Host RNA Biomarkers of Tuberculosis Disease and with People Living with HIV

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ABSTRACT

Tuberculosis remains a leading global health challenge, with early and accurate diagnosis critical for effective disease management. Transcriptomic studies have identified host blood RNA biomarkers as promising diagnostic tools, yet challenges remain in standardizing methodologies and ensuring diverse population representation. Tuberculosis in people living with HIV (PLHIV) presents unique immunological interactions that require further investigation.

This master's thesis project aimed to synthesize existing transcriptomic research on tuberculosis biomarkers through a scoping review and conduct a primary transcriptomic analysis to identify differentially expressed genes associated with tuberculosis in PLHIV.

A PRISMA scoping review was conducted to evaluate published transcriptomic studies from 2000 to 2024, focusing on host blood biomarkers identified using microarray and RNA sequencing technologies. Furthermore, a primary transcriptomic analysis was performed using whole-blood and PBMC samples from 96 participants across four cohorts: tuberculosis in PLHIV (n=29), tuberculosis alone (n=31), HIV alone (n=23), and non-infected individuals (n=13). Differential gene expression analysis was conducted using DESeq2, with batch effects controlled using ComBat-Seq. Candidate biomarkers were identified by comparing differentially expressed genes with those frequently reported in the scoping review.

The scoping review identified 60 tuberculosis gene signatures comprising 1,939 unique genes, with 15 genes appearing in at least 10 signatures. Microarray remained the dominant methodology; however, RNA sequencing datasets have increased in recent years. The primary study identified 10,308 differentially expressed genes, with six—GBP6, DHRS9, GBP5, CD274, FCGR1A, and ANKRD22—frequently appearing in tuberculosis gene signatures and showing significant upregulation in tuberculosis in PLHIV. These genes are linked to immune activation, inflammatory responses, and antigen processing, highlighting their potential as tuberculosis biomarkers.

This master's thesis project highlights the potential of transcriptomic biomarkers for tuberculosis diagnosis, particularly in PLHIV, while highlighting critical areas for future research. Expanding cohort recruitment in high tuberculosis burden countries such as India, Indonesia, China, the Philippines, Pakistan, Nigeria, Bangladesh, and the Democratic Republic of the Congo will be essential to enhance the generalizability of identified biomarkers. Additionally, considering tuberculosis as a disease spectrum—including incipient, minimal, and subclinical tuberculosis—will be crucial for refining diagnostic applications.

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TABLE OF CONTENTS

ABSTRACT II

ACKNOWLEDGEMENTS IV

TABLE OF CONTENTS V

LIST OF TABLES VIII

LIST OF FIGURES IX

LIST OF ABBREVIATIONS X

LIST OF APPENDICES XII

AUTHOR CONTRIBUTIONS XIII

CHAPTER I: INTRODUCTION 1

1.1 Tuberculosis 1

1.2 Tuberculosis Epidemiology 1
1.2.1 Global Epidemiology 1
1.2.2 Canadian Epidemiology 2

1.3 Immunology 4
1.3.1 Latent Tuberculosis Infection Immunology 4
1.3.2 Tuberculosis Disease Immunology 5
1.3.3 Tuberculosis Spectrum 7
1.3.4 Tuberculosis Disease in People Living with HIV Immunology 8

1.4 Diagnostics 11
1.4.1 Screening and Diagnosis of Tuberculosis Infection 11
1.4.2 Screening and Diagnosis of Tuberculosis Disease 11
1.4.3 Challenges in Diagnosing Tuberculosis in People Living with HIV 12

1.5 Biomarkers of Tuberculosis 16
1.5.1 Transcriptomic Technologies for Biomarker Discovery 16
1.5.2 Blood Sample Types for Tuberculosis Transcriptome Studies 18

1.6 Research Gaps 19

1.7 Rationale 19

1.8 Objectives and Hypotheses 20

CHAPTER II: SCOPING REVIEW – HOST BLOOD RNA TUBERCULOSIS BIOMARKERS BASED ON RNA-SEQUENCING & MICROARRAY METHODOLOGY 22

2.1 Introduction 22

2.2 Methods 22
2.2.1 Search Strategy 22
2.2.2 Definitions and Eligibility Criteria 22

2.2.3 Data Management and Extraction ... 26

2.3 Results ... *27*
2.3.1 Overview ... 27
2.3.2 Characteristics of the transcriptome studies ... 27
2.3.3 Comparison of gene methodology and tissue sample ... 35
2.3.4 Discovery of novel tuberculosis biomarkers through microarray and RNA-Seq ... 35
2.3.5 Publicly Available Datasets Used ... 41

2.4 Discussion ... *44*
2.4.1 Geographic Diversity of Transcriptomic Studies ... 44
2.4.2 Microarray and RNA-Seq comparisons ... 44
2.4.3 Tissue Sample comparisons ... 45
2.4.4 Potential Biomarkers ... 46
2.4.5 Publicly Available Datasets ... 48
2.4.6 Novel Profiling Approaches and Current Limitations of the Findings ... 49

2.5 Conclusion ... *50*

CHAPTER III: GENE EXPRESSION PROFILE OF TUBERCULOSIS DISEASE AMONG PEOPLE LIVING WITH HIV ... 51

3.1 Introduction ... *51*

3.2 Methods ... *51*
3.2.1 Participants ... 51
3.2.2 Published cohort sequences ... 52
3.2.3 Sample Processing ... 52
3.2.4 RNA-Seq Processing ... 55
3.2.5 Bioinformatics Analysis ... 55
3.2.6 Identifying Potential Gene Biomarkers ... 55
3.2.7 Ethics Declaration ... 59

3.3 Results ... *59*
3.3.1 Cohort Description ... 59
3.3.2 Differentially Expressed Genes ... 60
3.3.3 Enrichment Analysis ... 60
3.3.4 Candidate Gene Biomarkers for Tuberculosis in PLHIV ... 64

3.4 Discussion ... *69*
3.4.1 Differential Expression and Enrichment Analysis ... 69
3.4.2 Identification of Candidate Gene Biomarkers ... 70
3.5.3 Limitations ... 71

3.5 Conclusion ... *72*

CHAPTER IV: FINAL DISCUSSION AND FUTURE DIRECTIONS ... 73

4.1 Final Discussion ... *73*
4.1.1 Potential Biomarkers ... 73
4.1.2 Connecting the Goals of the Scoping Review and Primary Paper ... 74
4.1.3 Adjusting for Cohort and Geographic Effects ... 74
4.1.4 Addressing the Hypothesis ... 75
4.1.5 Combining Whole-Blood and PBMC Samples for Gene Expression Analysis ... 76
4.1.6 Overall Limitations of the Masters Project ... 77
4.1.6 Strengths of the Masters Project ... 78

4.2 Future Directions ... *79*

CHAPTER V: REFERENCES 81

CHAPTER VI: APPENDIX 97

LIST OF TABLES

Table 1.1. Estimated tuberculosis incidence and notification rates in high-burden countries compared to Canada (2023)

Table 1.2. Summary of the differences in tuberculosis spectrum

Table 1.3. Current diagnostic methods approved by the World Health Organization for *Mycobacterium tuberculosis*

Table 1.4. Summary of Comparison of Microarray and RNA-seq for Differential Gene Expression Analysis

Table 2.1. Search Strategy

Table 2.2. Search Criteria

Table 2.3. Studies retrieved from the PRISMA search depicting the gene signatures and publication characteristics that aimed to discover tuberculosis gene signatures

Table 2.4. Tissue Sample Overlap List

Table 2.5. Methodology Overlap List

Table 2.6. Usage Trends of Public Transcriptomic Datasets in tuberculosis Biomarker Discovery Studies

Table 3.1. Study design and recruitment characteristics of cohorts

Table 3.2. Sample and RNA processing information on all cohorts

Table 3.3. Baseline characteristics of people diagnosed with HIV and/or tuberculosis compared to healthy controls

Table 3.4. Top 10 Reactome pathways enrichment analysis of candidate gene biomarkers

LIST OF FIGURES

Figure 1.1. Reported tuberculosis in Canada per 100,000 population from 2014 to 2023. Infographic retrieved and modified from the Public Health Agency of Canada (PHAC)

Figure 2.1. PRISMA flowchart depicting the screening process for identified, screened and included papers

Figure 2.2. World map diagram depicting the number of studies that evaluated tuberculosis gene signatures conducted in each country

Figure 2.3. Venn Diagram depicting the comparisons of methodology and tissue sample in tuberculosis signature presentation

Figure 2.4. Heatmap depicting the genes reported in 10 or more tuberculosis signature

Figure 3.1. Principal Component Analysis of all 4 cohorts. A) Before correction B) After correction

Figure 3.2. Hierarchal heatmap of the sample-to-sample distances before Combat-Seq correction

Figure 3.3. Hierarchal heatmap of the sample-to-sample distances after Combat-seq correction

Figure 3.4. Venn diagram depicting the differentially expressed genes of people diagnosed with tuberculosis alone, HIV alone, tuberculosis among PLHIV, and non-HIV/non-tuberculosis cohorts

Figure 3.5. Volcano plot depicting differentially expressed genes

Figure 3.6. Gene Ontology enrichment analysis of DEGs shared across study cohorts

Figure 3.7. Consensus biomarkers identified in 10 or more tuberculosis gene signatures

Figure 3.8. Gene expression of potential tuberculosis biomarkers across conditions.

