Meta-Analysis Reveals Multiple Disease Processes Underlying Genetic Differences in Schizophrenia

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Introduction

- Schizophrenia is a severe mental illness that results in dysregulation and structural changes in multiple brain systems.
- Men and women have different presentations of schizophrenia according to age of onset, disease severity, symptoms and treatment response[1].
- The etiology is not completely understood, but studies have pointed to different genetic pathways between genders[2].
- **Our study, through meta-analysis, hopes to not only validate current genetic research but also reveal novel pathways and regulators in brain systems between genders.**

Aims and Objectives

1. Elucidate pathogenesis of schizophrenia by analyzing canonical and signaling pathways, regulation of receptors, enzymes and transcription factors.
2. Elucidate the difference of pathogenesis in schizophrenia between women and men.
3. Narrow down biomarkers that can be studied and used for therapeutic and prognostic markers.

Methods

- We employed the Search Tag Analyze Resource for GEO (STARGEO) platform to access Gene Expression Omnibus data base for genomic data.
- We examined samples in the superior temporal gyrus and prefrontal cortex because schizophrenic pathology has been indicated in these locations in the brain[3].
- We tagged 76 samples of superior temporal gyrus (STG) tissue (women: 19 cases, 18 control; men: 21 cases, 18 controls) and 171 samples of prefrontal cortex (PF) tissue (female: 28 cases/controls; male: 61 cases, 54 controls).
- We analyzed the data through Ingenuity Pathway Analysis (IPA) and filtered genes based on significance ($p<0.05$) and absolute log ratio of 0.1.

Figure 2: Cases and Controls in Prefrontal Cortex, by Gender

Prefrontal Cortex	Men	Women
Control	61	28
Cases	54	28

Figure 3: Cases and Controls in Superior Temporal Gyrus, by Gender

Superior Temporal Gyrus	Men	Women
Control	18	18
Cases	21	19

Results

Based on meta-analysis results, both gender STG tissues showed cancer as the top disease network. For STG tissue, in men, SOX2 and TCF7l2 was a top upstream regulator with predicted activation as downregulated; they were not present in women. For STG tissue, EIF2 signaling was a top canonical pathway for women. For PF tissue, seizure was in the top disease networks for men.

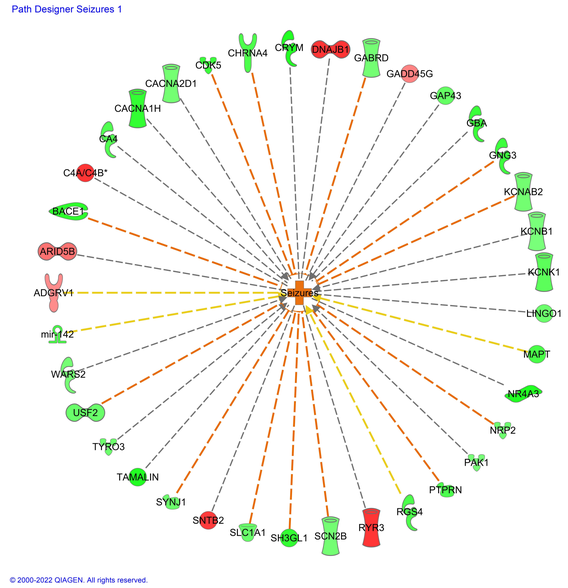

Figure 1: A diagram of genes active in schizophrenia in the prefrontal cortex that are implicated in seizure.

Conclusions

- There is a higher incidence and mortality of cancer among schizophrenic patients[3]; in our research, the most upregulated genes had a significant overlap with gene patterns in cancer.
- In PF male tissue, seizure was also another top disease network and previous research indicated that epilepsy has a stronger association with men in schizophrenia vs. women[4].
- Men showcase lower insight and treatment adherence than women[1]. SOX2, an upregulated enzyme in STG male tissue, has been associated with lower insight[5].
- TCF712 is also a strong risk factor for diabetes mellitus 2 (DM2)[6]. It was suppressed in men, but not women. This correlates with the higher incidence of DM2 among female schizophrenic patients relative to men[7].

References

[1]Li R, Ma X, Wang G, Yang J, Wang C. Why sex differences in schizophrenia?. *J Transl Neurosci (Beijing)*. 2016;1(1):37-42.

[2]Bychkov E, Ahmed MR, Gurevich EV. Sex differences in the activity of signalling pathways and expression of G-protein-coupled receptor kinases in the neonatal ventral hippocampal lesion model of schizophrenia. *Int J Neuropsychopharmacol*. 2011;14(1):1-15. doi:10.1017/S1461145710000118

[3] Lewis DA, Sweet RA. Schizophrenia from a neural circuitry perspective: advancing toward rational pharmacological therapies. *J Clin Invest*. 2009;119(4):706-716. doi:10.1172/JCI37335

4. Chang YT, Chen PC, Tsai IJ, et al. Bidirectional relation between schizophrenia and epilepsy: a population-based retrospective cohort study. *Epilepsia*. 2011;52(11):2036-2042. doi:10.1111/j.1528-1167.2011.03268.x

[5]Xavier RM, Vorderstrasse A, Keefe RSE, Dungan JR. Genetic correlates of insight in schizophrenia. *Schizophr Res*. 2018;195:290-297. doi:10.1016/j.schres.2017.10.021

[6] Hu Y, Shi P, He K, et al. Methylation of Tcf712 promoter by high-fat diet impairs β-cell function in mouse pancreatic islets. *Diabetes Metab Res Rev*. 2018;34(4):e2980. doi:10.1002/dmrr.2980

[7]Hsu J-H, Chien I-C, Lin C-H, Chou Y-J, Chou P. Incidence of Diabetes in Patients with Schizophrenia: A Population-Based Study. The Canadian Journal of Psychiatry. 2011;56(1):19-26. doi:10.1177/070674371105600105

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