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Original Article

Identification of Biomarker and Biological Risk Genes to Drive Drug Repurposing in Malaria Using Transcriptomics Database

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Abstract

This study applied the transcriptomic-based bioinformatics analysis to systematically integrate data on risk loci for malaria biology and drug discovery from various databases. It was hypothesized that genomic-driven drug repurposing can be utilized as an alternative approach for malaria drug repurposing. Herein, transcriptomic profiles were extracted and retrieved from the NCBI-GEO website by using the keywords *"malaria"* and *"Homo sapiens"*. In sum, the data mining analysis for malaria drug targets was conducted by integrating the three datasets, including GSE33811, GSE7586, and GSE5418. Limma package was used to detect differentially expressed genes (DEGs). The following cut-off criteria were used for screening DEGs: [log fold change (logFC)] > 1 and *p*-value < 0.05. This study employed a scoring system with seven criteria called functional annotations to prioritize the risk gene candidates for malaria. Following the scoring system, a score of> 2 was identified as a malaria biological risk gene. Overlapping analyses between gene target candidates and drug candidates were conducted using the DrugBank database to obtain new drug targets for malaria. Eighty drug-target genes were identified in this study, but only five genes exhibited druggability and overlapped with the targets of existing drugs, thereby presenting a potential avenue for malaria drug repurposing. These genes, namely *PSMB2*, *CXCR4*, *ITGA4*, *RAF1*, and *PTGER3*, hold promising prospects for malaria therapy. Interestingly, five genes were overlapped with 12 drug candidates (Sorafenib, Regorafenib, Dabrafenib, Natalizumab, Vedolizumab, Bimatoprost, Dinoprostone, Misoprostol, Gemeprost, Castor oil, Carfilzomib, and Plerixafor). In conclusion, an in-silico drug screening system not only can identify the biological risk genes but also potential to drives malaria drug repurposing.

Keywords: *CXCR4*; Drug repurposing; *ITGA4*; Malaria; *PSMB2*; *PTGER3*; Transcriptomics; *RAF1*.

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1. Introduction

Malaria affects approximately 40% of the world's population and remains a major public health problem in African regions such as Nigeria (26.6%), the Democratic Republic of

the Congo (12.3%), Uganda (5.1%) and Mozambique (4.1%) [1]. Ensuring the provision of new and effective treatments is crucial to prevent uncomplicated malaria progress. Several antibiotics have been used as a treatment or concurrently with antimalaria drugs [2-4]. It is important to note that the choice of antimalarial therapy depends on factors such as the severity of the infection, the species of *Plasmodium*, and the drug resistance patterns in the area [5].

Currently, limited disease-modifying drugs are available that can halt the progression of malaria. The discovery of new drugs is an expensive and time-consuming process. It takes ~15 years and more than $1 billion to develop and bring a new drug to market [6]. Furthermore, only <5% of the new molecules that enter first-phase clinical trials are approved by the US Food and Drug Administration (FDA) [7]. Therefore, drug repurposing has emerged as a promising strategy for addressing this challenge. Repurposing existing drugs for the treatment of malaria has been an area of active research to reduce cost and time [8, 9], and several novel drug candidates have shown promises, such as ivermectin [10], fosmidomycin [11] and metformin [12].

The identification of drug targets remains a significant challenge. Genome-wide databases have become increasingly valuable tools for identifying potential drug targets and biomarkers for various diseases, including malaria. These databases contain a vast amount of genomic and transcriptomic data, which can be analyzed to identify differentially expressed genes and genetic variations that may be involved in disease pathogenesis and progression. Transcriptomics is a powerful tool to lead drug repurposing efforts by providing insights into the molecular mechanisms underlying malaria pathogenesis and progression [13]. Recent studies identified candidate genes for drug repurposing using an integrative analysis of transcriptomic and genomic data from *Plasmodium falciparum* [14]. Another study used a genome-wide association study to identify genetic variations associated with resistance to the antimalarial [15]. The leveraging of OMICS based approach to drive drug repurposing also have been applied in previous study [16-18].

