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# Schizophrenia and Rheumatoid Arthritis Genetic Scenery: Potential Non-HLA Genes Involved in Both Diseases Relationship

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**Background**: The link between rheumatoid arthritis (RA) and schizophrenia (SZ) has long been a hot topic of deliberation among scientists from various fields. Especially when it comes to genetics, the connection between RA and SZ is still up for discussion, as can be observed in this study. The HLA genes are the most disputed in identifying a connection between the two diseases, but a more thorough investigation of other genes that may be ignored could yield something even more interesting. Thus, finding the genes responsible for this long-sought relationship will necessitate looking for them. **Materials and Methods**: Shared and overlapped associated genes involved between SZ and RA were extracted from four databases. The overlapping genes were examined using Database for Annotation, Visualization and Integrated Discovery (DAVID) and InnateDB to search the pertinent genes that concatenate between these two disorders. **Results**: A total of 91 overlapped genes were discovered, and that 13 genes, divided into two clusters, showed a similarity in function, suggesting that they may serve as an important meeting point. *FCGR2A*, *IL18R*, *BTNL2*, *AGER*, and *CTLA4* are five non-HLA genes related to the immune system, which could lead to new discoveries about the connection between these two disorders. **Conclusion**: An in-depth investigation of these functionally comparable non-HLA genes that overlap could reveal new interesting information in both diseases. Understanding the molecular and immune-related aspects of RA and SZ may shed light on their etiology and inform future research on targeted treatment strategies.

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Abbreviations: RA, Rheumatoid Arthritis; SZ, Schizophrenia; HLA, Human Leukocyte Antigen; non-HLA, non-Human Leukocyte Antigen; Neu5Ac, N-acetyl-D-neuraminic acid; NCAM, neural cell adhesion molecule; GO, Gene Ontology.

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## INTRODUCTION

### *The Link Between Genes and Diseases*

Researchers in the field of genetic specialization have been interested in the relationship between particular diseases and specific genes in order to uncover the continuity that may be associated with the mechanism of conflict [1,2]. In a given circumstance or environment, each gene has a certain direction or function that can affect the genesis or availability of the disease [3]. This can be seen in the findings of studies on the causes of diseases caused by specific genes, such as sickle cell anemia, cystic fibrosis, cri du chat syndrome, breast cancer, and fragile x syndrome [4].

Furthermore, deconstruction of what scientists have done and what tools they have built can explain these conditions in the endeavor to improve determinants in disease identification or remediation [5,6]. However, more research is needed to validate this genetic link. There are several trials and discoveries that need to be conducted to determine the most likely variables that contribute to the occurrence of the diseases. Although revealing the link between genes and disease is a difficult endeavor, it is vital and interesting to explore further.

### *Schizophrenia (SZ)*

SZ (OMIM 181500) is a serious, lifelong neurodevelopmental illness that affects how people think, feel, and behave [7,8]. Delusions, hallucinations, disorganized speech or behavior, and poor cognitive capacity are all symptoms of SZ [9,10]. They might hear or see things that are not there. They may believe that others are reading their brains, manipulating their ideas, or conspiring against them. It can also be frightening and disturbing for those around them. People suffering with SZ may occasionally express bizarre or unexpected ideas, making it difficult to carry on a discussion [11].

### *Rheumatoid arthritis (RA)*

RA (OMIM 180300) is a chronic, progressive inflammatory illness with an unclear etiology that causes joint inflammation [12,13]. It is distinguished by uncontrolled synovial tissue development and a large range of multisystem comorbidities [14]. The disease has an insidious onset and a fluctuating and unexpected course. RA most commonly appears as symmetrical polyarthritis, but it can also present with non-specific symptoms such as fatigue, malaise, and moderate fever. If therapy is delayed or poor, one erosion, cartilage breakdown, and full loss of joint integrity can occur over time. Numerous multicenter worldwide trials have shown that early and adequate treatment can slow disease development [15]. With the introduction of biologics and the deployment of a treat-to-target strategy, the treatment paradigm for RA has altered over the previous two decades as well as the need to obtain specific genetic testing for RA, which is still imprecise [16].

### *The Connection Between SZ and RA*

Although SZ and RA have distinct identities in both conditions, the link was discovered in 1936 by Nissen and Spencer [17], and they reported that none of their SZ patients had RA [18]. Much research has now been conducted to investigate and demonstrate the unfavorable connection between SZ and RA [12,19-24]. Their investigations have revealed that RA is missing in SZ patients and vice versa. Oken and Schulzer [25] came to this conclusion after doing a meta-analysis that confirmed this postulation. As a result of this exposure, numerous investigations have been conducted to determine the various reasons of this relationship.

