Unraveling the Genetic Tapestry of Schizophrenia Spectrum Disorder: Insights into Immune-Mediated Mechanisms

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Schizophrenia spectrum disorder (SSD) is a severe and often debilitating condition. The associated societal costs include financial burdens, premature years of life lost, and a myriad of other complications arising with the onset of SSD (U.S. Department of Health and Human Services, 2018). Despite this, the exact mechanism of SSD remains elusive, though its heritability is evident. Consequently, the current standard for treating SSD, typical and atypical antipsychotics, can have numerous side effects that reduce their efficacy for patients. In some cases, these medications can fail to address certain symptoms of SSD (Haddad *et al.*, 2018). Recent observations indicate that SSD typically co-occurs with an immune condition, leading to the hypothesis that SSD's mechanism may be genetically linked to immune diseases (Pouget *et al.*, 2019). Comparison of the genetic architectures of SSD and other immune conditions reveals a common association between SSD and certain inflammatory conditions. These findings are in accordance with a well-established theory that SSD symptoms arise from neuroinflammation, though the mechanism of this inflammation remains unclear. The knowledge that the immune response is not only somatic, but also has implications for brain health suggests that SSD may genetically underlie heritable immune conditions or vice versa. The genetic linkage between SSD and immune-mediated inflammatory conditions illuminates a potential pathophysiological mechanism for the onset of SSD, opening a new avenue of exploration for treatment options with anti-inflammatories.

In almost every respect, the condition of SSD is not yet fully understood. Ongoing discussions about whether the condition is a singular entity or a multiplicity of spontaneously occurring conditions prompt the search for a solid mechanistic underpinning for SSD. Given that the most predictive risk factor for the development of SSD is genetic, there has been a surge in the past few decades to identify specific genes associated with the development of symptoms.

This has been no small feat, as SSD is very complex and multigenic, encapsulating a wide range of symptoms (Zamanpoor, 2020). The symptoms of SSD are typically divided into positive and negative categories. Positive symptoms manifest at the onset of the condition, including delusions and hallucinations, while negative symptoms are deficits that occur with the onset of the condition, like flattened affect and cognitive impairment.

While each patient with SSD can experience slightly varying clusters of positive and negative symptoms, another commonality has arisen amongst SSD patients. Several studies in the past decade have recognized that patients with SSD are more likely to develop an immune disease and inversely, patients with immune conditions have a likelihood of developing SSD (Pouget *et al.*, 2019). This information provides a new avenue through which the pathophysiological mechanism of SSD may be better elucidated. By comparing genetic variants associated with SSD to the genetic variants associated with other immune conditions and immune related responses, certain genes may arise within the overlap of the genetic architecture of these conditions and suggest a mechanism of action or a new route for the treatment of SSD.

The co-occurrence of SSD with certain autoimmune disorders suggests some link in the development of symptoms between these two conditions. Notably, individuals with SSD exhibit elevated white blood cell counts relative to the general population (Steen *et al.*, 2023). White blood cell counts are relevant in the context of immune conditions, given their primary role in combating infection. Consequently, a 2023 study conducted a genome-wide association study (GWAS) to investigate shared genetic variants between SSD and white blood cell counts. The analysis revealed a significant linkage, identifying 383 shared independent genetic loci between the two traits, with 53% of those genes exhibiting the same orientation (Steen *et al.*, 2023). Moreover, the study determined that SSD is approximately 7.5 times more polygenic than white

blood cell count (Steen *et al.*, 2023), which is consistent with previous research on the polygenicity of SSD. This polygenicity was measured based on the assumption of 9600 variants being associated with SSD according to results from the GWAS, in contrast to approximately 1800 variants associated with white blood cell count (Steen *et al.*, 2023). The presence of many genetic variants all contributing to SSD onset underscores the elusive nature of its pathophysiological mechanism. These findings indicate that for certain SSD patients, immune system abnormalities might trigger the onset of their condition, suggesting potential avenues for treatment through immune system modulation (Steen *et al.*, 2023). Ultimately, the substantial overlap in genetic architectures for high white blood cell counts and SSD provides support for the prevailing theory that SSD may manifest as a form of immune-related condition.

With more research suggesting a genetic linkage between SSD and immune conditions, a 2019 study sought to identify the immune conditions most genetically linked to SSD. They compared the genetic architecture of SSD to 19 immune diseases through genome-wide association studies. The goal was to identify specific genetic variants associated with SSD which aligned significantly with those from any of the 19 immune diseases. This was assessed using a linkage disequilibrium value, which quantifies the amount of correlation that two nearby genetic variants possess within a given population. A few genetic variants at single base positions emerged as significantly linked between SSD and three of the 19 immune diseases studied: *rs296547,* influencing the risk of both SSD and Celiac disease; *rs1734907, rs13126505* and *rs6738825* influencing risk of Crohn's disease and SSD; and lastly, *rs7132277* affecting the risk of both SSD and Multiple Sclerosis.