In the present study, we applied the transcriptomic-based bioinformatics analysis to systematically integrate data on risk loci for malaria biology and drug discovery from various databases. We hypothesized that genomic-driven drug repurposing can be utilized as an alternative approach for malaria drug repurposing. The results of this study could provide important insights into the molecular mechanisms of malaria pathogenesis and identify potential drug targets for repurposing existing drugs.

2. Materials and Methods

2.1. Study design of transcriptomic-driven drug discovery approach for malaria

The workflow of identification drug repurposing for malaria is depicted in detail in **Figure 1**. In this study, transcriptomics data from the NCBI-GEO website (https://www.ncbi.nlm.nih.gov/geo/) [19] were obtained by employing the search terms "malaria" and "Homo sapiens".

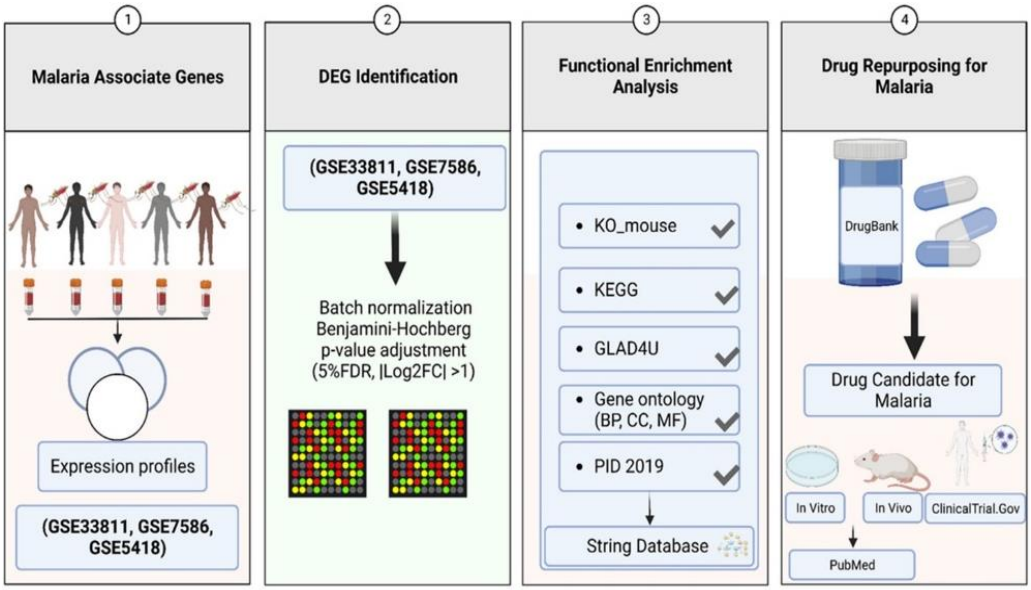

Figure 1. The flow chart shows the utility of omics data to drive drug repurposing for malaria. This figure was created with BioRender.com under agreement number "NU24UFDU9T".

Our primary objective was to perform data mining to identify potential drug targets for malaria by amalgamating information from three distinct datasets: GSE33811, GSE7586, and GSE5418. Limma, an R package, was utilized to identify differentially expressed genes (DEGs). The following cut-off criteria were used for screening DEGs: [log fold change (logFC)] > 1 and p-value < 0.05.

A scoring system with seven criteria called functional annotations was used to prioritize the risk gene candidates for malaria. Following the scoring system, a score greater than two (score > 2) was identified as a malaria biological risk gene. In this study, the scoring system was modified based on Yukinori Okada and colleagues' study [20] and Irham et al. [21-25]. Next, the malaria biological risk gene was expanded with the STRING database to obtain more drug target genes for malaria [26]. Malaria biologic risk genes were mapped to the DrugBank database to identify potential drug targets [27]. Validation was performed by using ClinicalTrials.gov and PubMed for drugs undergoing clinical trials and preclinical studies (in vitro and in vivo, respectively) [28, 29].