As discussed in previous publications, the etiology of negative liaison between both diseases was caused by a variety of factors including the environment, infection, and heredity [12,26]. Psychologically, RA and SZ patients treat themselves differently. SZ patients are more expressive than rheumatoid patients, who are more symptomatic. The link between SZ and RA is also influenced by pharmacologic variables [27]. There is strong evidence that standard antipsychotics, such as haloperidol, may have an anti-inflammatory effect that protects against RA. Haloperidol medication for acute mania was shown to ameliorate synovitis and CRP levels in RA patients, and induced acute inflammation in blood cultures resulted in a significant reduction of TNF-α and IL-1β production. These inflammatory cytokines have been associated with RA. Thus, haloperidol may prevent SZ patients from developing RA by suppressing TNF-α and IL-1β levels [28].

Aside from that, scientific evidence suggests that SZ may be linked to a lack of prostaglandins [29-33]. Prostaglandin levels in RA patients' synovial fluids have been found to be elevated [34]. It is possible that elevated prostaglandin inhibits the development of SZ symptoms in RA.

High levels of prostaglandins, especially PGE2 in RA may be involved as mediators exerting central anti-inflammatory activity [29]. Such an anti-inflammatory milieu might contribute to the suppression of neuroinflammation, which is postulated to play a role in SZ pathophysiology. Prostaglandins can influence neurotransmitter activity such as dopamine and glutamate that has been linked to abnormal pathways in SZ. Given that prostaglandins are known to be elevated in RA, this alteration may contribute to the same neurotransmitter pathways and thus ameliorate symptoms of SZ or slow its

progression [29-32,34].

The impact of alpha keto acid sugar; sialic acid in shaping the occurrence of RA and SZ is also indisputable. The involvement of sialic acid in the process of immunology and inflammation plays an important role in forming and providing guidance in the development of both diseases as sialic acid manifests in various human tissues, mainly in the brain, and performs important biological functions, including information biological process among cells [35,36]. Studies in glycobiology have shown evidence of the concurrence effect of sialic acid involvement in causing RA and SZ.

The amount of the main type of sialic acid, N-acetyl-D-neuraminic acid (Neu5Ac) in the serum of RA patients showed an equivalent increase despite the different severity compared to healthy subjects [35]. Elevated levels of modified neural cell adhesion molecule (NCAM) by polysialic acid (polysia) in SZ serum also stand out in the involvement of sialic acid in the formation of SZ [36].

However, the sialic acid level is different at different regions. This shows that its role in a certain disease is also different. And of course, this is all related to the susceptibility of genes that control the behavior of each cell component that might be linked to the disease development.

In addition, a negative correlation means that SZ patients have a genetic make-up that RA patients do not have, or vice versa. This is demonstrated by Euesden et al. [27] study, which discovered that polygenic risk scoring in a RA case control had a minimal contribution of SZ genetic risk to RA risk.

Although there are a few studies that fail to find and provide the same conclusions as others on the inverse relationship between RA and SZ [27,37], this does not discourage researchers to find the underlying cause of these two disorders. Many recommendations and speculations have been generated by the research, but the concrete findings are still being sought.

### *Previous Research on Shared Genes Linked to RA and SZ*

According to history, the link between these two diseases involves a number of variables that are not solely influenced by genetics, as previously established. For example, studies that link exposure to domestic cats is often related to the outcome of infection from *toxoplasma gondii* in time to an increased risk of RA and SZ [38,39].

Since the beginning of the introduction of the conjugation between RA and SZ, the human leucocyte antigen (HLA) gene has been linked to the trigger that causes the relationship between the two disorders. To summarize, these two disorders are related to the immune system, and the HLA gene produced by the MHC complex is in charge of directing the traffic associated with the human immune system [40]. For example, it can be seen in HLA DRB1 and HLA DR4 serotypes, showing a positive association with RA, but expose a negative correspondence with SZ [35]. However, non-HLA genes also do not fail to show a connection to these two diseases as there were also many non-HLA genes that contribute in the immune system. Clearly, immunology plays a very important role in the relationship between RA and SZ which corroborate that there are variants or biomarkers that have different tasks in the immune response pathway in different situations and positions [41].

