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Bioinformatics Project Proposal

*Introduction*

Schizophrenia is a mental disorder that affects roughly 1% of the population [1]. It is characterized by two or more of the following: delusions, hallucinations, disorganized speech, and catatonia. Schizophrenia usually manifests in a patient’s late adolescence or young adulthood [2] and is currently incurable and, for some patients, untreatable.

Unfortunately, the mechanisms surrounding the disorder are vastly unknown. The “original dopamine hypothesis” states that schizophrenia may be caused by an overabundance of dopamine in the cerebral fluid; however, it is now widely accepted that this, if true, can not possibly be the entire story [3]. Unfortunately, the first-line treatment for schizophrenia are antipsychotics, all of which target the type-ii-dopaminergic receptor [1]. While these treatments do appear to work well for some patients, there are a significant number that respond only slightly or not at all. For these patients, it is overwhelmingly important that other causes for this disorder are discovered and published so that other treatments may be introduced.

Specifically, the *N*-methyl-D-aspartate (NMDA) receptor is one that is beginning to get more attention. Some researchers believe that this receptor’s hypofunction may be a key contributor to schizophrenia symptoms. A few articles cite the glycine modulatory site (GMS), a regulator of the NMDA receptor, as another potential target. Overall, though, there is not an obvious/agreed upon pathway for this mechanism [4].

Another potential route of research is looking into identifying the loci associated with schizophrenia. Currently, there are around 100 identified loci [1]; however, there are disagreements among the research community about which of these are specific to schizophrenia or significant to treatment at all. These loci are important because they may be able to pinpoint the specific location of singular nucleotide polymorphisms (SNPs) in schizophrenia patients, and this information can be used in further research to identify the implications and genetic transmissibility of those particular mutations. Also, schizophrenia is understood to be hereditary [5]; however, it is not clear which genes are the ones responsible or even if there is solely a genetic cause. Therefore, even identifying a way to predict the development of schizophrenia may be very helpful in the field.

For both of these approaches, better understanding could lead to both preventative treatments and/or symptom management for those suffering from this schizophrenia.

*Proposed Project*

For my project, I have not decided on whether I want to focus on the loci for schizophrenia or the NMDA pathway; however, it seems that there is a significant overlap in the research anyway and so I may be able to delve into both. I expect that when I start actually performing manipulations of the data that I will more easily be able to decide which route I want to explore deeper.

I began collecting articles that I judged to be relevant to this project. Some were meta-analyses, and for these ones I also retrieved some articles that they cited in their supplementary data. From these, I determined which articles were available on *PubMed Central*, and I discarded the ones that were not (because I intend to use Pr. Hansen’s machine reader which uses PMCIDs). I also did a reassessment of the remaining articles and discarded some that I believed no longer fit into either the NMDA or loci categories.

Here are the PMCIDs of the papers that I expect to be using:

[PMC34453](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC34453) (focus on COMT)

[PMC3910086](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3910086) (focus on COMT)

[PMC3077530](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3077530) (FINISHED)

[PMC2775422](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2775422) (FINISHED)

[PMC3912837](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3912837) (FINISHED)

[PMC2890845](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2890845) (FINISHED)

[PMC3603134](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3603134) (FINISHED)

[PMC4724864](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4724864) (FINISHED)

[PMC6927206](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC6927206)

[PMC3872086](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3872086)

[PMC3923972](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3923972)

[PMC3827979](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3827979)

[PMC4059435](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4059435)

[PMC3905728](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3905728)

[PMC3905227](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3905227)

[PMC5518924](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5518924)

Using these papers, I intend to first run them through the aforementioned machine reader and see if any obvious patterns emerge. For the ones pertaining to loci, I expect that I will utilize primarily the visualization techniques in R to create density graphs. I also may attempt to do a discretization of the loci into the chromosomes that they are on and then output a density plot that highlights this. If there is a chromosome with a significant number of loci, I may go deeper into this one and see if there are any specific areas that are particularly dense. A common theme in some of the meta-analyses that I have read are inverse-weighted fixed effects models, so I might also consider adopting that technique.

For the NMDA papers, I downloaded OmniPath [7] onto my computer because it seems that it may be useful in creating an igraph and/or map of the pathway. I want to expand this diagram to a detailed but still useful level, and I think that OmniPath seems to be a good choice for this. Pathview [8] is another choice that I am looking forward to experimenting with, and I expect that at least one – or maybe both – of these will help create a useful visualization. I believe that I want to focus more on the regulatory aspects of the pathway, which I believe are sometimes ignored in favor of the overall design.

Overall, I am hoping that this project helps in organizing the current research that is being performed in the area of schizophrenia and related psychotic illnesses. With a more solid understanding of the true mechanism of the disorder, researchers can begin to develop more comprehensive treatments to improve the quality of life for these patients.

References

\*\* References 1-8 are cited in proposal; 9-22 correspond to aforementioned PMCIDs

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