2.2. Biological risk gene for malaria

This study employed seven rigorous functional annotation criteria, and a scoring system was applied to prioritize genes associated with biological risk in malaria. According to these criteria, each functional annotation received a score of one. Seven functional annotation criteria, including 1) missense mutation obtained from HaploReg version 4.1. In this step, we used a missense mutation to be one of the functional annotations due to changes in amino acids that later on can change protein function; 2) cis-eQTL; cis expression quantitative trait locus became the second functional annotation, used to determine whether genetic variants affect protein expression causing changes in gene expression towards the involved tissue; 3) Kyoto Encyclopedia of Genes and Genomes (KEGG),

was used to determine the involvement of the molecular pathway based on data from the KEGG with a significance of false discovery rate (FDR) q < 0.05; 4) biological process, was used to determine the involvement of genes in biological protein networks and can be concluded to be important in inhibiting proteins by prioritizing them as biological processes. Considered significant if FDR q < 0.05; 5) cellular components; 6) molecular functions; 7) Primary Immunodeficiency (PID) gene, PID is an innate immune disease that has been reported to be associated with malaria.

2.3. Expanded gene with STRING database

The STRING database was used to integrate publicly accessible sources of information regarding direct (physical) and indirect (functional) protein-protein interactions [26]. The STRING database was utilized to expand the malaria biologic risk genes to obtain more potential drug targets.

2.4. Drug target genes overlapped using drug databases

Overlapping analyses between gene target candidates and drug candidates were conducted using the DrugBank database to obtain new drug targets for malaria [27]. Several criteria are used as requirements for drug targets, such as candidate drug targets must have pharmacological activity, guaranteed effectiveness, approved annotations, clinical trials, or experimental. Each new drug will be checked through ClinicalTrial.gov and PubMed to see if it is in clinical trials for malaria or another disease [29].

3. Results and Discussion

3.1. Transcriptomic Data of Malaria Retrieved from GEO Database

Transcriptomic data were extracted from GEO databases (GSE33811, GSE7586, and GSE5418) [30-32] shown in **Figure 2**. The GSE33811 dataset includes five children with severe malaria and five children with mild malaria. The GSE7586 dataset contained ten women who were negative for placental malaria and ten women who experienced active placental malaria episodes. In contrast, the GSE5418 included 22 data sets from experimentally infected US volunteers, 22 data sets from healthy US volunteers, and 15 data sets from naturally infected Cameroonian volunteers. In the following step, we gathered all DEGs based on the intersection of GSE33811, GSE7586, and GSE5418.

Through this step, we obtained 50 DEGs. Further, all DEGs will be used to drive the biological risk genes for malaria based on the functional annotation applied.

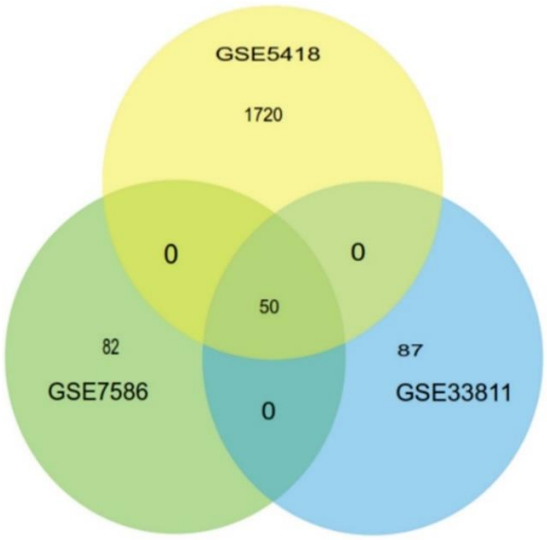

Figure 2. The intersection data of three datasets using the Venn diagram.

3.2. Biological Risk Gene Associated with Malaria

Biological risk genes associated with malaria were acquired using a functional annotation filtering strategy, including the KO-Mouse Phenotype, KEGG, GLAD4U, GO, and PID. The gene with a score minimum of more than two will be prioritized for the biological risk genes for malaria. Based on the following information, we emphasized that the HLA-DQB1 gene is the highest score; a total of 30 biological risk genes were obtained based on the scoring system, as shown in **Table 1**. A higher score implies a greater likelihood of genes being selected for characterization as potential biological risk genes for malaria.