Previous studies postulated and detailed in full some of the ideas and controversies surrounding the association of genes in the association of various diseases [42]. Many studies findings have identified a number of genes that may be linked to these two disorders, which can provide insights and potential beginning points for current and future study [38,43]. However, most of the research over the last several decades involving RA and SZ have been particularly focused on the genes from the MHC group compared to the genes from the non-HLA group that may also have a relationship to be demonstrated [7,9,12,16,20,23,24,26,27]. It would be a success if the relationship between these two disorders could be resolved by actually finding the genes that links RA to SZ in general. So, for that reason, it is absolutely necessary to conduct studies that include biological analysis related to both diseases in search of non-HLA genes association that may play an important hidden role.

## MATERIALS AND METHODS

The genes linked to RA and SZ have been discovered through a variety of studies and then aggregated by many databases. In this study, we used four databases which are the Schizophrenia Database [44,45], Database of Rheumatoid Arthritis [46], DisGenet [47], and GeneCards database [48], to search and extract for all of the associated genes involved in SZ and RA separately to fill gaps in the various population and published gene data that may be present in one database, but may not be retrieved by others (Table 1).

Then, all of the retrieved genes were merged to see whether there are any genes in all databases that overlapped in both disorders. The implementation that we used was Ablebits (https://www.ablebits.com/excel-find-similar/), which is the ultimate suite for Microsoft Excel, to assist us locating the overlapping genes between RA and SZ, in particular (Figure 1). Gene overlapping for each database group was collected, which necessitated 57 calculations, starting from overlap between two groups, up to six database groups involved. Then, Meta Chart (https://www.meta-chart.com/auth) was used to discover and illustrate Venn diagrams for all overlapping genes

**Table 1. The List of Databases Used to Find the Overlapped Genes Involved Between RA and SZ**

| No | Database | Disease | No. of Genes | Data source |
|---|---|---|---|---|
| 1 | Schizophrenia Database (SZDB) | Schizophrenia | 8265 | [44,45] |
| 2 | Database of Rheumatoid Arthritis (RADB) | Rheumatoid Arthritis | 636 | [46] |
| 3 | DisGenet Database (SZ_DisGenet) | Schizophrenia | 2872 | [47] |
| 4 | DisGenet Database (RA_DisGenet) | Rheumatoid Arthritis | 2723 | [47] |
| 5 | GeneCards Database (SZ_GeneCards) | Schizophrenia | 9987 | [48] |
| 6 | GeneCards Database (RA_GeneCards) | Rheumatoid Arthritis | 4465 | [48] |

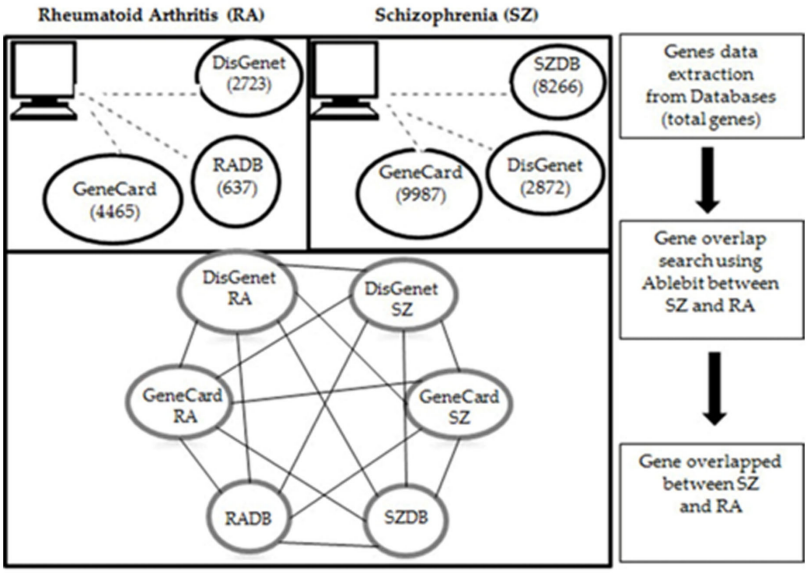


**Figure 1**. **The genes overlapping search flow**.

based on the databases involved.

The overlapping genes were then examined using DAVID Bioinformatics Resources 6.8 [49,50] to find the relevant HLA and non-HLA genes that demonstrate the best connection between these two disorders, which may then be tailored to the pathway involved.

Further study of biological functions for selected non-HLA genes were carried out using GO terms, KEGG, and systematic characterization of the discovered DEGs using InnateDB [51], followed by functional annotation and pathway enrichment analysis.

In the end, cross validation was done by searching and listing a list of published journals that showed significance findings between selected non-HLA genes involved in RA and SZ.