LIST OF ABBREVIATIONS

Abbreviation	Definition
AFB	Acid-fast bacilli
AIDS	Acquired immunodeficiency syndrome
ANKRD22	Ankyrin repeat domain 22
APOL6	Apolipoprotein L6
ART	Antiretroviral therapy
ATTB	Anti-tuberculosis treatment
BATF2	Basic leucine zipper ATF-like transcription factor 2
BP	Biological processes
C1QB	Complement C1q B chain
C1QC	Complement C1q C chain
CC	Cellular components
CD274	Cluster of differentiation 274
COVID-19	Coronavirus disease 2019
CT	Computed tomography
DEG	Differentially Expressed Genes
DHRS9	Dehydrogenase/reductase 9
EMB	Ethambutol
ENA	European Nucleotide Archive
ETV7	ETS variant transcription factor 7
FcGR1A	Fc gamma receptor Ia
GBP5	Guanylate binding protein 5
GBP6	Guanylate binding protein 5
GEO	Gene Expression Omnibus
GO	Gene ontology
GSE	Gene Expression Omnibus Series
GTPase	Guanosine triphosphate hydrolase
HC	Healthy Controls
HIV	Human Immunodeficiency Virus
IGRA	Interferon Gamma Release Assay
INH	Isoniazid
INPEC	Instituto Nacional Penitenciario y Carcelario
INSL3	Insulin like 3
ITB	Incipient Tuberculosis
LTBI	Latent Tuberculosis Infection
MDM	Monocyte-derived macrophages
MF	Molecular functions

MHC	Major Histocompatibility Complex
miRNA	Micro ribonucleic acid
MMP	Matrix Metalloproteinases
NAATs	Nucleic Acid Amplification Tests
NCBI-GEO	National Center for Biotechnology Information - Gene Expression Omnibus
OD	Other Diseases
PBMC	Peripheral Blood Mononuclear Cells
PCA	Principal Component Analysis
PD-L1	Programmed death-ligand 1
PLHIV	People living with HIV
PMID	PubMed Identifier
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR	Preferred Reporting Items for Systematic Reviews and Meta-Analyses - Scoping Reviews
RAB20	RAB20, member RAS oncogene family
RES	Resolution
RMP	Rifampin
RNA	Ribonucleic acid
RNA-Seq	Ribonucleic acid - Sequencing
RT-qPCR	Reverse transcription quantitative real-time polymerase chain reaction
SCARF1	Scavenger receptor class F member 1
scRNA-Seq	Single-cell ribonucleic acid - Sequencing
SEPT4	Septin-4
SERPING1	Serpin family G member 1
STB	Subclinical Tuberculosis
TIMPs	Tissue Inhibitors of Metalloproteinases
TST	Tuberculin skin testing
UK	United Kingdom
USA	United States of America
WHO	World Health Organization
XPERT MTB/RIF	Xpert Mycobacterium tuberculosis and rifampin

LIST OF APPENDICES

Appendix 1. Scoping review codes (R script)

Appendix 2. PBMC extraction protocol

Appendix 3. Galaxy project protocol

Appendix 4. Primary transcriptomic profiling codes (R script)

Appendix 5. Enrichment analysis of tuberculosis in PLHIV vs. tuberculosis alone via clusterProfiler

Appendix 6. Enrichment analysis of tuberculosis in PLHIV vs HIV via clusterProfiler

Appendix 7. Enrichment analysis of tuberculosis in PLHIV vs non-infected via clusterProfiler

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CHAPTER I: INTRODUCTION

1.1 Tuberculosis

Tuberculosis is caused by *Mycobacterium tuberculosis*, a slow-growing, aerobic bacterium that primarily infects the lungs but can also affect other organs. *M. tuberculosis* has been around since ancient times, with earliest documents of tuberculosis disease 3,300 years and 2,300 years ago in India and China respectively[1,2]. An early ancestor of *M. tuberculosis* is hypothesized to have originated in East Africa 3 million years ago, potentially infecting early hominids[3]. Transmission occurs through inhalation of aerosolized droplets containing the bacterium, which can remain suspended in the air for prolonged periods[4]. Once inhaled, *M. tuberculosis* is engulfed by alveolar macrophages, where it employs immune evasion strategies such as inhibiting phagosome-lysosome fusion and modulating host immune responses to persist and establish infection[5,6]. The pathogenesis of tuberculosis is influenced by host genetic susceptibility, environmental factors, alcohol consumption, and co-infections such as diabetes and human immunodeficiency virus (HIV)[7–9].

1.2 Tuberculosis Epidemiology

1.2.1 Global Epidemiology

Tuberculosis remains a leading cause of morbidity and mortality worldwide surpassing coronavirus disease 2019 (COVID-19)[8]. The World Health Organization (WHO) estimated 10.8 million people developed tuberculosis in 2023, with 1.25 million deaths[8]. The South-East Asia region and Africa region accounts for 45% and 26% of the population who developed tuberculosis respectively[8]. Specifically, the highest burden of tuberculosis disease is found in low- and middle-income countries (Table 1.1) , with India (26%), Indonesia (10%), China (6.8%), the Philippines (6.8%), Pakistan (6.3%), Nigeria (4.6%), Bangladesh (3.5%), and the Democratic Republic of the Congo (3.1%) collectively contribute to two-thirds of global cases[8].

Table 1.1 Estimated tuberculosis incidence and notification rates in high-burden countries compared to Canada (2023)

Country	Estimated TB Incidence (2023)	Rate per 100 000 population
Canada	2,300 (2,000 – 2,600)	5.8(5 - 6.7)
India	2,800,000 (2,360,000 – 3,280,000)	195 (164 – 228)
Indonesia	1,090,000 (995,000 – 1,210,000)	387 (354 – 432)
China	741,000 (626,000 – 864,000)	52 (44 – 61)
Philippines	739,000 (340,000 – 1,280,000)	643 (296 – 1120)
Pakistan	686,000 (465,000 – 911,000)	277 (188 – 368)
Nigeria	499,000 (326,000 – 709,000)	219 (143 – 311)
Bangladesh	379,000 (276,000 – 499,000)	221 (161 – 291)
Democratic Republic of the Congo	334,000 (215,000 – 479,000)	316 (204 – 453)

Statistics retrieved and modified from World Health Organization[10].

People living with HIV (PLHIV) are at a higher risk of tuberculosis progression, with individuals with latent tuberculosis infection being 16 times more likely to progress to tuberculosis disease compared to HIV-negative individuals[8]. Additionally, some studies estimate a 30% lifetime risk of tuberculosis disease progression in PLHIV compared to a 10% risk of progression in people without HIV[11]. Tuberculosis remains the leading killer in PLHIV, with a reported 161,000 deaths in 2023[8].

1.2.2 Canadian Epidemiology

In Canada, the overall tuberculosis incidence rate is 5.5 per 100,000 population (Figure 1.1), with 2,217 cases confirmed nationally in 2023[12]. In terms of regions, the northern territories (Yukon Territory, Northwest Territory and Nunavut) consistently report the highest incidence per year[13]. The Western region consisting of Manitoba, Saskatchewan, Alberta and British Columbia is reported to have the second highest annual incidence rate[13]. Manitoba reported 129 cases confirmed in 2022 with a rate of 9.2 per

100,000 population, making it the third highest incidence of tuberculosis in Canada behind Saskatchewan (12.1 per 100,000) and Nunavut (130.8 per 100,000)[14]. Tuberculosis disproportionately impacts specific populations such as Indigenous communities mainly the Inuit and First Nations population, and foreign-born Canadian residents[13,14]. About 1 in 4 foreign-born individuals (mainly from high burden countries) fell ill to tuberculosis, with a 2023 report accounting for 79% of tuberculosis cases in Canada[12,15]. Indigenous communities had the highest rate of tuberculosis incidence for 2 decades, with socioeconomic factors such as over-crowding in housing, particularly in Inuit communities contributing to the disparity[12,13,16].

In the HIV coinfection context, only 12 cases (1.5%) of Canadian individuals with tuberculosis were reported to be among people living with HIV[14]. While the proportion of tuberculosis cases in PLHIV has remained low over the years, it is important to note that the HIV status reporting is limited, 58.4% of the tuberculosis cases in 2022 did not have reported HIV status. The underreporting of the HIV status in tuberculosis cases makes it difficult to assess the true burden of tuberculosis and HIV coinfection in Canada, as the low proportion of HIV-positive cases with tuberculosis could be due to incomplete data[13,14]. Therefore, the epidemiological trends in Canada regarding tuberculosis and HIV must be interpreted cautiously.

Overall, regions and specific populations in Canada are disproportionately affected. Factors such as financial barriers, education, housing environments, incarceration, healthcare access contributes to the high incidence in tuberculosis and thus needs to be addressed urgently contributing to tuberculosis response[13,17].