The database availability of malaria-susceptibility genes is still limited, although such studies have shown several genes involved in host susceptibility to malaria severity. Herein, we showed 30 DEGs from human blood samples infected by *Plasmodium falciparum*. Among them, HLA class II genes are presented with the highest DEG risk score, and they are HLA-DPA1, HLA-DQB1, HLA-DQA1, HLA-DRB4, and HLA-DRA. We found a complete chain (alfa and beta) of HLA-DQ and HLA-DR genes are differentially expressed. This evidence confirms another study that found the expression of DRB, an HLA/MHC class II gene, was increased in both *P. falciparum* and *P. vivax* infected patients [33, 34].

Table 1. Prioritization of transcriptomic information drives biological risk gene-associated malaria using Functional annotations.

Gene Name	KO_Mouse	KEGG	GLAD4U	Gene Ontology			PID	Total score
				BP	CC	MF		
HLA-DQB1	0	1	1	1	1	1	0	5
HLA-DPA1	0	1	1	1	1	1	0	5
HLA-DRA	0	1	1	1	1	1	0	5
HLA-DQA1	0	1	1	1	1	1	0	5
HLA-DRB4	0	1	1	1	1	0	0	4
IL1RN	1	0	1	1	0	0	1	4
STAT1	1	0	1	1	0	0	1	4
CCL3	1	1	1	1	0	0	0	4
CXCL10	1	0	1	1	0	0	0	3
PSMB9	1	0	1	0	0	0	1	3
CD86	0	1	1	1	0	0	0	3
FCGR3A	0	0	1	1	0	0	1	3
CX3CR1	1	0	1	1	0	0	0	3
OLFM4	1	0	0	1	0	0	0	2
HAMP	1	0	0	1	0	0	0	2
IGHM	0	0	1	0	0	0	1	2
RGS1	0	0	1	1	0	0	0	2
LILRA3	0	0	1	1	0	0	0	2
BCL2A1	1	0	1	0	0	0	0	2
CCL3L3	0	1	0	1	0	0	0	2
AQP9	1	0	0	1	0	0	0	2
TLR8	0	0	1	1	0	0	0	2
FCGR3B	0	0	1	1	0	0	0	2
MX1	0	0	1	1	0	0	0	2
PTGER4	0	0	1	1	0	0	0	2
PILRA	1	0	0	1	0	0	0	2
IFIT1	1	0	0	1	0	0	0	2
CCL3L1	0	1	1	0	0	0	0	2
GBP5	1	0	0	1	0	0	0	2
FGL2	1	0	0	1	0	0	0	2

Note: The higher the score, the more pathogenic genes were associated with malaria. KO-Mouse: KnockOut Mouse; KEGG: Kyoto Encyclopedia of Genes and Genomes; GLAD4U: Gene List Automatically Derived for You; BP: Biological Processes; CC: Cellular Component; MF: Molecular Function; PID: Primary Immunodeficiency

Malaria induces inflammatory chemokines, such as CXCL10, CCL2, and CCL3, as well as cytokines, TNF-α, IL-8, and IL-6. Though there is limited evidence for the influence of DEG on malaria phenotypes, our study found three genes related to immune have a significant risk score in malaria infection, which are IL1RN, CCL3, and CXCL10. However, It should be noted that there is heterogeneity in genetic susceptibility regarding gene expression in malaria infection. A study found that IL1RN allele polymorphism was associated with total Ig-E in *P. falciparum* infection in the endemic Tanzanian population [35]. CCL3 gene expression was highly increased in placental malaria infection and correlated with monocyte density [36]. As a CXCR3 ligand, CXCL10 gene expression was highly related to poor prognosis and significantly increased in severe malaria *P. falciparum* and *P. vivax* infection [37, 38]. CXCL10 upregulation in *P. vivax* infection was also markedly correlated with severe thrombocytopenia and hepatic impairment [37].