## RESULTS

### *Overlapping Genes Between RA and SZ3.1*

A total of 91 genes have been found to overlap between six data groups after going through a series of gene overlap search sequences (Figure 2). All 91 genes are listed in Appendix A.

### *RA-SZ Best Genes Connection Involved*

As a result of analysis using kappa score, 13 genes showed similarity functions which are divided into two clusters (Table 2) accordingly. From the results, five non-HLA genes were found.

### *Correlation Between Five Selected Non-HLA Genes*

These five non-HLA genes (*FCGR2A*, *IL18R*, *BTNL2*, *AGER*, and *CTLA4*) were further analyzed using InnateDB software to see the relationship between these genes. Surprisingly, four genes other than *FCGR2A* exhibited favorable results. Pathway analysis discovered 43 distinct pathways, as listed in Table 3. After evaluating for route over representation analysis using hypergeometric algorithm with Benjamin Hochberg as a correction method, only one pathway that contributed to the immune system (Figure 3a) was found with a p-value of 0.01369, involving mainly *AGER* and *CTL4* (Figure 3b).

After that, gene ontology (GO) terms were analyzed,

**Table 2. The List of 13 Genes that Present the Similarity Function and its Kappa Score for Cluster 1 and Cluster 2 as a Result of Analysis using The Database for Annotation, Visualization and Integrated Discovery (DAVID) 6.8**

| | No | Gene Name | Functionality Related Gene | Chromosome | Kappa |
|---|---|---|---|---|---|
| Cluster 1 Enrichment Score: 7.98 | 1 | *HLA-DMA* | Major histocompatibility complex, class II, DM alpha | 6 | 0.84 |
| | 2 | *HLA-DQB1* | Major histocompatibility complex, class II,DQ beta 1 | 6 | 0.81 |
| | 3 | *HLA-DRA* | Major histocompatibility complex, class II, DR alpha | 6 | 0.75 |
| | 4 | *HLA-DMB* | Major histocompatibility complex, class II, DM beta | 6 | 0.75 |
| | 5 | *HLA-G* | Major histocompatibility complex, class I, G | 6 | 0.68 |
| | 6 | *HLA-C* | Major histocompatibility complex, class I, C | 6 | 0.55 |
| | 7 | *HLA-B* | Major histocompatibility complex, class I, B | 6 | 0.51 |
| Cluster 2 Enrichment Score: 7.14 | 1 | *FCGR2A* | Fc Fragment of IgC receptor IIa | 2 | 0.78 |
| | 2 | *IL18R1* | Interleukin 18 receptor 1 | 6 | 0.64 |
| | 3 | *BTNL2* | Butyrophilin like 2 | 2 | 0.58 |
| | 4 | *AGER* | advanced glycosylation end-product specific receptor | 1 | 0.56 |
| | 5 | *CTLA4* | Cytotoxic T-lymphocyte associated protein 4 | 6 | 0.55 |
| | 6 | *MICB* | MHC class 1 polypeptide-related sequence B | 6 | 0.55 |