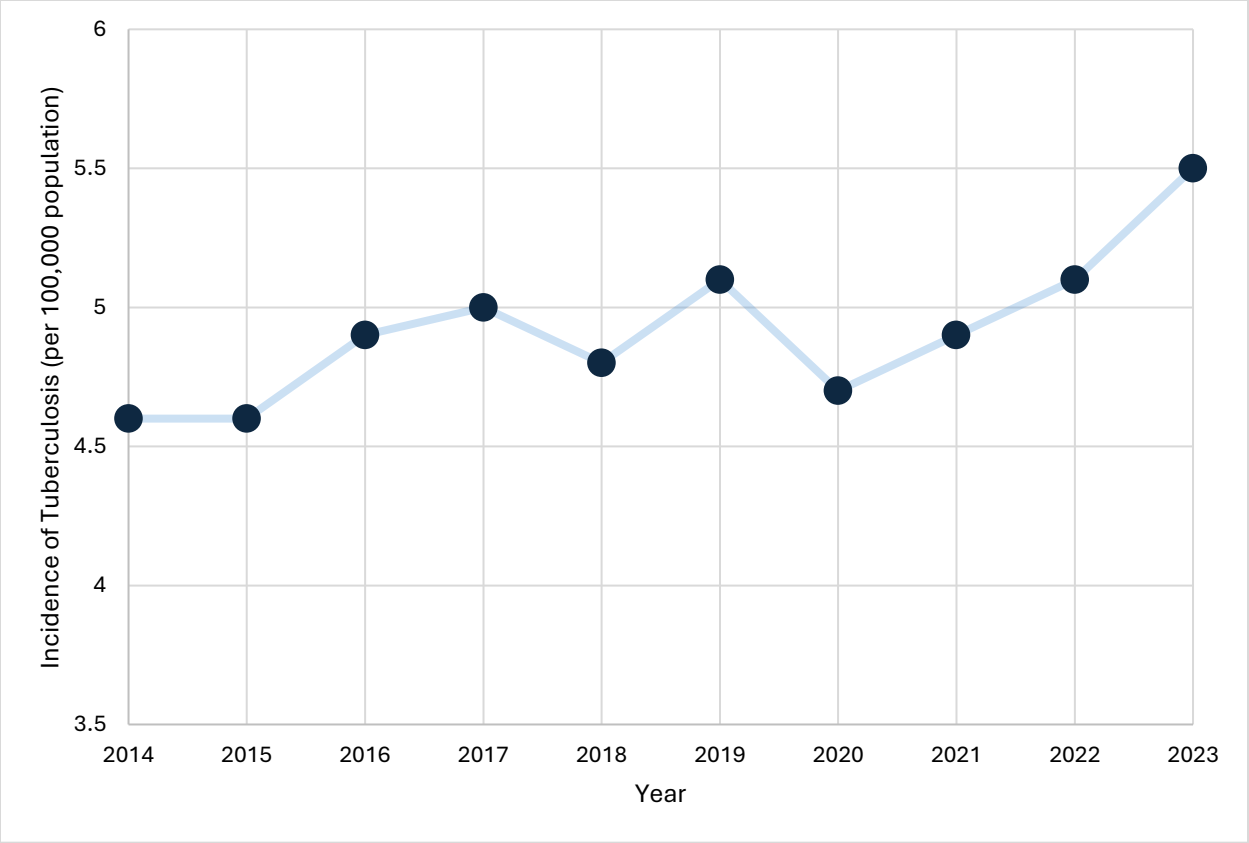


Figure 1.1 Reported tuberculosis in Canada per 100,000 population from 2014 to 2023. Infographic retrieved and modified from the Public Health Agency of Canada (PHAC)[12].

1.3 Immunology

1.3.1 Latent Tuberculosis Infection Immunology

Latent tuberculosis infection (LTBI) represents a state in which *M. tuberculosis* persists within the host without causing active disease and clinical presentation. The host immune system successfully contains the bacteria within granulomas, preventing its replication and dissemination. The balance between immune activation and bacterial persistence characterizes LTBI, with the host immune response playing a critical role in maintaining control over infection.

1.3.1.1 Innate Immune Response to LTBI

Upon inhalation, *M. tuberculosis* is phagocytosed by alveolar macrophages, where it employs various strategies to evade immune clearance. Instead of being destroyed, the bacterium can inhibit phagosome-lysosome fusion, resist reactive oxygen and nitrogen species, and persist within macrophages in a dormant state[5,6]. Neutrophils and dendritic cells contribute to early immune responses by producing proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β), which are essential for granuloma formation[18,19].

Granulomas, consisting of macrophages, lymphocytes, and fibroblasts, serve as immunological barriers that contain *M. tuberculosis*. The core of granulomas often harbors infected macrophages, including multinucleated giant cells and foamy macrophages, which provide a nutrient-rich environment for bacterial persistence[6,20,21]. Hypoxic conditions within granulomas promote bacterial dormancy and upregulation of *M. tuberculosis* dormancy survival genes[22–24].

1.3.1.3 Adaptive Immune Response to LTBI

CD4+ T cells play a pivotal role in controlling LTBI through interferon-gamma (IFN-γ) secretion, which activates macrophages to enhance intracellular bacterial killing[25,26]. CD8+ T cells contribute by releasing cytotoxic granules, such as perforin and granulysin, that target infected cells[27]. Regulatory T cells (Tregs) help modulate excessive inflammation, but an imbalance in Treg activity may contribute to bacterial persistence[28].

While the immune response successfully contains the infection in most individuals, approximately 5–10% of latently infected individuals progress to tuberculosis disease, often due to immune suppression or external risk factors such as HIV coinfection, malnutrition, diabetes, or immunosuppressive therapy[4,8].

1.3.2 Tuberculosis Disease Immunology

Tuberculosis disease results from an inadequate immune response that fails to control *M. tuberculosis* replication, leading to progressive tissue damage and

dissemination. Unlike LTBI, where granulomas restrict bacterial growth, tuberculosis disease is marked by granuloma necrosis, excessive inflammation, and increased bacterial burden.

1.3.2.1 Breaking Down Granuloma and Tuberculosis Disease Progression

In individuals who progress from latent infection to disease, granuloma integrity is compromised. Increased production of matrix metalloproteinases (MMPs) degrades extracellular matrix components, leading to granuloma breakdown and bacterial release into lung airways[29,30]. The necrotic core of granulomas, also known as caseous necrosis, provides an extracellular environment where *M. tuberculosis* can actively replicate and spread[31]. Several studies have explored potential ways at blocking MMP degradation of granulomas, including targeting the MMPs and using MMP inhibitors such as endogenous tissue inhibitors of metalloproteinases (TIMPs), hydroxamates and tetracyclines[32]. However, therapeutic applications to tuberculosis are still under investigation and remains limited due to concerns about unintended side effects and toxicity[33].

1.3.2.2 Immune Dysregulation and Tuberculosis Disease

A dysregulated immune response contributes to disease pathogenesis, characterized by an overproduction of proinflammatory cytokines (TNF-α, IL-6, IL-1β) and an insufficient adaptive immune response. While CD4+ T cells remain critical for immune control, tuberculosis disease is associated with functional exhaustion of T cells, marked by decreased IFN-γ production and upregulation of inhibitory molecules such as PD-1[26].

The excessive inflammatory response can lead to lung tissue destruction, cavitation, and increased transmission potential. Additionally, macrophage apoptosis and necrosis further contribute to bacterial dissemination and immune evasion[26].

1.3.2.3 Systemic Tuberculosis Disease

Beyond the lungs, disseminated tuberculosis can affect various organs, including the lymph nodes, central nervous system, and gastrointestinal tract[34]. Extrapulmonary

tuberculosis is often associated with a weaker localized immune response, allowing *M. tuberculosis* to evade immune surveillance and establish infections in distant tissues[35,36].

1.3.3 Tuberculosis Spectrum

The categories that define the tuberculosis spectrum can be understood by looking at the regulation of *M. tuberculosis* metabolic activity and the host's innate and acquired immunity to tuberculosis. The classical latent and active tuberculosis stages have been reclassified with the addition of three groups: incipient, minimal, subclinical tuberculosis and clinical tuberculosis, that overall characterize what is known as the tuberculosis spectrum (Table 1.2).

In **latent tuberculosis infection**, tuberculosis disease is not expected to progress with the assumption of no signs of a compromised immune system[37]. Individuals in this category can generate an immune response to control the infection and remain clinically asymptomatic.

In **incipient tuberculosis**, the pathogen is alive but not culturable (meaning it is viable) with alternating periods of dormant metabolic activity and replication[37,38]. While tuberculin skin test (TST) and Interferon Gamma Release Assays (IGRAs) remain positive in individuals with incipient stage, the person is likely to be non-infectious. Incipient tuberculosis has been defined by others as an "asymptomatic, early pre-clinical disease during which pathology evolves, such as mycobacterial replication or the inflammatory response. Radiological abnormalities or positive microbiological tests may or may not be present. This state may either evolve and lead to symptomatic clinical tuberculosis or regress and remain asymptomatic"[39]. The pathogenesis of incipient and subclinical tuberculosis involves a complex interplay between genetic and phenotypic variations of the bacteria and host-pathogen interactions[37].

In **Subclinical tuberculosis**, the *M. tuberculosis* pathogen is viable however it does not cause the traditional symptoms that would be found in clinical tuberculosis disease[37]. Abnormalities can be found using existing radiological or microbiological assays[38]. This stage emphasizes the evolution from tuberculosis infection to tuberculosis disease. At this

stage, people may be potentially infectious with no symptoms or have unrecognizable ones.

Clinical tuberculosis or its previous name **active tuberculosis** is the traditional tuberculosis disease, where the *M. tuberculosis* pathogen is viable and cause the clinical symptoms such as the four traditional screen symptoms by WHO like fever, coughing, night sweats and weight loss. The *M. tuberculosis* pathogen infects the lung macrophage. The immune system attempts to clear out these pathogens and accumulates in the lung forming the debris called granulomas. This accumulation of granuloma in the lungs can be detected through chest X-rays by a healthcare provider.

1.3.4 Tuberculosis Disease in People Living with HIV Immunology

The immune response to tuberculosis in people living with HIV is significantly altered due to CD4+ T cell depletion and immune dysfunction[40,41]. HIV significantly increases the risk of tuberculosis progression, with co-infected individuals experiencing higher bacterial loads, reduced granuloma formation, and increased mortality compared to HIV-negative individuals[40,42].

1.3.4.1 Impact of HIV on Innate Immunity in Tuberculosis

HIV infection impairs macrophage function by reducing phagocytosis and cytokine production[40,43]. Macrophages from HIV-positive individuals exhibit decreased responsiveness to IFN-γ stimulation, limiting their ability to kill intracellular *M. tuberculosis*[40]. Neutrophil dysfunction further compromises early immune responses, leading to ineffective bacterial containment[44]. Dendritic cells in HIV-positive individuals show reduced antigen-presenting capacity, impairing their ability to activate naïve T cells[45]. This results in a weaker initial adaptive immune response and delayed tuberculosis control [40,41,45,46].