3.3. Drug Repurposing for Malaria Treatment Based on the Transcriptomic Information

In a subsequent phase, we used the STRING database (https://string-db.org/, accessed November 12, 2022) to broaden the biological malaria risk genes network. Fifty interactions were selected to calculate and expand the number of genes. Novel therapeutic targets for diseases can be rapidly identified with more disease-protein networks [39]. Finally, we found 80 drug target genes using the STRING database **(Figure 3).**

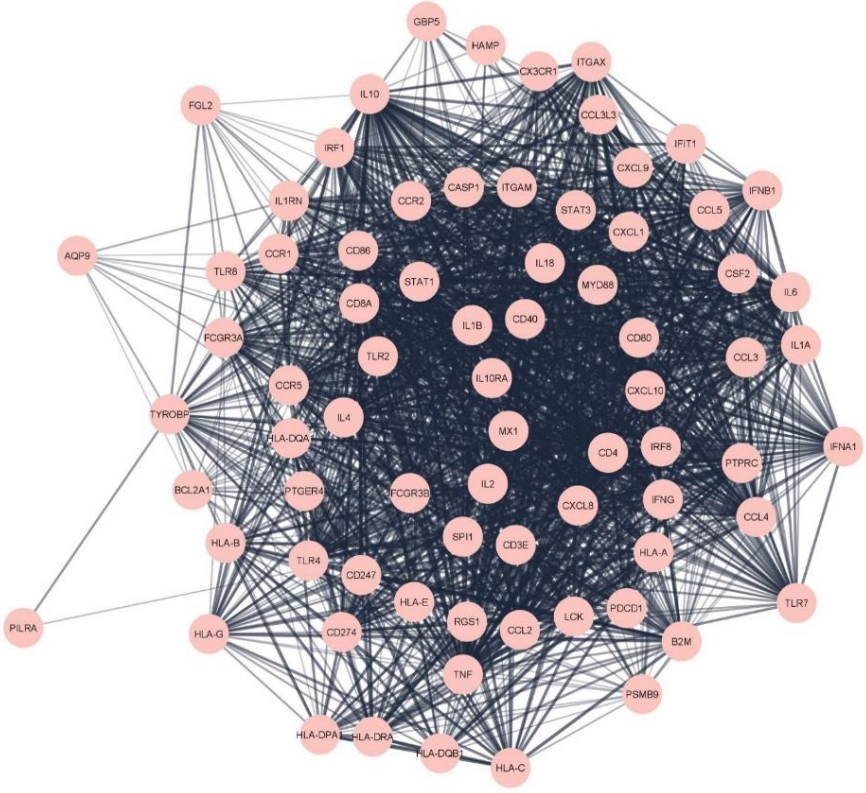

Figure 3. Expansion network by STRING database. Biological malaria risk genes (30 genes). Number of interactions = 50 The first shell proteins. The string database was accessed from https://string-db.org/. Note: the expansion network in the Table S1.

These drug-target genes were mapped to DrugBank (https://go.drugbank.com/, accessed on November 12, 2022). However, only five drug target genes were druggable to bind 12 drugs based on DrugBank **(Figure 4)**.

Notably, out of the 80 drug-target genes identified, only five genes exhibited druggability and overlapped with the targets of existing drugs, thereby presenting a potential avenue for drug repurposing in malaria. These genes, namely *PSMB2, CXCR4, ITGA4, RAF1*, and *PTGER3*, hold promising prospects for targeted therapy in malaria. PSMB2 is a gene that encodes the β2 subunit of the proteasome, a critical component of the ubiquitin-proteasome system (UPS) responsible for cellular protein degradation. Recent research suggested that targeting the proteasome in P. *falciparum* could be a viable approach for developing novel antimalarial therapy [40]. It has been found that PSMB2 was a promising target for designing new drugs to treat malaria.

Interestingly, carfilzomib (DB08889), a synthetic proteasome inhibitor, has been identified as a drug that targets PSMB2. Carfilzomib has shown a potent antimalarial activity, suggesting that PSMB2 could be an effective target for developing antimalarial drugs. Studies have shown that carfilzomib could potently block *P. falciparum* replication in vitro at effective concentrations, and it could also kill the asexual blood-stage parasites that cause the clinical symptoms of malaria [41, 42].

