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Levels of Inhibitor Proteins of the Immune System in Schizophrenia and Bipolar Disorder: SUSD4 and SEZ6

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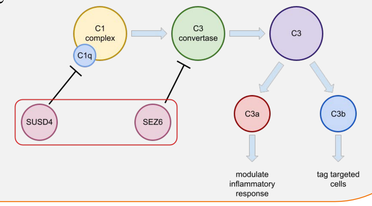
Background

The complement immune system is known to play a role in CNS development by contributing to the tagging of synapses for elimination (Westacott & Wilkinson, 2022). Specifically, the classical pathway has been determined to contribute to synaptic pruning during brain development and maturation (Woo et al., 2020). In schizophrenia (SCZ), there is an abnormal activation of the classical complement pathway (Woo et al., 2020), as well as gray matter reduction and synapse loss (Feinberg, 1982). As for bipolar disorder (BD), increased concentrations of the complement component C3a have been found in patients with BD (Reginia et al., 2018), suggesting that there is lowered inhibition of the complement system. The tight regulation of the complement system includes several proteins that contain complement control protein (CCP) domains (Qiu et al., 2021). Although originally characterized for their role in immunity, inhibitory proteins with CCP domains, including Sushi Domain Containing 4 (SUSD4) and Seizure Related 6 (SEZ6), have recently been recognized to contribute to synaptic function (González-Calvo et al., 2021), however there is a gap in knowledge of whether SUSD4 and SEZ6 proteins play a role in psychiatric disorders, such as SCZ and BD.

Aim

The aim of this study was to compare SUSD4 and SEZ6 mRNA levels in the post-mortem brain tissue of patients with SCZ or BD and the control (CON) subjects.



Methods

Samples: All samples were obtained from the Stanley Medical Research Institute (Torrey et al., 2000)

SEZ6 and SUSD4: Expression of the genes SUSD4 and SEZ6 was quantified in OFC samples from 93 subjects (32 CON, 31 SCZ, 30 BD) by quantitative RT-PCR, with SYBR green detection, using a LightCycler 480 (Roche Diagnostics, Mississauga, Canada) Reference housekeeping genes GAPDH, TBP, and ACTB were used to normalize levels.

Statistical Analyses: Data was log2 transformed and group differences were investigated using ANOVA, with contrasts to determine specific differences between control and SCZ or control and BD groups, along with two-tailed independent t-tests as needed. Exploratory analyses were performed to examine the influence of BMI, age, tissue pH, post-mortem interval (PMI), RNA integrity (RIN), medications, substance use, and smoking on gene expression.

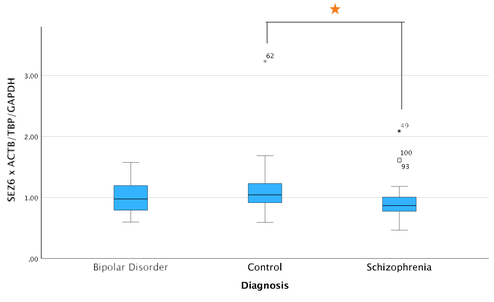
Subject Demographics

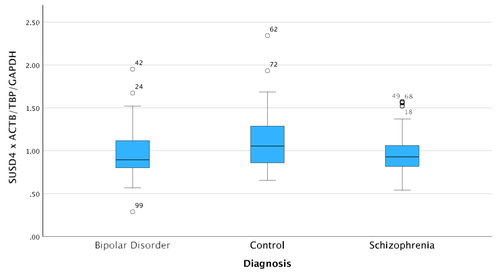
	Control (n=32)	SCZ (n=31)	BD (n=30)
Age (years, mean, SD)	43.4(7.4)	42.5(8.9)	45.3(11.0)
Sex (male/female)#	23/9	23/8	14/16
BMI (mean, SD)	31.1(10.6)	31.1(10.8)	28.1(12.5)
PMI (hours, mean, SD)	30.1(13.0)	30.5(13.5)	36.7(18.4)
Brain pH (mean, SD)	6.6(0.3)	6.5(0.3)	6.5(0.3)
Brain weight (grams, mean, SD)	1444.8(153.9)	1444.0(107.9)	1408.0(136.9)
RIN (mean, SD)	7.2(0.9)	7.3(0.7)	7.4(0.8)
Age at onset (years, mean, SD)	n/a	21.1(6.0)	25.0(9.0)
Duration of illness (years, mean, SD)	n/a	21.4(10.3)	20.3(10.0)
Mood stabilizer	0	10	20
Antidepressant	0	9	18
Alcohol history (none/social:moderate/heavy)#	27:5	14:17	10:19
Smoking (no:yes)#	8:9	3:21	6:13

Results

Mean SEZ6 mRNA level was **significantly lower** in **SCZ** (p=.025)
Mean SEZ6 mRNA level did not differ between BD and control.

Mean SUSD4 mRNA level did not differ between groups.





mRNA levels represented as ratios of normalized C_p values of the target gene to those of the reference housekeeping genes

Levels of **SEZ6**, but not SUSD4, were inversely correlated with **smoking** (r=-.285, p=.035)

No significant correlations have been found between each of the SUSD4 and SEZ6 mRNA levels with BMI of patients at the time of death, age, tissue pH, PMI, RIN, uses of mood stabilizer or antidepressant, nor uses of alcohol or drugs.

Conclusions

- **SEZ6 mRNA levels are reduced in SCZ, compared to the control**
- **No change in SEZ6 expression was observed in BD**
- **No change in SUSD4 expression was observed in either SCZ or BD**
- **Our findings are consistent with the association between an abnormal activation of the classical complement pathway and schizophrenia.**

References

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