Table 1.2. Summary of the differences in tuberculosis spectrum

	LATENT	INCIPIENT	SUBCLINICAL	CLINICAL
BACILLI ACTIVITY	Dormant	Slow/intermittent replication	Replication	Active replication
INFECTIOUS	-	-	+/-	+
SYMPTOMS	-	-	+/-	+
DIAGNOSIS[A]:	Assuming no additional comorbidities or immunosuppressed status**			
TST	+	?	+	+
IGRA	+	+	+	+
CULTURE	-	-	+	+
SPUTUM SMEAR	-	-	-	+
XPERT MTB/RIF	+	+	+	+
XRAY	-	-	+	+
TREATMENTS[B]	Tuberculosis preventive treatment: INH and RMP (4 months) Alternative regiments: HP and INH (3 months) RMP (4 months) INH (9 or 6 months)		Approved multidrug therapy for susceptible tuberculosis disease **Initial phase**: INH RMP PZA EMB (2 months) **Continuation phase:** INH RMP EMB (4 months)	

[A] Listed diagnostics and (+/-) were all under the assumption of no additional comorbidities or immunosuppressed status.

Note: while it is possible test positive using a specific diagnostic test, there are no current tools that can differentiate each state in the spectrum.

[B] Abbreviations: INH (isoniazid), RMP (rifampin), PZA (pyrazinamide), EMB (ethambutol), HP (rifapentine)

1.3.4.2 Disrupted Granuloma Formation and Maintenance

Granuloma formation in HIV-associated tuberculosis is compromised due to the depletion of CD4+ T cells, which are essential for macrophage activation and cytokine signaling[40,47,48]. Studies have shown that granulomas in HIV-positive individuals are poorly organized and contain higher bacterial loads, leading to increased disease severity[42,49]. HIV-associated tuberculosis is often characterized by disseminated disease rather than localized pulmonary infection[50–52]. This is attributed to the inability to form well-structured granulomas, leading to early bacterial escape into the bloodstream and other organs[48].

1.3.4.3 Adaptive Immune Dysfunction in HIV-Associated Tuberculosis

CD4+ T cell depletion in HIV leads to impaired IFN-γ production, which weakens macrophage activation and bacterial killing. Additionally, the proportion of exhausted T cells expressing PD-1 and TIM-3 is significantly higher in co-infected individuals, reducing their ability to mount an effective immune response[53,54].

B cell responses are also altered in HIV-positive individuals, leading to reduced antibody-mediated immunity against tuberculosis[55–57]. Dysregulated humoral responses contribute to impaired bacterial clearance and increased susceptibility to reinfection[58].

1.3.4.4 Increased Mortality and Poorer Clinical Outcomes

Due to immune system suppression, tuberculosis in HIV-positive individuals presents with atypical clinical manifestations, including extrapulmonary disease, miliary tuberculosis, and rapid progression to disseminated disease[59,60]. HIV-associated tuberculosis has higher case fatality rates and poorer treatment outcomes, emphasizing the urgent need for early detection and integrated tuberculosis-HIV treatment strategies[8].

1.4 Diagnostics

1.4.1 Screening and Diagnosis of Tuberculosis Infection

Detecting tuberculosis infection is important for identifying individuals at risk of developing tuberculosis disease. Two primary immunological tests are used for this purpose: the tuberculin skin test (TST) and interferon-gamma release assays (IGRAs)[61]. These tests measure the host's immune response to *M. tuberculosis* antigens and are designed to identify latent tuberculosis infection, rather than tuberculosis disease[61].

The TST involves injecting purified protein derivative into the skin and measuring induration after 48–72 hours[5,62]. A study showed that TST sensitivity to detect tuberculosis infection with a ≥10 mm threshold for HIV-negative individuals is 77%[63]. While this test has a good sensitivity towards detecting tuberculosis, it has several limitations, including it does not differentiate between infection and disease, varied and false positive results in the context of Bacillus Calmette-Guérin (BCG) vaccination and significantly lowered sensitivity for PLHIV with 60%[5,61,63,64].

IGRAs, such as QuantiFERON-TB and T-SPOT.TB, offer higher specificity with approximately 78% and 90%, respectively, compared to TSTs, and do not cross-react with BCG vaccination status[61,63]. However, like the tuberculin skin test, their sensitivity is lower in people living with HIV, with 69% and 89% for QuantiFERON-TB and T-SPOT.TB, respectively[61,65]. This is partly due to those individuals with CD4 counts below 200 cells/μL, leading to a higher rate of false-negative results[61,64].

Multiple studies determined that TSTs and IGRAs are inadequate for confirming or ruling out tuberculosis disease in PLHIV[61,63–65].

1.4.2 Screening and Diagnosis of Tuberculosis Disease

The diagnosis of tuberculosis disease requires microbiological, molecular, and radiological imaging-based methods (Table 1.3). Sputum smear microscopy, a commonly used diagnostic tool in resource-limited settings, has low sensitivity (40–60%), which decreases to 20–50% in people living with HIV due to paucibacillary tuberculosis[66,67].

However, molecular tests such as Xpert MTB/RIF and Xpert Ultra are the preferred initial diagnostic tests[68,69]. These tests detect *M. tuberculosis* DNA and rifampin resistance, offering higher sensitivity (60–88%) than smear microscopy. Xpert Ultra is more sensitive in people living with HIV (75%), making it an essential tool for diagnosing tuberculosis in immunocompromised populations.

For cases where sputum-based testing is not feasible, alternative tests such as urine lipoarabinomannan assays (Alere LAM and Fujifilm SILVAMP TB LAM) can be used[70,71]. These tests are particularly beneficial for people living with HIV, especially those with advanced immunosuppression (CD4 ≤ 200 cells/μL), where urine-based detection achieves a sensitivity of up to 42 - 70%[70]. However, these assays are less effective in individuals with higher CD4 counts (CD4 ≥ 200 cells/μL) with sensitivities significantly decreasing to 11-66% depending on the LAM assay and thus cannot replace molecular tests for definitive tuberculosis diagnosis[72–75].

Culture-based methods, including the Löwenstein-Jensen medium and the BACTEC MGIT 960 system, remains the gold standard for tuberculosis diagnosis, with high sensitivity (80–87%) and specificity (99 - 100%)[76,77]. However, culture requires 1-2 weeks (MGIT 960) to 6 weeks (Löwenstein-Jensen) for bacterial growth, delaying treatment initiation[78–80]. Chest radiography is frequently used as a supplementary diagnostic tool, with a sensitivity of up to 85% - 97% in immunocompetent individuals[81–83]. However, in people living with HIV, pulmonary tuberculosis often presents with atypical radiographic features, reducing its sensitivity to approximately 72%[84].

1.4.3 Challenges in Diagnosing Tuberculosis in People Living with HIV

The World Health Organization (WHO) recommends systematic tuberculosis screening for all people living with HIV (PLHIV) at every healthcare visit. The WHO four-symptom screen (W4SS), which assesses fever, cough, night sweats, and weight loss, is widely used in HIV care settings due to its accessibility and high sensitivity (82 – 90 %)[84,85]. However, its low specificity (30 – 40 %) results in a high rate of false-positive cases, limiting its use as a definitive diagnostic tool[84,85]. Despite routine symptom-based screening,

studies suggest that up to 77% of individuals diagnosed with tuberculosis do not report any symptoms, leading to underdiagnosis and untreated cases that contribute to increased tuberculosis-related mortality in this population[86].

Diagnosing tuberculosis in PLHIV remains challenging due to immune suppression, atypical clinical presentations, and reduced bacterial loads, all of which lower test sensitivity. The paucibacillary nature of tuberculosis in immunocompromised individuals reduces the accuracy of microbiological tests such as sputum smear microscopy and molecular assays. In PLHIV, sputum smear microscopy has a sensitivity of approximately 55%, while lateral flow urine lipoarabinomannan (LF-LAM) assays have even lower sensitivity at 42%[87,88]. Moreover, widely available diagnostic tools such as smear microscopy and chest radiography perform poorly in this population, as many PLHIV with tuberculosis present with either sputum acid-fast bacilli (AFB) smear-negative pulmonary tuberculosis or extrapulmonary tuberculosis[66,78].

Given these diagnostic limitations, the WHO's post-2015 End TB Strategy aims to eliminate the tuberculosis epidemic, targeting an 80% reduction in new cases and a 90% decrease in tuberculosis-related deaths by 2030[8]. There is an urgent need to develop new diagnostic tools for tuberculosis in PLHIV, who are at higher risk of progression to active disease. Several tuberculosis diagnostic methods are currently available, each with distinct advantages and limitations (Table 1.3.). Sputum smear microscopy, one of the oldest diagnostic tools, detects AFB under a microscope but has low sensitivity, particularly in individuals with HIV co-infection or extrapulmonary tuberculosis[78]. Nucleic acid amplification tests (NAATs), such as the Xpert MTB/RIF assay and Xpert Ultra (Table 1.3), offer rapid and accurate tuberculosis detection while also identifying rifampicin resistance, making them valuable in high-burden settings[89,90]. However, their use as first-line diagnostic tools are limited in many settings due to their higher cost, and infrastructure demands (e.g., temperature-controlled environments) [91–93]. Moreover, NAATs require sputum to which is a diagnostic challenge for individuals unable to produce sputum, specially for those[94,95].

Although culture-based methods remain the gold standard due to their high sensitivity, they require several weeks to grow *Mycobacterium tuberculosis* from clinical samples, limiting their utility in urgent cases and resource-constrained settings[8,67,78].

Immunological tests such as the tuberculin skin test (TST) and interferon-gamma release assays (IGRAs) detect immune responses to *M. tuberculosis* but cannot differentiate between latent infection and active disease, reducing their diagnostic utility for tuberculosis disease[78,96]. Imaging techniques, including chest X-rays and computed tomography (CT) scans, can reveal lung abnormalities suggestive of tuberculosis but lack disease specificity and often require additional laboratory confirmation[78,85]. Given that no single test is definitive, a combination of approaches—symptom-based screening, molecular tests, urine-based assays, and imaging—is often necessary to improve diagnostic accuracy and guide treatment decisions[85].