Many studies have described the role of RAF1 as a targeted therapy in various solid tumors [43]. RAF1 is a protein kinase that regulates cell proliferation, differentiation, and survival by transmitting signals from growth factors and other extracellular signals to intracellular pathways. In addition to being a targeted therapy for cancer, RAF1 could also be a potential target for malaria. Studies have shown that inhibiting RAF1 kinase activity using specific inhibitors or RNA interference significantly reduced the growth and proliferation of *Plasmodium* parasites in vitro and in vivo [44]. Furthermore, RAF1 inhibitors are highly effective against drug-resistant strains of malaria [44]. It suggests that targeting RAF1 could be a promising approach for developing new antimalarial therapy.

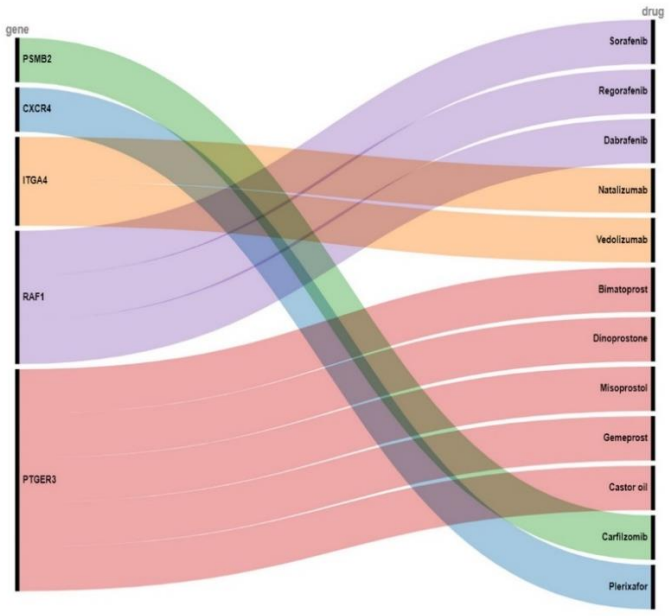

Figure 4. Five genes overlap with 12 drug candidates to be repurposed for malaria treatment.

Proteasome 20S Subunit Beta 2 (PSMB2) is a crucial gene in proteasome regulation. Bortezomib and carfilzomib are proteasome inhibitors that induce cell cycle arrest and apoptosis, reportedly associated with malaria therapy [40]. CXCR4, a protein involved in immune response and inflammation, has been widely studied as a drug target in various diseases such as cancer, human immunodeficiency virus (HIV), and autoimmune diseases. In the context of malaria research, drugs targeting CXCR4 might be effective therapeutics in inhibiting malaria proliferation by blocking erythrocyte invasion by the malaria parasite [45]. The discovery of novel antimalarial drugs targeting the CXCR4 receptor was effective against *P. vivax* [46]. PTGER3, also known as EP3, played a role in regulating the production of pro-inflammatory cytokines and the convocation of immune cells to the site of infection. Misoprostol, an anti-gastric ulcer agent targeting PTGER3, is used to reduce inflammation and prevent the harmful effects of cytokine storms associated with severe malaria [47]. ITGAP (integrin alpha-3-binding protein) is a gene that encodes a protein involved in cell adhesion and signaling processes. A study by Riggle [48] mentioned that Natalizumab, an FDA-approved monoclonal antibody used to treat multiple sclerosis and Chron' disease that targets ITGA4, has a pharmacological effect for malaria by blocking the adhesion of immune cells to blood vessels.

Bioinformatics-driven drug repurposing is a computational method that uses various techniques to identify new potential uses for existing drugs [49]. By identifying existing drugs targeting the underlying molecular disease mechanisms, drug repositioning can provide a promising alternative approach that rapidly identifies and prioritizes new potential treatment options for malaria patients. The current study used the transcriptomic data to conduct a bioinformatics-based drug repositioning analysis for malaria. This comparative analysis helped identify upregulated or downregulated genes, which could suggest potential targets for drug repositioning. This process helped us to identify 12 drugs that could target five genes associated with malaria. Only Sorafenib, a protein tyrosine kinases (PTKs) inhibitor, had antimalarial activity *in vitro* [50].