Upon analyzing the genomic risk-variants shared between SSD and these immune conditions, four arose as having a significant genetic risk association with SSD. This genetic

correlation, denoted as r_g, reflects the proportion of shared genetic variants between the two conditions, ranging from zero (no correlation) to one (genetically identical). The conditions that had significant genetic correlation with SSD were Crohn's disease (r_g = 0.097, standard error (SE) = 0.03), primary biliary cirrhosis (r_g = 0.131, SE = 0.05), psoriasis (r_g = 0.182, SE = 0.07) and systemic lupus erythematosus (r_g = 0.130, SE = 0.05) (Pouget *et al.*, 2019). Interestingly, all these conditions are either autoinflammatory or associated with inflammation. This indicates that certain SSD patients may have comorbid inflammatory conditions contributing to the onset of SSD symptoms. Moreover, it implies that treatment approaches for this subgroup of SSD patients might align with those used for inflammatory conditions (Pouget *et al.*, 2019). In contrast with Steen et al. (2023), it is now clear that the development and treatment of SSD in specific patients could more precisely parallel not only immune conditions in general but, more specifically, a subset of inflammatory conditions.

Recent evidence indicates a potential role of inflammation in the onset of SSD, yet a precise pathophysiological mechanism for SSD remains undiscovered. To delve deeper into the probable development of this condition, a 2020 study utilized human-induced pluripotent stem cell-derived astrocytes derived from SSD patients and individuals without SSD to observe differences in gene expression between these two groups of astrocytes when responding to perceived external threats which elicit an inflammatory response for adaptation. Human induced pluripotent stem cell-derived astrocytes are instrumental in maintaining central nervous system homeostasis and are commonly used in therapeutic research due to their ability to mature within three weeks. Inflammatory responses were induced in the astrocytes by temporary exposure to the IL-1β protein, mimicking inflammasome activation, a process triggered by damage or

infection in the cellular material. The resulting gene expression was measured using RNA sequencing.

Two genes, *HILPDA* and *CCL20,* exhibited significantly lower up-regulation post-treatment in SSD astrocytes compared to the control astrocytes (Akkouh *et al.*, 2020). The logFC values further support this, with the *HILPDA* gene having a logFC value of -1.58 and a p-value of less than 0.05, indicating approximately three times lower expression in the treatment than in the control (Akkouh *et al.*, 2020). Similarly, the *CCL20* gene had a logFC value of -1.06 and a p-value of less than 0.05, indicating about two times lower expression in the treatment than in the control (Akkouh *et al.*, 2020). Additionally, a regulatory T cell marker called *FOXP3* ($p=0.0137$, $\beta =-0.044$) was found to be expressed far less frequently in the blood of a significant number of SSD patients (Akkouh *et al.*, 2020). These results, consistent with *CCL20*'s association with SSD in various studies, suggests its potential as a treatment target. Given its involvement in anti-inflammatory responses in the brain, a variant of this gene might contribute to the neuroinflammation underlying SSD (Akkouh *et al.*, 2020).

In light of substantial evidence suggesting the involvement of inflammatory conditions in the mechanism of SSD, anti-inflammatory drugs emerge as a potential frontier for treating or preventing SSD at its early onset (Çakici *et al.*, 2019).The aforementioned study delved into specific genes that exhibited less activity in the brains of SSD patients during inflammatory responses compared to the control (Akkouh *et al.*, 2020). Consequently, anti-inflammatory drugs could serve as a means to counteract these effects, enhancing the brain's protective measures against inflammatory responses in SSD patients. In a comprehensive 2019 review, 56 studies were considered to evaluate the efficacy of 16 anti-inflammatory drugs in alleviating SSD symptoms. The analysis revealed that aspirin (mean weighted effect size (ES) = 0.30), estrogens

(ES = 0.78), minocycline (ES = 0.40), and N-acetylcysteine (ES = 1.00) improved symptoms with statistical significance ($p < 0.05$ in the mean weight effect size) across at least two studies. These drugs were more effective at improving symptoms when administered during a first episode of psychosis or in cases where patients had not been experiencing symptoms for an extended period (Çakici *et al.*, 2019). These results further suggest the role of neuroinflammation in SSD development, suggesting a promising avenue for the development of more effective SSD treatments (Çakici *et al.*, 2019).

While a universally accepted pathophysiological mechanism for SSD remains elusive, recent genetic studies have significantly contributed to a greater understanding of this condition. A substantial body of evidence indicates a genetic association between SSD and immune conditions, supported by the observed genetic link between SSD and white blood cell counts (Steen *et al.*, 2023). Furthermore, the genetic architecture of SSD compared to various immune conditions revealed a striking resemblance to immune-mediated inflammatory conditions (Pouget *et al.*, 2019). These results lend specificity to an understanding of SSD's probable development, aligning with the prevalent theory implicating neuroinflammation in certain SSD symptoms. Building on this foundation, *CCL20* arises as a potential treatment target (Akkouh *et al.*, 2020). Considering the observed co-occurrence of SSD with inflammatory conditions, anti-inflammatory drugs present a promising avenue for treatment in specific patient groups (Çakici *et al.*, 2019). This information not only validates the genetic link between SSD and immune-mediated inflammatory conditions but also provides a meaningful path forward for future research. Identifying a well-defined pathophysiological mechanism for SSD will catalyze the development of more effective treatments, marking significant progress in improving the lives of those affected and benefitting society at large.

Works Cited

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