Ongoing research efforts aim to develop faster, more sensitive, and accessible diagnostic tools, such as point-of-care tests, to enhance tuberculosis detection in PLHIV and drug-resistant tuberculosis cases. These advancements are critical for achieving global tuberculosis elimination targets and reducing the burden of tuberculosis in high-risk populations[8,68].

Table 1.3. Current diagnostic methods approved by the World Health Organization for *Mycobacterium tuberculosis*

Test	Type	Sample Type	Sensitivity (%)	Specificity (%)	Sensitivity in PLHIV (%)	Specificity in PLHIV (%)
IMMUNOLOGICAL						
Tuberculin Skin Test (TST)	Screening (Infection)	Blood (Immune Response)	77%	97%	60%	~
Interferon-Gamma Release Assay (IGRA)						
QFT	Screening (Infection)	Blood (Immune Response)	78%	98%	69%	76%
T-SPOT.TB			90%	93%	89%	87%
Urine LAM (Alere LAM)						
Alere LAM	Diagnostic	Urine	11%	92%	42%	95%
> 200 CD4 cells/μL			~	~	12%	97%
Fuji LAM			53% - 66%	99%	70%	91%
> 200 CD4 cells/μL			~	~	44%	97%
CLINICAL						
WHO 4-Symptom Screening	Screening (Disease)	Clinical Symptoms	79%	50%	85–90%	27%
RADIOLOGICAL						
Chest X-ray	Screening (Disease)	Imaging	85% - 97%	75%	72%	62%
MICROBIOLOGICAL						
Smear Microscopy	Diagnostic	Sputum	40–60%	98%	20–50%	98%
Culture (Solid/Liquid Media)						
BACTEC MGIT 960	Diagnostic	Sputum	82% - 87%	99%	~	~
Löwenstein-Jensen			80%	100%	~	~
MOLECULAR						
Xpert MTB/RIF	Diagnostic	Sputum	85%	98%	75%	99%
Xpert Ultra			91%	96%	88%	93%

1.5 Biomarkers of Tuberculosis

A potential way to develop and improve detection of tuberculosis is through transcriptomic and proteomic studies for blood-biomarker diagnostic. Biomarkers are measurables substances in the body that can be used to detect disease or monitor disease progression, and it can be measured at a transcriptional level or proteomic level[97,98]. Biomarkers can be derived and can be analyzed from a wide range of sources including the blood, tissues and bodily fluids like urine and sputum. The identification and validation of reliable biomarkers are crucial for early diagnosis, monitoring diseases progression, and evaluating therapeutic responses. With my master's project, the focus will be on studying host blood transcriptomics for persons diagnosed with tuberculosis in the context of HIV infection.

Transcriptomics involves studying the complete set of RNA transcripts or genes, expressed by the genome under certain conditions such as diseases in individuals. By analyzing the gene expression profiles, researchers can identify differentially expressed genes that are either significantly upregulated or downregulated which may serve as biomarkers or signatures for various aspects of tuberculosis.

Gene expression signatures have the ability and potential to distinguish progression stages of tuberculosis within the spectrum[99–102]. Additionally, changes in gene expression can also track the response to therapy including the anti-tuberculosis therapy or anti-retroviral drug therapy[99,101,103,104]. Lastly, biomarkers may help identify eligible candidates for new tuberculosis vaccines and therapeutic trials[105].

1.5.1 Transcriptomic Technologies for Biomarker Discovery

The two main methods for tuberculosis biomarker discovery in host blood are microarray and RNA-Seq methodologies:

1.5.1.1 Microarray Technology

Microarrays have historically been used to identify tuberculosis-associated gene signatures by measuring predefined transcripts through hybridization to complementary probes. An early study using microarrays identified a 393-transcript whole-blood signature

capable of distinguishing active tuberculosis from latent tuberculosis infection[106]. However, microarray technology has inherent limitations, including dependence on probes, lower sensitivity to low-expressed genes, and reduced ability to detect novel transcripts[107,108].

1.5.1.2 RNA-Seq: A Next-Generation Approach

RNA-seq has revolutionized transcriptomic analysis by providing an unbiased and high-resolution view of gene expression. Unlike microarrays, RNA-seq does not require prior knowledge of gene sequences, allowing for the detection of novel transcripts, splice variants, and low-abundance genes[109,110]. RNA-seq studies have revealed key immune pathways in tuberculosis pathogenesis, including interferon signaling and inflammatory responses, particularly in tuberculosis-HIV co-infection[111,112]. The rise of RNA sequencing analysis has enabled comprehensive profiling of the transcriptome, which can overcome any biases and limitations associated with microarray analysis (Table 1.4) [110,113,114]. A combination of biomarkers findings to generate a signature have the potential to improve diagnostic accuracy.

Table 1.4. Summary of Comparison of Microarray and RNA-seq for Differential Gene Expression Analysis

Feature	Microarray	RNA-seq
Transcript Coverage	Limited to known genes	Detects novel transcripts and isoforms
Sensitivity	Lower, especially for low-abundance genes	Higher, detects rare transcripts (identifies 50–60% more differentially expressed genes)
Dynamic Range	Narrow	Broad (captures weak and strong signals)
Cost	Lower for large sample sizes	Higher per sample but decreasing over time
Suitability for Tuberculosis Biomarker Discovery	Useful for predefined gene panels	More comprehensive and better suited for complex disease profiling

Overall, RNA-Seq enables a more comprehensive analysis of host transcriptional responses and is well-suited for tuberculosis biomarker discovery. Its ability to detect subtle yet significant gene expression changes provide critical insights into host-pathogen dynamics and disease progression[100,113].

1.5.2 Blood Sample Types for Tuberculosis Transcriptome Studies

Whole-blood and peripheral blood mononuclear cell (PBMC) samples are commonly used in transcriptomic studies for tuberculosis biomarker discovery, each offering distinct advantages:

Whole-blood samples capture systemic immune responses, including granulocytes and platelets, which are excluded in PBMC isolations. This allows for a broader representation of immune activation, particularly in tuberculosis-HIV co-infection, where systemic inflammation and immune exhaustion play a key role in disease progression. Whole-blood transcriptomic signatures, such as the Sweeney-3 signature, have demonstrated high sensitivity in tuberculosis screening[115,116]. This signature forms the basis of the Xpert HR test, that measures the expression of GBP5, DUSP3, and KLF2 genes to tuberculosis disease[115,116]. While a study showed that Xpert HR met the WHO sensitivity (90%) for a non-sputum-based triage test, it did not reach the minimum specificity target (70%), achieving around 62.6%[117]. Despite this, its high sensitivity and negative predictive value make it a promising rule-out test to reduce the need for confirmatory sputum testing, though further evaluation of cost-effectiveness, usability, and acceptability is needed before making any policy changes[117].

PBMC samples contain lymphocytes and monocytes, which are central to tuberculosis-specific adaptive immunity, particularly CD4+ T cell responses that are compromised in individuals with HIV[40,118,119]. PBMC-focused studies enable the identification of cell-type-specific dysregulation, such as activities in the IL-6/TNF pathway, which can provide mechanistic insights into tuberculosis pathogenesis[120–122].

1.6 Research Gaps

1) Reproducibility and Methodological Differences in Tuberculosis Biomarker Studies: RNA biomarkers have emerged as promising tools to detect tuberculosis, offering potential diagnostic applications. Gene expression studies using microarray and RNA-Seq have led to the identification of potential biomarkers for detecting and monitoring tuberculosis progression[100,115,116,123]. However, there are still gaps in understanding the reproducibility, methodology and applicability of tuberculosis biomarkers[123,124].

2) Research in Gene Expression Profiles in PLHIV: There is a pressing need for research focused on elucidating the gene expression profiles of tuberculosis in PLHIV. Understanding the genetic patterns and molecular signatures in this specific population can provide valuable insights into the disease's progression and manifestation. Numerous studies have explored potential biomarkers for tuberculosis, but these findings require further validation and evaluation to establish their reliability and clinical utility[112,125–129].

3) Integrating Molecular Networks and Pathways: While biomarker studies have made significant contributions, there is a need for research that integrates and deciphers the molecular networks and pathways involved in tuberculosis pathogenesis, particularly in the context of HIV co-infection. By investigating these intricate molecular mechanisms, we can gain a deeper understanding of the disease's progression and develop more targeted interventions.

1.7 Rationale

The aims of this Master's thesis were to **1) Conduct a scoping review to evaluate tuberculosis gene biomarker studies, assessing methodologies, tissue samples and population diversity:** The objective is to identify and summarize transcriptomic studies on host tuberculosis biomarkers. Evaluating these studies can further highlight our understanding the trends and our current understanding of tuberculosis transcriptome studies as well as assessing its reproducibility and applicability. **2) Investigating DEGs in Tuberculosis in PLHIV and Pathway Analysis:** The second objective is to explore the gene expression profile of tuberculosis in PLHIV and assess the biological pathways and

immune responses associated with the coinfection. The goal is to identify key biomarkers in tuberculosis in PLHIV.

With these two approaches, this study aims to provides a comprehensive understanding of tuberculosis biomarkers and their potential applicability for improving tuberculosis diagnostics, particularly in PLHIV. Additionally, addressing these research gaps is crucial for advancing our understanding of the interplay between tuberculosis and HIV. By identifying specific biomarkers and elucidating the underlying molecular mechanisms, this thesis project has the potential to contribute significantly to improving the health outcomes of tuberculosis in PLHIV.

1.8 Objectives and Hypotheses

The main objective of this thesis is to identify unique host gene biomarkers and understand the molecular mechanisms and signaling pathways of tuberculosis in PLHIV coinfections. The main hypothesis is:

A distinct set of genes is involved in the progression of tuberculosis within the context of HIV infection, including previously identified genes like GBP5 and BATF2. From an immunological perspective, tuberculosis and HIV infections are characterized by complex interactions that alter interferon signaling, antigen presentation, and metabolic pathways. While certain pathways may remain consistent with tuberculosis-only disease, coinfection is expected to amplify or suppress specific immune modules, particularly interferon-driven and proinflammatory responses, thereby producing patterns that are unique to tuberculosis in PLHIV.