4. Conclusion

Bioinformatics-driven drug repositioning represents a promising strategy for identifying potential malaria treatments. We highlighted five genes that were overlapped with 12 drug candidates. Furthermore, our results suggested that an in silico drug screening system is valuable for prioritizing malaria-related biological risk genes and facilitating drug repurposing efforts.

Conflict of interest

The authors declare to have no conflict of interest.

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Tabel S1. List of genes expansion network using STRING

#node	identifier	#node	identifier
AQP9	9606.ENSP00000219919	IRF9	9606.ENSP00000380073
BCL2A1	9606.ENSP00000267953	JAK1	9606.ENSP00000343204
CCL3	9606.ENSP00000477908	JAK2	9606.ENSP00000371067
CCL3L3	9606.ENSP00000480558	KPNA1	9606.ENSP00000343701
CCL4	9606.ENSP00000482259	MX1	9606.ENSP00000381601
CCR1	9606.ENSP00000296140	OAS1	9606.ENSP00000388001
CCR5	9606.ENSP00000292303	OASL	9606.ENSP00000257570
CD247	9606.ENSP00000354782	OLFM4	9606.ENSP00000219022
CD28	9606.ENSP00000324890	PIAS1	9606.ENSP00000249636
CD74	9606.ENSP00000009530	PILRA	9606.ENSP00000198536
CD86	9606.ENSP00000332049	PSMA1	9606.ENSP00000414359
CREBBP	9606.ENSP00000262367	PSMA2	9606.ENSP00000223321
CTLA4	9606.ENSP00000303939	PSMA3	9606.ENSP00000216455
CX3CL1	9606.ENSP00000006053	PSMA4	9606.ENSP00000044462
CX3CR1	9606.ENSP00000351059	PSMA5	9606.ENSP00000271308
CXCL10	9606.ENSP00000305651	PSMA6	9606.ENSP00000261479
CXCR3	9606.ENSP00000362795	PSMA7	9606.ENSP00000359910
EP300	9606.ENSP00000263253	PSMB1	9606.ENSP00000262193
FCGR3A	9606.ENSP00000356946	PSMB10	9606.ENSP00000351314
FCGR3B	9606.ENSP00000433642	PSMB2	9606.ENSP00000362334
FGL2	9606.ENSP00000248598	PSMB3	9606.ENSP00000483688
GBP5	9606.ENSP00000359488	PSMB4	9606.ENSP00000290541
HAMP	9606.ENSP00000471894	PSMB5	9606.ENSP00000355325
HLA-DMA	9606.ENSP00000363976	PSMB7	9606.ENSP00000259457
HLA-DMB	9606.ENSP00000398890	PSMB8	9606.ENSP00000364016
HLA-DPA1	9606.ENSP00000393566	PSMB9	9606.ENSP00000363993
HLA-DQA1	9606.ENSP00000339398	PSMC1	9606.ENSP00000261303
HLA-DQB1	9606.ENSP00000364080	PSMC4	9606.ENSP00000157812
HLA-DRA	9606.ENSP00000378786	PSMC6	9606.ENSP00000401802
HLA-DRB1	9606.ENSP00000353099	PSMD4	9606.ENSP00000357879
HLA-DRB5	9606.ENSP00000364114	PSMD8	9606.ENSP00000215071
IFIT1	9606.ENSP00000360869	PTGER4	9606.ENSP00000302846
IFIT3	9606.ENSP00000360883	RGS1	9606.ENSP00000356429
IFNAR1	9606.ENSP00000270139	RSAD2	9606.ENSP00000371471
IFNGR1	9606.ENSP00000356713	SLC40A1	9606.ENSP00000261024
IL1R1	9606.ENSP00000386380	STAT1	9606.ENSP00000354394
IL1RN	9606.ENSP00000259206	TLR8	9606.ENSP00000312082
IRF1	9606.ENSP00000245414	TRADD	9606.ENSP00000341268