Dear Editor,

Please find enclosed a modified version of my Microreview manuscript “The Genetic Influence of Schizophrenia Spectrum Disorders”. To address the concerns and comments raised by the 2 reviewers, I made the following changes to improve and clarify the manuscript. It is my hope that these changes make the manuscript acceptable for publication in Microreviews in Cell and Molecular Biology.

Sincerely,

Abigail K Peters

Reviewer 1:

1. I did not find the feedback from reviewer 1 very helpful. All of their feedback was based around including more sources and adding more information that was not able to be found in my original article. This was not helpful to be because from what I have been able to gather a micro review is usually over one singular article unless there is cause for an addition and I feel as if I included enough information for the topic.

2. I made small changes to the information I previously had to address the issue reviewer 1 had with “the flow of the paper.” Other changes to the paper were in regards to minor errors found in grammar and sentence structure.

Reviewer 2:

1. The comments from reviewer 2 were not very helpful because they were not constructive. I appreciate getting good feedback to be able to improve on my work and reviewer 2 had no feedback whatsoever.

2. I made no changes based on the comments of reviewer 2.

The Genetic Influence of Schizophrenia Spectrum Disorders

**Abstract**

 Authors Jennifer K. Forsyth and Robert F. Asarnow discuss the overlap and prevalence of Adult Onset Schizophrenia (AOS) and Child Onset Schizophrenia (COS). There are a number of variants associated with schizophrenia spectrum disorders (SSDs), these variants often work together to increase the likelihood that an individual will have the genes to indicate a prevalence of these disorders along with symptoms, and the possibility of a psychotic event to solidify the diagnosis of such disorders. The diagnosis of COS often overlaps with the diagnosis of Autism Spectrum Disorder (ASD) because of their similarities in genetics and symptoms in children under 13 years old. The ability to test for genetic variances is currently limited so the ability to treat by an individual basis is not where it should be however, there is much hope for the future of genetic screening. Future studies of these variances are very promising for the development of model interventions for neurological disorders such as AOS and COS.

**Introduction**

 Can genetics have an impact on psychological disorders? In the article, “Genetics of Childhood-Onset Schizophrenia 2019 Update” authors Forsyth and Asarnow aim to answer just that; specifically focusing on COS, which specifically children under 13 years old being diagnosed with schizophrenia. Until recently there have not been proper diagnostic criteria for the diagnosis of COS, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V). COS was often confused with ASD and until the DSM-5 COS did not have its own diagnostic criteria available. The children who are being looked at for this study could possibly be diagnosed with ASD, an unspecified neurodevelopmental disorder, or a schizophrenia spectrum disorder. The prevalence for COS is quite low in comparison to AOS because of the amount known from previous studies.

 Previous studies of epidemiology and family prevalence have deemed that genetics do in fact play a factor in the cause of AOS. COS has a low prevalence rate so the genetic factors that increase the risk for diagnosis of COS are less known. COS is less prevalent because it is difficult to diagnose at such a young age and many individuals have their first psychotic event in adulthood. Modern studies show that schizophrenia spectrum disorders exhibit a familial tie, this study is focusing on parents of individuals who have been diagnosed with COS because siblings of this individual probably have not reached the age that is of risk for schizophrenia. These studies have shown a relative risk for parents of AOS probands as compared to the parents of controls. Adoption and twin studies conducted further supported the idea of genetics rather than environment playing a role in the diagnosis of schizophrenia. These studies focusing on fraternal and identical twins showed a greater likelihood of monozygotic twins than dizygotic twins for being diagnosed with these neurodevelopmental disorders. Dizygotic twins are a better representation of siblings on average than monozygotic twins because of the difference in genetic diversity they possess.

**Discussion**

 A study at UCLA found an increased rate of SSDs in people who are related to COS probands. This suggests that SSDs may aggregate stronger in families of COS probands than AOS probands. The specific disorders that were being looked at as a subset of COS are: schizoaffective disorder, schizotypal personality disorder, and atypical psychosis. The specific disorders being used as a subset for AOS are: schizophrenia, schizotypal personality, and paranoid personality disorder. These subsets were split by age as well for accuracy of results. Looking at risk for SSDs, there are some neurobiological abnormalities that are often found to be present in individuals who have been diagnosed with AOS or COS and it has also been found that a large number of their immediate relatives also have these abnormalities but they are interpreted as an increased risk for SSDs if the relative is nonpsychotic. The neurobiological abnormalities that are found in concordance between a parent that is nonpsychotic and a child with COS show that these abnormalities may have more to do with different genetic factors rather than strictly being a predictor of psychosis. Studying this link more closely can hopefully help identify different markers within the genome that can influence the prevalence of different schizophrenia spectrum disorders instead of just the possible risk each individual possesses.

Understanding how DNA works, meaning how nucleotides interact with proteins and amino acids, is very helpful in understanding the weight of these variants in these individuals. Gene interactions play an integral part of the function of these disorders. There are many ways certain genes interact with one another to create the outcome of risk factors that contribute to the onset of these disorders. Before knowing for sure if a variant is something to be concerned about, it first has to be ascertained if the gene or variant in question is active or benign. Some genes are non-coding which means that they are present genotypically but they are not of importance phenotypically. Currently, there are studies being conducted that are delving into the range of genetic variation present in the human genome. This is important for future studies because it will give a better idea about how variants and traits in the human genome can influence an individual. The genes that influence these disorders are polygenic so many of them interact with one another to influence the genetic variance that leads to the risk of a psychotic event that can lead to a diagnosis of a schizophrenia spectrum disorder.

**Conclusion**

 The future of this field is beginning to look up. More and more people are asking the question of how diseases are perpetuated and how genetics plays a factor in the diagnosis of these disorders. There are many genes that are thought to influence the association and diagnosis of AOS and COS. The main question is which genes specifically and how do they interact with one another to contribute to the psychosis portion of schizophrenia spectrum disorders. In a large study, there were 108 loci that were found to be associated with schizophrenia status. These individual loci did not have much impact on the possible effects of schizophrenia but working together there was a significant variance so the genes associated with SSDs are thought to be polygenic, more than one gene working together. It is thought that these variants contributed to the risk of disease by altering the level of expression of certain proteins rather than protein structure. More specifically with COS, there are associations with variants shared with ASD which can be an influence as to why COS is seen to be as rare as it is. The signs and genetic markers could point to ASD, which is something that most parents would probably be more comfortable with as a diagnosis because of the stigma that schizophrenia carries. Developments in studies around genetics have some ways to go but the overall trajectory for diagnosing and finding genetic variants for different disorders within psychiatry have potential to be successful and the possibility to be very helpful to the field of precision medicine as a whole.

**Works Cited**

Forsyth, J. K., & Asarnow, R. F. (2020). Genetics of Childhood-onset Schizophrenia 2019 Update. *Child and Adolescent Psychiatric Clinics of North America*, *29*(1), 157–170. doi: 10.1016/j.chc.2019.08.007