To address this hypothesis, there will be aims:

1. **Review and evaluate tuberculosis gene biomarker studies, assessing methodologies, tissue samples and population diversity.**

Specific hypothesis: Common tuberculosis associated biomarkers can be detected across independent datasets despite differences in experimental platforms (RNA-Seq and Microarray) and study populations.

2. **To identify the gene expression profile of tuberculosis in PLHIV.**

Specific hypothesis: A gene signature is associated with tuberculosis progression in the context of HIV co-infection.

3. **To analyze gene functions and pathways associated with tuberculosis in PLHIV transcriptome profile.**

Specific hypothesis: Tuberculosis and HIV co-infection alters immune pathways compared with tuberculosis disease alone, revealing both preserved and unique pathways.

CHAPTER II: SCOPING REVIEW – HOST BLOOD RNA TUBERCULOSIS BIOMARKERS BASED ON RNA-SEQUENCING & MICROARRAY METHODOLOGY

2.1 Introduction

In this scoping review, we analyzed RNA transcriptomic studies that focuses on tuberculosis biomarker discovery. By evaluating the existing literature on host blood RNA biomarkers identified based on study populations, methodologies and tissue samples, we aimed to elucidate the similarities and differences across studies and identify frequently reported gene signatures. In addition, this study aims to provide a comprehensive overview of the field, identify knowledge gaps, and highlight areas for future research in the application of RNA-based biomarkers for tuberculosis diagnosis.

2.2 Methods

2.2.1 Search Strategy

This protocol was written using the Preferred Reporting Items for Scoping Reviews (PRISMA-ScR)[130]. Articles were searched on PubMed (MEDLINE) database, Scopus and Cochrane, using a combination of keywords reported in the Table 2.1. on July 2024.

2.2.2 Definitions and Eligibility Criteria

The definitions and eligibility criteria are summarized in Table 2.2. We included original research studies, including observational studies and clinical trials, as well as review articles and meta-analyses that provide relevant information on synthesis of tuberculosis host blood gene biomarker identification with validation, or application, published or translated to English, between 2000s to 2024. Exclusion criteria included animal studies, non-human research, case reports, editorials, and studies lacking primary data on host blood biomarkers for tuberculosis.

Table 2.1. Search Strategy

Topic	Search Terms	Engine
Latent Tuberculosis	((latent tuberculosis[Title/Abstract]) OR (Latent TB[Title/Abstract])) AND ((Gene expression profile[Title/Abstract]) OR (transcriptome profile[Title/Abstract]) OR (gene signature[Title/Abstract]) OR (signature[Title/Abstract]) OR (signatures[Title/Abstract]) OR (TB signatures[Title/Abstract]))	PubMed
	(TITLE-ABS("latent tuberculosis") OR TITLE-ABS("latent TB")) AND (TITLE-ABS("gene expression profile") OR TITLE-ABS("transcriptome profile") OR TITLE-ABS("gene signature") OR TITLE-ABS("signature") OR TITLE-ABS("signatures") OR TITLE-ABS("TB signatures"))	Scopus
	("latent tuberculosis" OR "latent TB") AND ("gene expression profile" OR "transcriptome profile" OR "gene signature" OR "signature" OR "signatures" OR "TB signatures")	Cochrane
Incipient Tuberculosis	((Incipient Tuberculosis[Title/Abstract]) OR (Incipient TB[Title/Abstract])) AND ((Gene expression profile[Title/Abstract]) OR (transcriptome profile[Title/Abstract]) OR (gene signature[Title/Abstract]) OR (signature[Title/Abstract]) OR (signatures[Title/Abstract]) OR (TB signatures[Title/Abstract]))	PubMed
	(TITLE-ABS("incipient tuberculosis") OR TITLE-ABS("incipient TB")) AND (TITLE-ABS("gene expression profile") OR TITLE-ABS("transcriptome profile") OR TITLE-ABS("gene signature") OR TITLE-ABS("signature") OR TITLE-ABS("signatures") OR TITLE-ABS("TB signatures"))	Scopus
	("incipient tuberculosis" OR "incipient TB") AND ("gene expression profile" OR "transcriptome profile" OR "gene signature" OR "signature" OR "signatures" OR "TB signatures")	Cochrane
Subclinical Tuberculosis	((Subclinical Tuberculosis[Title/Abstract]) OR (Subclinical TB[Title/Abstract])) AND ((Gene expression profile[Title/Abstract]) OR (transcriptome profile[Title/Abstract]) OR (gene signature[Title/Abstract]) OR (signature[Title/Abstract]) OR (signatures[Title/Abstract]) OR (TB signatures[Title/Abstract]))	PubMed
	(TITLE-ABS("subclinical tuberculosis") OR TITLE-ABS("subclinical TB")) AND (TITLE-ABS("gene expression profile") OR TITLE-ABS("transcriptome profile") OR TITLE-ABS("gene signature") OR TITLE-ABS("signature") OR TITLE-ABS("signatures") OR TITLE-ABS("TB signatures"))	Scopus

	("subclinical tuberculosis" OR "subclinical TB") AND ("gene expression profile" OR "transcriptome profile" OR "gene signature" OR "signature" OR "signatures" OR "TB signatures")	Cochrane
Clinical Tuberculosis	((Active tuberculosis[Title/Abstract]) OR (Active TB[Title/Abstract])) AND ((Gene expression profile[Title/Abstract]) OR (transcriptome profile[Title/Abstract]) OR (gene signature[Title/Abstract]) OR (signature[Title/Abstract]) OR (signatures[Title/Abstract]) OR (TB signatures[Title/Abstract]))	PubMed
	(TITLE-ABS("active tuberculosis") OR TITLE-ABS("active TB")) AND (TITLE-ABS("gene expression profile") OR TITLE-ABS("transcriptome profile") OR TITLE-ABS("gene signature") OR TITLE-ABS("signature") OR TITLE-ABS("signatures") OR TITLE-ABS("TB signatures"))	Scopus
	("active tuberculosis" OR "active TB") AND ("gene expression profile" OR "transcriptome profile" OR "gene signature" OR "signature" OR "signatures" OR "TB signatures")	Cochrane

Table 2.2. Search Criteria

Concept	Inclusion Criteria	Exclusion Criteria
Study Design	• Primary papers: observational studies, clinical trials, and cross-section studies • Secondary papers: systematic reviews, meta-analyses focusing on synthesis of host-blood gene biomarkers, providing validation and application • Studies including RNA-sequencing and microarray methodologies	• Animal studies (e.g., macaques) and in vitro experiments • Case reports, editorials, commentaries, letters, scoping reviews and opinion pieces. • Studies lacking primary data on host blood biomarkers for tuberculosis. • Studies reporting sequencing methodologies other than RNA-sequencing and microarray
Population	• Studies involving human participants of all age groups and genders. • Participants diagnosed of tuberculosis within the spectrum (latent, incipient, subclinical, clinical, or active tuberculosis) • Studies conducted in countries in both high tuberculosis burden and low tuberculosis burden settings	• Studies exclusively involving animal models of tuberculosis
Intervention / Exposures	• Studies investigating host blood biomarkers for tuberculosis diagnosis, prognosis, treatment response, or monitoring of disease progression. • Studies assessing whole blood or PBMC specimens. • Studies evaluating the performance of host-blood gene biomarkers.	• Studies evaluating biomarkers for conditions other than tuberculosis or diseases unrelated to tuberculosis infection. • Studies assessing biomarkers derived from specimens other than blood (e.g., sputum, urine, bronchoalveolar lavage sample, cerebrospinal fluid). • Studies assessing subpopulations of PBMC specimens (T cells etc.)
Outcomes	• Studies reporting on the identification, validation, or clinical utility of host blood biomarkers for tuberculosis. • Studies evaluating the association between blood biomarkers and tuberculosis disease severity, treatment outcomes, or other clinical endpoints.	• Studies which do not clearly report or identify host-blood biomarkers from gene expression profiles. • Studies that report protein biomarkers, cytokines, chemokines, metabolites, and immune cell subsets.
Publication Characteristics	• Studies written in English or translated to English. • Studies published from year 2000 - 2024	• Studies that cannot be translated to English or have subpar translation. • Studies published before year 2000. • Published full-text access is not available.

Participants of all age groups, sex at birth and genders that adheres to the tuberculosis diagnostic criteria across the spectrum: latent, incipient, subclinical, and clinical tuberculosis were included. We did not find any manuscript studying biomarkers to detect minimal tuberculosis. We also included studies conducted in both high and low tuberculosis burden settings to capture a wide range of contexts and ethnic groups that may affect gene expression. Studies exclusively involving animal models of tuberculosis were excluded.

The review included studies that provided host gene expression in response to tuberculosis for the purpose of diagnosis, treatment response, and disease progression monitoring focusing on the RNA biomarker discovery of tuberculosis. Eligible studies assessed biomarkers using whole blood or peripheral blood mononuclear cells (PBMC) specimens and evaluated the performance of these biomarkers. Studies assessing biomarkers derived from non-blood specimens, such as sputum, urine, or cerebrospinal fluid, or subpopulations of PBMC specimens (e.g., T cells) were excluded. Additionally, studies evaluating biomarkers for diseases unrelated to tuberculosis were not considered.

The outcomes of interest were studies reporting the identification, validation, or clinical utility of host blood biomarkers for tuberculosis. The review also included studies evaluating associations between biomarkers and tuberculosis severity, treatment outcomes, or other clinical endpoints, as well as those evaluating their diagnostic accuracy, predictive value, sensitivity, specificity, or other performance metrics. Studies that did not clearly report host blood biomarkers from gene expression profiles or focused solely on protein biomarkers, cytokines, chemokines, metabolites, or immune cell subsets were excluded.