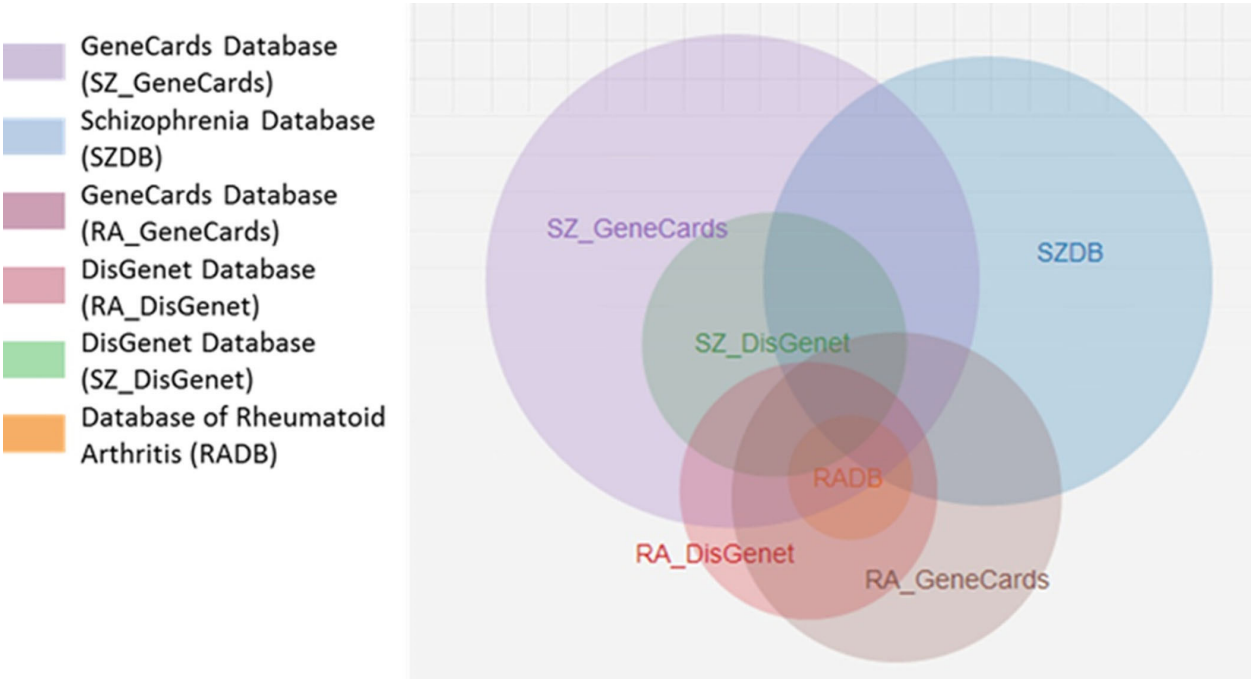


**Figure 2**. **The Venn diagram represents the shared genes among the datasets involved**. The total commonality of overlapped genes for all groups were 91 genes. This Venn diagram was generated online using Meta_Chart, a visualization app (https://www.meta-chart.com/) for graphing or charting and general data.

**Table 3. The Significant Pathways Found from Pathway Analysis**

| Genes | ID | Pathway name |
|---|---|---|
| *IL18R1* | ENSG00000115604 | Il12 and stat4 dependent signaling pathway in th1 development |
| | | JAK STAT pathway and regulation |
| | | IL12 signaling mediated by STAT4 |
| | | Cytokine-cytokine receptor interaction |
| | | IL23-mediated signaling events |
| | | IL12-mediated signaling events |
| *CTLA4* | ENSG00000163599 | CTLA4 inhibitory signaling |
| | | Autoimmune thyroid disease |
| | | The co-stimulatory signal during t-cell activation |
| | | TCR |
| | | Adaptive Immune System |
| | | Calcineurin-regulated NFAT-dependent transcription in lymphocytes |
| | | Immune System |
| | | T cell receptor signaling pathway |
| | | Cell adhesion molecules (CAMs) |
| | | Co-stimulation by the CD28 family |
| *AGER* | ENSG00000204305 | RIG-I/MDA5 mediated induction of IFN-alpha/beta pathways |
| | | Advanced glycosylation endproduct receptor signaling |
| | | amb2 Integrin signaling |
| | | TRAF6 mediated induction of NFkB and MAP kinases upon TLR7/8 or 9 activation |
| | | DEx/H-box helicases activate type I IFN and inflammatory cytokines production |
| | | MyD88 dependent cascade initiated on endosome |
| | | Toll Like Receptor 4 (TLR4) Cascade |
| | | Toll-Like Receptors Cascades |
| | | Toll Like Receptor 5 (TLR5) Cascade |
| | | TAK1 activates NFkB by phosphorylation and activation of IKKs complex |
| | | Toll Like Receptor 7/8 (TLR7/8) Cascade |
| | | Toll Like Receptor 9 (TLR9) Cascade |
| | | MyD88 cascade initiated on plasma membrane |
| | | Toll Like Receptor 10 (TLR10) Cascade |
| | | RIP-mediated NFkB activation via ZBP1 |
| | | TRIF-mediated TLR3/TLR4 signaling |
| | | Activated TLR4 signaling |
| | | MyD88-independent cascade |
| | | Toll Like Receptor TLR1:TLR2 Cascade |
| | | Toll Like Receptor TLR6:TLR2 Cascade |
| | | TRAF6 mediated NF-kB activation |
| | | Toll Like Receptor 2 (TLR2) Cascade |
| | | Toll Like Receptor 3 (TLR3) Cascade |
| | | Cytosolic sensors of pathogen-associated DNA |
| | | ZBP1(DAI) mediated induction of type I IFNs |
| | | MyD88:Mal cascade initiated on plasma membrane |
| | | Innate Immune System |
| | | Immune System |

