Unravelling the Immunological Nexus: The Role of Complement Factor I and Cub and Sushi Domains in Schizophrenia Pathogenesis

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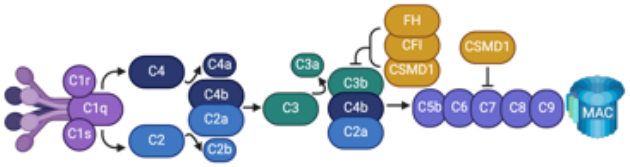
Introduction

- The complement system, an effector of innate immunity, also plays a role in synaptic pruning & plasticity, opsonizing synapses for elimination via microglial activation[1].
- In GWAS, genes linked to the complement system, including Cub and sushi multiple domains (CSMD1), have emerged as Schizophrenia (SCZ) risk genes[2,3].
- CSMD1 and its cofactors Complement Factor I (CFI) and Factor H (FH) negatively regulate complement activity[4]. SCZ patients display alterations in serum levels of complement inhibitors [5,6].

Little is known of the mechanisms by which these regulators influence SCZ risk and synaptic pathogenesis in humans.



AIM: To determine whether CSMD1, CFI and FH expression is altered in frontal cortex in SCZ and BD compared to CON, and explore the relationship with synaptic density.

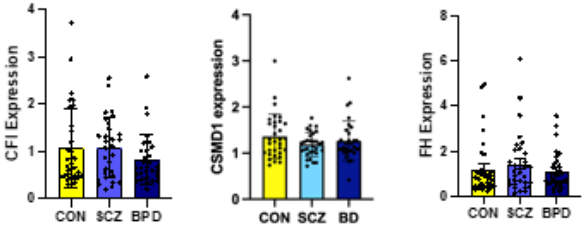
Materials and Methods

- Sample: SCZ (33), BD (32) and control (34) post-mortem brain samples of prefrontal cortex.
- Procedures: mRNA expression was quantified by qPCR. Normalization was performed by geometric averaging of reference genes (ACTB, GADPH, TBP). Pre-synaptic marker SNAP-25 was quantified by ELISA.
- Statistical Analysis: Between-group differences were investigated using ANCOVA, with diagnoses as contrasts. Potential confounders were evaluated with Spearman's correlations.

Clinical and Demographic Data

	CON (n=34)	SCZ (n=33)	BD (n=32)
Age (years)	43.8 ± 1.3	42.3 ± 1.5	45.1 ± 1.9
PMI (hours)	29.5 ± 2.2	31.8 ± 2.7	37.9 ± 3.4
Brain pH	6.6 ± 0.05	6.5 ± 0.04	6.5 ± 0.05
RNA integrity	7.2 ± 0.15	7.4 ± 0.11	7.3 ± 0.16
Body Mass Index	30.9 ± 1.6	31.3 ± 1.4	29.0 ± 1.9
Sex (M:F)	25:9	25:8	15:17
Cause of death	cardiac n=32 other n=2	cardiac n=14 suicide n=7 accident/od n=4 other n=8	cardiac n=8 suicide n=15 accident/od n=8 other n=1
Age at onset (years)	NA	21.4 ± 1.1	25.1 ± 1.6
Illness duration (years)	NA	20.9 ± 1.8	20.0 ± 1.7
Lifetime antipsychotic dose	NA	78338 ± 16702	15610 ± 6368
Mood stabilizer (no:yes)	NA	23:10	10:22
Cigarette Smoker (no:yes)	9:9	4:21	6:14
Serum CRP	12.5 ± 4.9	74.4 ± 22.3	33.7 ± 16.6

Results: Effects of Diagnosis

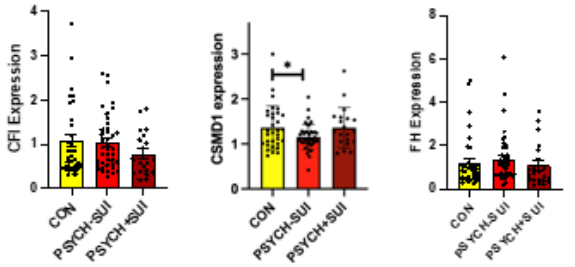


CSMD1, CFI and FH mRNA expression is unaltered across groups.

Effect of Confounders: CFI expression correlates with PMI (p=.012), pH (p=.01) and RIN (p=<.001). FH correlates with pH (p=.007) and RIN (p=<.001). CSMD1 was not significantly correlated with any of the above. Sex, smoking at time of death, age at onset and duration of illness did not impact gene expression.

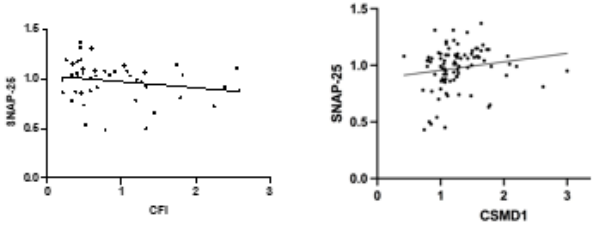
In psychiatric subjects, CFI expression correlates with lifetime antipsychotic dose (p=0.045).

Results: Effects of Suicide



CSMD1 expression is lower in psychiatric patients who did not die by suicide relative to CON (p=0.046).

Results: Synaptic Markers



CSMD1 (r=0.252, p=0.015) and CFI (r=-0.208, p=0.047) are significantly correlated with SNAP-25 levels.

Conclusions and Future Steps

- CSMD1 expression is altered in psychiatric disorders.
- CSMD1 and CFI correlate with synaptic density.
- CSMD1, CFI and FH protein expression will be quantified. Expression will be correlated with other markers of synaptic density and complement activation.

References

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Acknowledgements

Funding was provided by the Canadian Institutes of Health Research. Postmortem brain samples were donated by the Stanley Medical Research Institute brain collection.