2.2.3 Data Management and Extraction

All search terms for each database were uploaded to Covidence web-based platform[131]. The articles identified were subjected to title and abstract screening. Lastly, all eligible records underwent full-text review and data extraction. Details on data visualization can be found on Appendix 1.

2.3 Results

2.3.1 Overview

A total of 510 records were identified from three databases: PubMed (157), Cochrane (9), and Scopus (344). After the removal of 252 duplicates, 258 unique studies remained for screening of title and abstract. Following the title and abstract screening, 69 studies were excluded. The remaining 189 studies underwent full-text assessment for eligibility, leading to the exclusion of 146 studies due to various reasons, including study designs (83 studies), outcomes (47 studies), interventions (11 studies), and patient populations (5 studies). Ultimately, 43 full-text articles were included in the final analysis (Figure 2.1).

2.3.2 Characteristics of the transcriptome studies

The 43 included studies covered a diverse range of study populations, with participants from both endemic and non-endemic tuberculosis regions. The list of countries involved in the studies includes a diverse geographic and sociodemographic range from across the globe (Figure 2.2). There were 21 distinct countries mentioned including the United Kingdom (UK), South Africa, China, Indonesia, Malawi, Venezuela, Kenya, Thailand, Taiwan, the United States of America (USA), The Gambia, Germany, India, Spain, Mozambique, Vietnam, Singapore, Uganda, Brazil, France, and Ethiopia. The most frequent study cohorts were from United Kingdom, South Africa and Malawi, with frequencies of 27, 19, and 14 studies respectively.

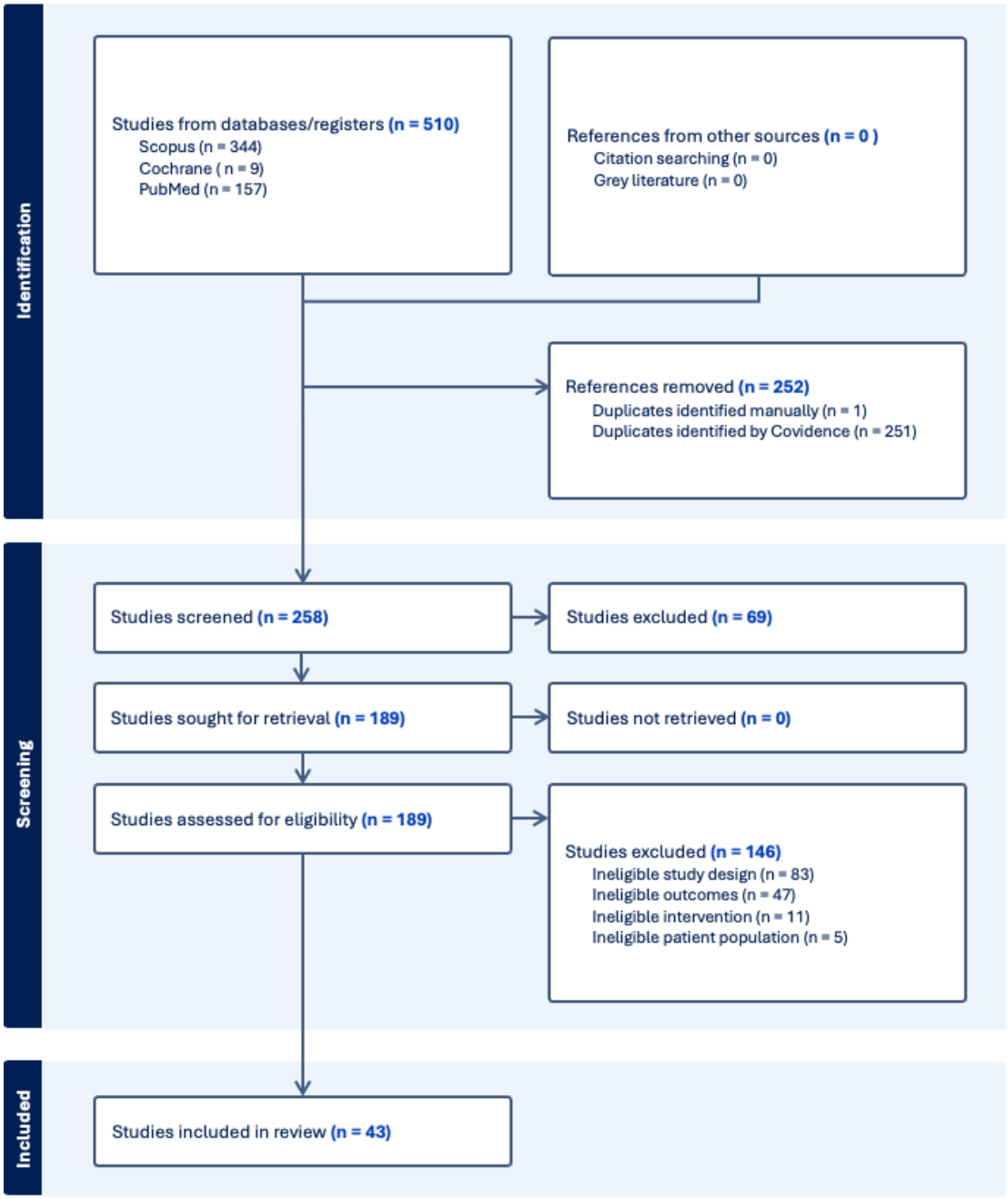


Figure 2.1 PRISMA flowchart depicting the screening process for identified, screened and included papers

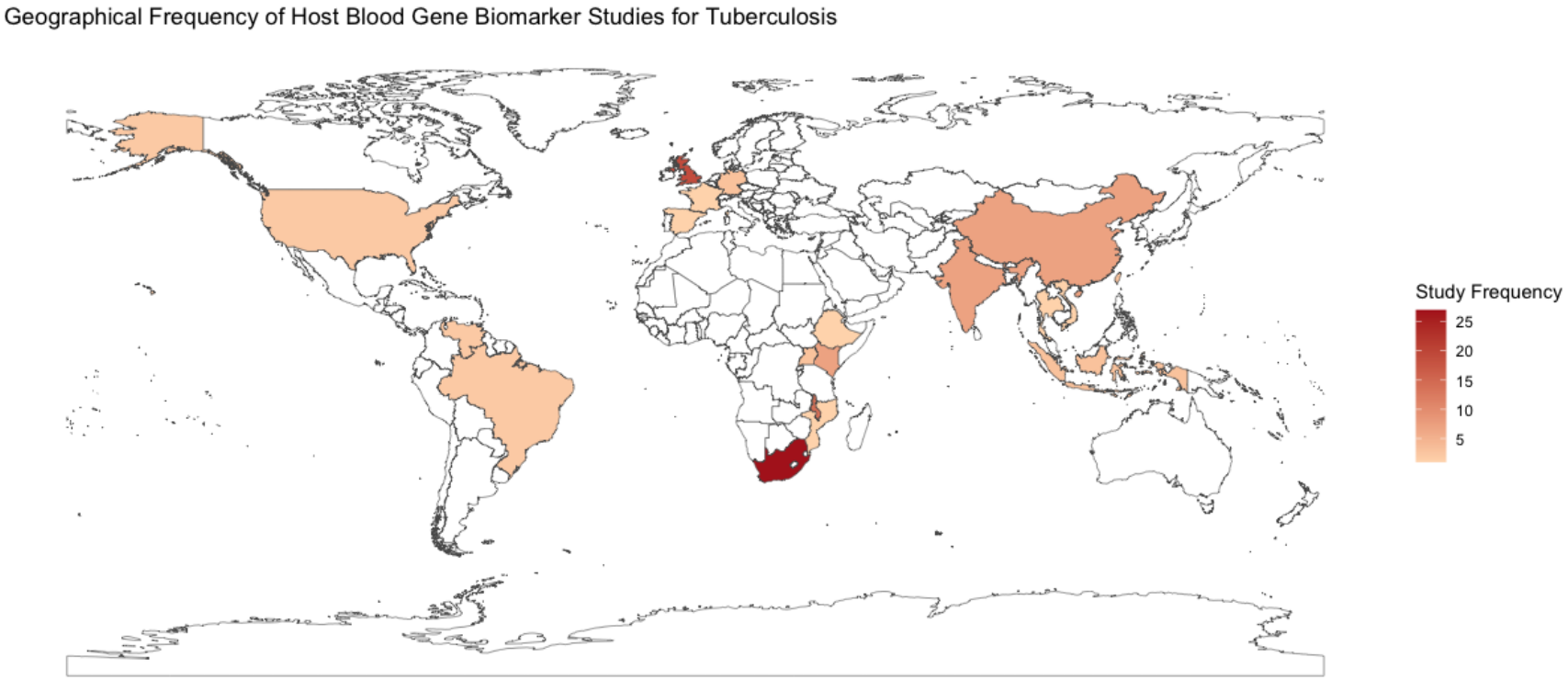


Figure 2.2. World map diagram depicting the number of studies that evaluated tuberculosis gene signatures conducted in each country

Table 2.3. Studies retrieved from the PRISMA search depicting the gene signatures and publication characteristics that aimed to discover tuberculosis gene signatures