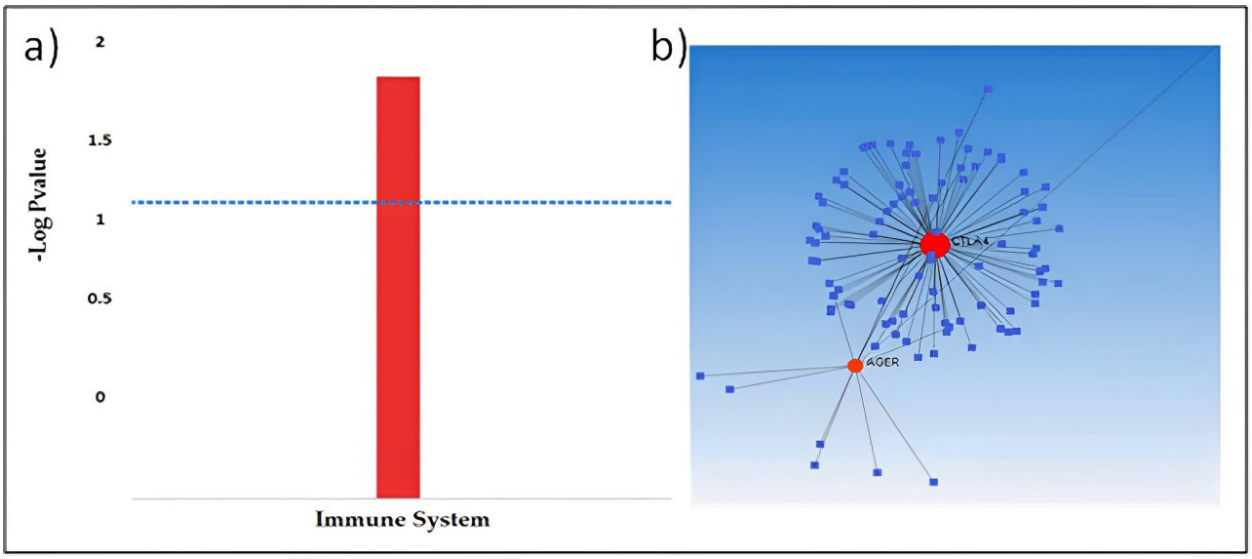


**Figure 3**. **The significant pathway involved of targeted genes involved**.

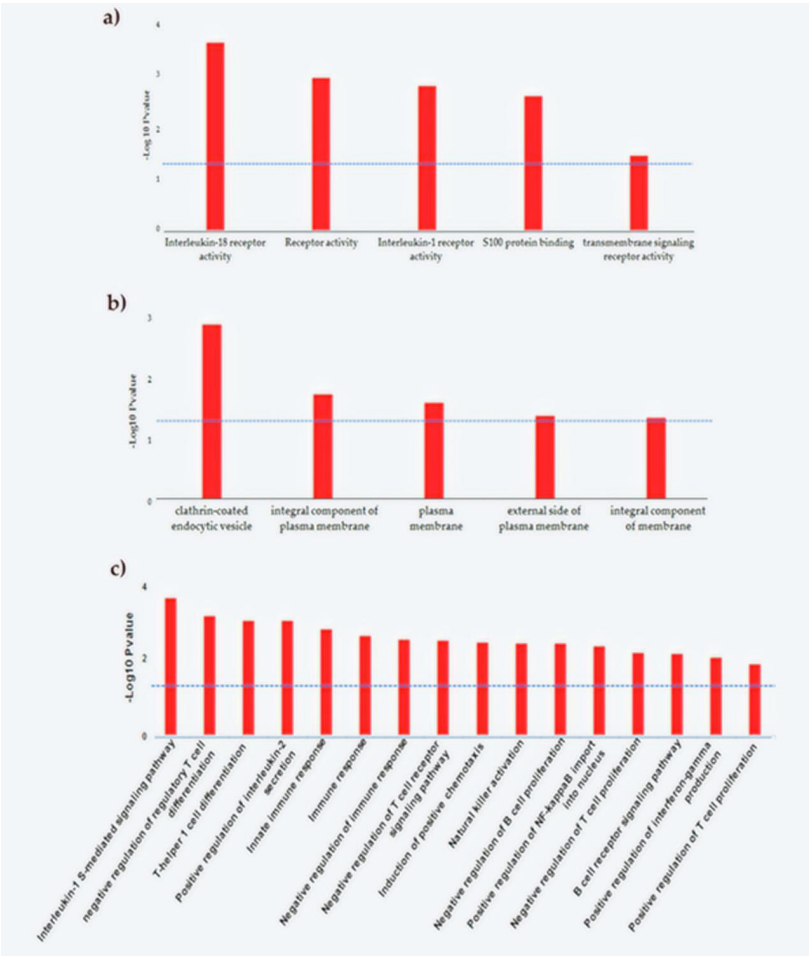


**Figure 4**. **The significant GO analysis, GO Terms that categorized to molecular function** (**a**) Cellular component (**b**) and biological process (**c**) involving four genes (*IL18R*, *BTNL2*, *AGER*, and *CTLA4*).

