACAM5 [p-value=0.035], TNC [p-value=0.037]). In addition, 39 proteins were found to be associated with BD-PRS with a p-value<0.05 (i.e. IL1RAP [p-value=0.0012], IL6R [p-value= 0.0016], CCL5 [p-value=0.0019]) (Figure 1).

No.	Name	No.	Name	No.	Name	No.	Name	No.	Name
1	MIF	20	CCL5	39	CFP	58	HP	77	APOF
2	CD40LG	21	CEACAM5	40	IL15	59	CSF2	78	F7
3	C4BPA	22	FCN2	41	AXL	60	C4B	79	AGER
4	C8B	23	NRG1	42	APOD	61	IL1A	80	IL5
5	CFB	24	CCL11	43	IL12B	62	SERPING1	81	IL6
6	CFI	25	LTA	44	IL13	63	CFH	82	APOE
7	C1R	26	C1RL	45	IL7	64	APOB	83	CCL8
8	MBL2	27	ERBB4	46	IL4	65	TNF	84	C7
9	C1QA	28	VIP	47	CCL16	66	APOM	85	IL25
10	CSK	29	APOL1	48	C6	67	APOC1	86	ACE
11	IL6R	30	IL16	49	IL11	68	C4BPB	87	EGF
12	VWF	31	PTK2B	50	IGFBP2	69	IL17A	88	C9
13	VCAM1	32	C8A	51	BACE1	70	CFD	89	FCN3
14	APOH	33	MASP2	52	IL1B	71	IFNG	90	AVP
15	A2M	34	CD40	53	C8G	72	XCL2	91	APOA2
16	TNFRSF1B	35	LEP	54	C4A	73	CXCL8	92	APOC3
17	TNC	36	IL3	55	APOA1	74	KITLG	93	TNIK
18	ROCK2	37	IL1RAP	56	CCL18	75	APOC4	94	aAlbumin
19	PPBP	38	PPY	57	TGFB1	76	IL10	95	hIgG

Table 1. List of 95 assayed serum proteins by antibody-based microarray in this study

	SCZ	BD
Subjects (n)	108	100
Sex (%female)	40.7 %	58%
Age	45 ± 14	46 ± 14
Duration of illness(years)	14.9	13.5
PANSS_Positive	12.8 ± 5.1	9.4 ± 2.9
PANSS_Negative	13.9 ± 6.1	10.5 ± 3.9
PANSS_General	26.6 ± 8.4	23.6 ± 6.5
YMRS	2.4 ± 4.3	4.2 ± 5.9
BDI_II	11.4 ± 10.7	12.6 ± 12.2
IDSC	14.4 ± 9.7	14.1 ± 11.2

Table 2. Demographic and psychopathological data of the patients

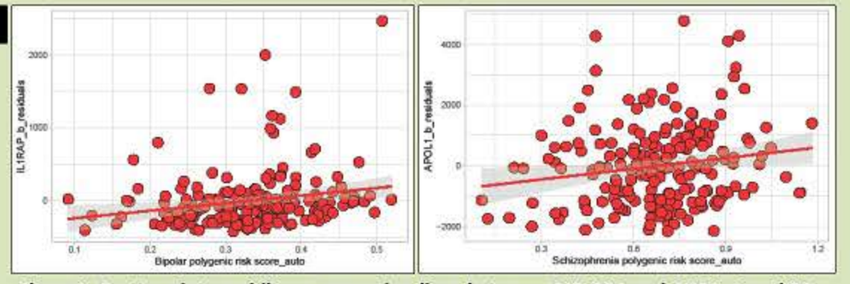

Figure1. Scatter plots and linear regression lines between SCZ-PRS and APOL_1 and BD-PRS and IL1RAP serum Levels

Therefore, our results indicate that genetic risk for BD has a greater association with the assayed serum proteins than genetic risk for SCZ. It should be noted that none of the measured protein parameters remained significant after Bonferroni adjustment.

DISCUSSION

The immune system's role in psychiatric disorders has been highlighted in different studies, and inflammatory cytokines have been linked to it in a variety of ways. Here, we found that the serum levels of many proteins involved in the immune system, particularly inflammation, are significantly modulated by BD polygenic risk scores and, to a lesser extent, SCZ polygenic risk. Our study is limited by the relatively modest sample size, which has an inevitable impact on the study's power. Moreover, the effects of medication or daily fluctuation were not controlled, but this is ongoing work in our group. Taken together, our primary results in this pilot study indicate the importance of the immune system and the inflammation process in SCZ and BD and lay the groundwork for large-scale studies to find more reliable biomarkers in SCZ and BD.

REFERENCES

Schwarz E, Bahn S. Biomarker discovery in psychiatric disorders. Electrophoresis. Juli 2008;29(13):2884–90.

Comes et al. Proteomics for blood biomarker exploration of severe mental illness: pitfalls of the past and potential for the future. Transl Psychiatry.2018;8(1):160.

Mistry et al. The use of polygenic risk scores to identify phenotypes associated with genetic risk of bipolar disorder and depression: A systematic review. J Affect Disord.2018;234:148–55.

Borrebaeck CAK, Wingren C. High-throughput proteomics using antibody microarrays: an update. Expert Rev Mol Diagn.2007;7(5):673–86.

Khandaker et al. Immunopsychiatry: important facts. Psychol Med. 2017;47(13):2229–37.