numerous GO terms were discovered containing only four genes that did not include the *FCGR2A*, which were classified as molecular function, biological process, and cellular component (Figure 4a, Figure 4b, and Figure 4c respectively). Interleukin-18 receptor activity, receptor activity, interleukin-1 receptor activity, S100 protein binding, and transmembrane signaling receptor activity were identified as molecular activities conducted by the genes by GO molecular function (Figure 4a). Cellular component terms are mainly involved in plasma membranes (Figure 4b). GO terms biological processes reveal 16 processes won with the interleukin-18-mediated signaling pathway, followed by negative control of regulatory T cell differentiation and T-helper 1 cell differentiation (Figure 4c).

## DISCUSSION

In this study, we summarized and identified the overlapping genes that can shed light on the link between SZ and RA in order to reveal the genetic link to the diseases. As a result, we plan to devise a strategy for identifying genes association that may be linked to the discovery of a link between these two diseases. However, we are very excited to find non-HLA genes that may be able to explain the hidden contribution behind the huge involvement of the HLA genes or work with the HLA genes in the association of SZ and RA.

After using Ablebits Excel add-on tools to look for gene overlap, 91 genes were discovered to be overlapping between SZ and RA. Then, in order to reduce the area of relevant gene research in linking these two diseases, we attempted to group these overlapping genes systematically based on functional similarities in order to facilitate and broaden the biological participation that may be engaged using DAVID 6.8 [52]. Utilizing kappa similarity, the Functional Classification tool provides a shared functional annotation based on gene to gene similarity using over 75,000 items from 14 functional annotation sources. This innovative clustering approach divides highly related genes into functionally similar categories.

To accomplish this purpose, a novel clustering approach producing aggregated genes with comparable functionality utilizing The Functional Classification Tool with high classification stringency was applied. Surprisingly, following a thorough examination, two clusters of 13 genes were discovered to play a significant role in defining the link between these two disorders. The two groups were formed based on the functional similarity of genes, which systematically improves biological interpretation from a list of 91 genes produced from overlapping genes.

It is even more impressive when one of these clusters involves genes from the HLA family. These findings clearly demonstrate how the immune system is linked to RA and SZ in general, as previously stated. Another cluster, on the other hand, contains genes with quite diverse roles, which may provide a fascinating new exposure. Only five of the 13 similarity function genes involved do not belong to the MHC region, and *FCGR2A* has the highest kappa value among them. *IL18R*, *BTNL2*, *AGER*, and *CTLA4* are the other four genes.

Results obtained from pathway analysis suggests that the immune system is actually inextricably linked to the discovery of a relationship between the two diseases as several studies have revealed that SZ and RA have a relationship with the immune system [53-60]. This proves that non-HLA genes also play a role in engaging the relationship between the immune system and both diseases. This admission reveals the significance of this immune system in the phenomena of the relationship between RA and SZ, despite the fact that the diseases are highly different in nature and characteristics.

This concept is supported and consistent with various data indicating that these immune responses play distinct roles in the immune response pathway in different situations or in response to different stressors [12,40,61-63].

Overall, biological processes reveal a predominance of association by interleukin pathways, T cell association, and B cell association in general. Indeed, as de la Fontaine et al. 2006, demonstrated and described, genetic regulated inflammatory reactions such as dopamine-induced activation of autoimmune T cells in brain tissue and/or immune system are irrefutable. In terms of cellular components, the involvement of clathrin-coated endocytic vesicles in these genes has been noted. Clathrin's primary roles include its participation in the processes of pinocytosis and phagocytosis [64].

The relationship between HLA genes with RA and SZ should not be underestimated because since the beginning they have been crowned as the main cause in this incident [65-71]. In any case, the validity of the contributions of these five non-HLA genes found should be thoroughly explored in discovering the accuracy of the interesting association between these genes with RA and SZ in detail.

To further explore the effectual candidate genes involved in RA and SZ, we select FCGR2A gene for cross validation to prove the validity of the involvement of these genes in realizing the search for candidate genes that may be implicated between the relationship of RA and SZ. The *FCGR2A* encodes a member of the immunoglobulin Fc receptor gene family, which is located on the surface of many immune response cells. The protein encoded by *FCGR2A* is a cell surface receptor located on phagocytic cells such as macrophages and neutrophils that is involved in phagocytosis and immunological complex clearance [72] multiple transcript variations result from

alternative splicing. Studies have evaluated heterogeneity in the *FCGR2A* gene and functionally related genes in synovial RA macrophages with respect to gene expression profiling of RA [73]. Moreover, the response to RA treatments may not only vary among patients, but also be tied up with certain genetic factors such as single-nucleotide polymorphisms (SNPs) in genes, eg, *FCGR2A* [74].

Research based on combined transcriptomic and genomic analyses has yielded the identification of gene co-expression modules (GCMs) in synovial tissue from patients with RA, providing insight into an altered molecular state characterizing their landscape [75]. Furthermore, subsequent gene expression profiling studies have identified highly upregulated genes which could be mechanistic in RA disease pathogenesis [76].

The potential implications of *FCGR2A* upregulation in RA include enhanced binding of IgG antibodies on *FCGR2A* receptors on the immune cells. As a result, those immune cells become more active to attack the tissue, which worsens the inflammation changes in the synovial joint in RA [73,74]. In addition, the high level of this Fc-receptor exacerbates the effects of autoantibodies. RA involves rheumatoid factor and anti-citrullinated protein antibodies, and *FCGR2A* affects this activity. Therefore, joint inflammation and damage are more severe. Lastly, the variation of Fc-receptors' gene affects the severity of the RA. *FCGR2A* might be overexpressed in RA, and this correlates with the more severe phenotypes and increased joint destruction [73-75].

The investigation of gene expression involving the *FCGR2A* gene among SZ patients likewise exhibited diverse study outcomes with no consistency of expression results from total samples studied [77,78]. Eva et al. [77] identified three distinct subtypes of SZ based on gene expression patterns in the DLPFC transcriptome. These discrepancies emphasize the variety within SZ and imply that various subtypes may have distinctive genetic and immune-related properties [77,78].

Downregulation of *FCGR2A* may be connected to immunological dysregulation, potentially contributing to SZ pathogenesis [78]. Further research on immune-related genomic subtypes in SZ has shown discrete molecular subtypes defined by variable gene expressions, illuminating the disorder's complicated genetic landscape [77]. Overexpression of *FCGR2A* in SZ may contribute to altered immunological responses, affecting brain activity or neurodevelopmental processes and may impact neuroinflammatory pathways, exacerbating symptoms or contributing to SZ pathogenesis [79]. There is convincing proof that immune-related variables influence neurotransmission and neuronal connection in SZ.

It would be really exciting if this selected *FCGR2A* and another 4 non-HLA genes could be properly analyzed in relation to RA and SZ. Conceivably, in order to link the interaction between SZ and RA, HLA, and non-HLA genes function in tandem, with the major focus on immune response complexity in general. It is possible to draw the conclusion that immune response does not entail simple linear channels but rather complicated networks of pathways and interactions, positive and negative feedback loops, and various transcriptional responses [73,74].

In depth exposure as well as disassembly is essential in determining and confirming the association that may be the driving force for the occurrence of association between RA and SZ generally.

## CONCLUSION

This study unveiling five non-HLA genes that are involved in the immune system engaging RA and SZ as a result of exploration from several bioinformatic tools. SZ and RA are linked genetically and our finding could help solve the puzzle of genetic relationship between the two diseases. This discovery could serve as a springboard for further research.

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## Appendix A

IL6
IL10
TNF
MIF
CTLA4
LTA
HLA-B
HLA-DQB1
IL1B
FAS
IL1RN
IL18
TNFRSF1B
FCGR2A
ITGAM
IL1A
BTNL2
IL4
VEGFA
ICAM1
PTGS2
IL6R
CD40
HLA-C
MTHFR
HLA-DMA
CAT
HLA-DMB
HLA-DRA
CD4
ACAN
PSMB9
MICB
NR3C1
PRRC2A
IL18R1
CX3CR1
NPSR1
MYD88
TLR3
IL3
TAP1
IGF1
TP53

TLR7
TLR5
IL12B
SERPINE1
TAPBP
CD14
C5
ADIPOQ
HTR2A
HLA-G
IL12A
GSTM1
AGER
P2RX7
MECP2
MBP
DNASE1
AFF3
RUNX1
GHRL
F2
GC
ESR2
PSORS1C1
DHFR
CFH
NOTCH4
ACP1
IGF2
SPRED2
CYP1A2
CFB
CD46
SYNGR1
PLCL2
TCF7L2
KLF12
ERBB3
PHACTR3
MSRA
MTNR1B
DDR1
C2
VARS2

DAXX
CELF2
MYO9B