Study	Gene Signatures (Comparisons)	Countries (Discovery & Validation)	Age Population	Sample Type	Methodology	Study design	PMID
Berry et al. (2010)	Berry_393 (TB vs LTBI) Berry_86 (TB vs OD)	UK (Test set) and South Africa (Validation set)	Adults	Whole Blood	Microarray	Prospective study	20725040
Lu et al. (2011)	Lu_3 (TB vs LTBI)	China	Adults	PBMC	Microarray	Cohort study	21904626
Maertzdorf et al. (2011)	Maertzdorf_4 (TB vs LTBI & HC)	South Africa	Adults	Whole Blood	Microarray	Cohort study	20861863
Bloom et al. (2012)	Bloom_664 (TB vs LTBI) Bloom_320 (TB Treatment)	South Africa, UK	Adults	Whole Blood	Microarray	Longitudinal cohort study	23056259
Ottenhoff et al. (2012)	Ottenhoff_3 (TB_treatment)	Indonesia	Adults	PBMC	Microarray	Longitudinal cohort study	23029268
Kaforou et al. 2013	Kaforou_27 (TB vs LTBI) Kaforou_44 (TB vs OD)	South Africa, Malawi	Adults	Whole Blood	Microarray	Case control study	24167453
Verhagen et al. (2013)	Verhagen_10 (TB vs LTBI & HC)	Venezuela (Warao Amerindians)	Children	Whole Blood	Microarray	Cohort study	23375113
Anderson et al. (2014)	Anderson_51 (TB vs OD) Anderson_42 (TB vs LTBI)	South African and Malawian children (discovery cohort). Kenyan children (validation cohort)	Children	Whole Blood	Microarray	Prospective study	24785206
Dawany et al. (2014)	Dawany_251 (HIV-TB vs HIV)	South Africa, UK	Adults	PBMC	Microarray	Pooled published dataset plus new cohort data	24587128
Satproedprai et al. (2015)	Satproedprai_10 (TB vs HC)	South Africa, UK, Thailand (Validation)	Adults	Whole Blood	Microarray	Pooled published dataset plus	25764116

						new cohort data	
Blankley et al. (2016)	Blankley_380 (TB vs HC)	London UK	Adults	Whole Blood	Microarray	Retrospective study	27706152
Lee et al. (2016)	Lee_4 (TB vs LTBI & HC)	Taiwan	Adults	PBMC	Microarray	Cross sectional study	26818387
Roe et al. (2016)	Roe_4 (TB vs OD) BATF2 (TB from Healthy)	United Kingdom	Adults	Peripheral Blood	Microarray	Pooled published datasets	27734027
Walter et al. 2016	Walter_47 (TB vs Pneumonia) Walter_51 (TB vs LTBI) Walter_119 (TB vs LTBI vs Pneumonia)	U.S.A	Adults	Whole Blood	Microarray	Prospective study	26582831
Zak et al. (2016)	Zak_16 (TB Progression)	South Africa and The Gambia	Adolescents	Whole Blood	RNA Sequencing	Prospective study	27017310
Sambarey et al. (2017)	Sambarey_10 (TB vs LTBI & HC)	India Cohort (UK, South Africa, Gambia, Germany and London for computational validation)	Adults	Whole Blood	Microarray & RNA Sequencing	Pooled published datasets	28065665
Thompson et al. (2017)	Thompson_9 (TB Progression) Thompson_FAIL_13 (TB Treatment Failure) Thmopson_RES_5 (TB Treatment Response)	South Africa	Adults	Whole Blood	RNA Sequencing	Cohort study	29050771
Qian et al. (2018)	Qian_7 (TB vs HC)	China	Adults	PBMC	Microarray & RNA Sequencing	Cohort study	29248507
Singhania et al. (2018)	Singhania_20 (TB vs LTBI vs OD)	London, Leicester, South Africa	Adults	Whole Blood	Microarray & RNA Sequencing	Cohort study	29921861

Verma et al. (2018)	Verma_2 (HIV-TB vs HIV) FcGR1A and BATF2	Uganda	Adults	Whole Blood	RNA Sequencing	Cohort study	29764370
Deng et al. (2019)	Deng_24 (TB vs LTBI)	London, UK and Cape Town, South Africa	Adults	Whole Blood	Microarray	Pooled published datasets	30787624
Duffy et al. (2019)	Duffy_10 (HIV-TB vs TB vs HIV-LTBI vs LTBI vs HIV-OD vs OD)	South Africa, Malawi, UK	Both	Whole Blood	Microarray	Pooled published datasets	31306460
Rajan et al. (2019)	Rajan_5 (HIV-TB vs HIV)	Uganda	Adults	Whole Blood	Microarray	Case control study	30462176
Wang et al. (2019)	Wang_3 (TB vs LTBI & HC)	China	Adults	PBMC	RNA Sequencing	Case control study	31921195
Estevez et al. (2020)	Estevez_259 (TB vs HC) Estevez_133 (TB vs LTBI)	Spain and Mozambique	Adults	Whole Blood	RNA Sequencing	Comparative study	32760401
Ho et al. (2020)	Ho_7 (TB vs HC) Ho_8 (TB vs LTBI)	Vietnam	Adults	Whole Blood	RNA Sequencing	Case control study	32330522
Kwan et al. (2020)	Kwan_186 (HHC vs HC) BATF2 and SCARF1 (associated with ITB)	Singapore	Adults	PBMC	RNA Sequencing	Cross sectional study	32517725
Roe et al. (2020)	Roe_3 (LTBI to Progressors)	South Africa and United Kingdom	Adults	Whole Blood & Peripheral Blood	Microarray & RNA Sequencing	Pooled published dataset plus new cohort data	30919880
Tornheim et al. (2020)	Tornheim_71 (TB vs HHC) Tornheim_25 (TB treatment)	India	Children	Whole Blood	RNA Sequencing	Pooled published dataset plus new cohort data	31796955
Gliddon et al. (2021)	Gliddon_3 (TB vs LTBI) Gliddon_4 (TB vs OD)	South Africa and Malawi	Adults	Whole Blood	Microarray	Case control study	33763081

Kulkarni et al. (2021)	Kulkarni_2 (HIV-TB vs HIV) RAB20 and INSL3	India and Uganda	Adults	Whole Blood	RNA Sequencing	Case control study	33692804
Li et al. (2021)	Li_3 (TB vs LTBI)	China (Test), UK, South Africa, Malawi, Kenya (Validation)	Adults & Children	Whole Blood & PBMC	Microarray	Pooled published datasets	34751089
Shao et al. (2021)	Shao_15 (TB vs LTBI)	South Africa, Malawi, and Kenya	Children	Whole Blood	Microarray	Pooled published datasets	33592820
Tabone et al. (2021)	TaboneITB_30 (ITB vs HC) TaboneSTB_30 (STB vs HC) TaboneTB_30 (TB vs HC) TB_10 (TB Diagnosis) TREAT-TB27 (TB Treatment) EarlyRESP-TB25 (Early Treatment Response)	United Kingdom, South Africa, Gambia, India	Adults	Whole Blood	Microarray & RNA Sequencing	Pooled published dataset plus new cohort data	34491266
Geng et al. (2022)	Geng_3 (TB vs LTBI & HC)	China	Adults	PBMC	RNA Sequencing	Retrospective study	36059536
Natarajan et al. (2022)	Natarajan_7 (TB vs LTBI)	South Africa and Malawi	Adults	Whole Blood	Microarray	Pooled published datasets	35456421
Sivakumaran et al. (2022)	Sivakumaran_11 (STB vs TB & ITB & HC)	South India	Adults	Peripheral Blood	RNA Sequencing	Case control study	36713386
Chen et al. (2023)	Chen_9 (TB vs LTBI)	Kenya, South Africa and Malawi	Children	Whole Blood	Microarray	Pooled published datasets	37163321
Liu et al. (2023)	Liu_3 (TB vs LTBI)	South Africa	Adults & Children	PBMC	Microarray	Pooled published datasets	38029270

Phat et al. (2023)	Phat_10 (TB vs LTBI & HC) and (TB Treatment)	South Africa, India, Brazil, Malawi, United Kingdom, France	Adults	Whole Blood	Microarray & RNA Sequencing	Pooled published datasets	38022579
Vargas et al. (2023)	Vargas_45 (TB vs LTBI & HC & OD)	UK, South Africa, The Gambia, Malawi, Kenya, Venezuela, Indonesia, China, Germany, Taiwan, US, Brazil, India, Ethiopia	Adults	Whole Blood & PBMC	Microarray & RNA Sequencing	Pooled published datasets	37471455
Dai et al. (2024)	Dai_6 (TB vs LTBI)	London UK, South Africa, Taiwan, The Gambia	Adults	Whole Blood & PBMC	Microarray	Pooled published datasets	38312744
Yu et al. (2024)	Yu_7 (TB vs LTBI)	Kenya, South Africa, Malawi	Children	Whole Blood	Microarray	Pooled published datasets	38890657

Abbreviation:
Tuberculosis (TB), Latent tuberculosis infection (LTBI), Healthy controls (HC), Other diseases (OD), Incipient tuberculosis (ITB), Subclinical tuberculosis (STB)

Regarding methodologies, 25/43 studies focused on microarray methodologies for their biomarker discovery studies, 11/43 Studies were on RNA-sequencing, and 7/43 studies included the combination of both RNA-sequencing and microarray methodologies (Table 2.3). 31/43 studies have utilized whole-blood samples, 9/43 studies used PBMC samples, and 3/43 studies used a combination of PBMC and whole blood tissue samples for synthesized tuberculosis biomarkers and for biomarker validation purposes. Most studies focused exclusively on adults with 32/43 studies, though a few included solely pediatric populations with 6/43 studies, 4/43 studies included both adult and children population, while 1/43 reported an adolescent population.

2.3.3 Comparison of gene methodology and tissue sample

In comparing methodology, there are 1232 unique genes for microarray, and 379 genes for RNA-seq, and 329 unique genes have shown to be common in both microarray or RNA-seq. With regards to the use of tissue sample, 1169 genes are unique to whole blood and 345 genes for PBMC samples. There are 426 genes that have been shown to be common in both whole blood or PBMC tissue samples (Figure 2.3, Table 2.4 – 2.5)

2.3.4 Discovery of novel tuberculosis biomarkers through microarray and RNA-Seq

There were 60 tuberculosis gene signatures that were retrieved (Table 2.3). Overall, 1939 unique genes have been observed from all 60 tuberculosis signatures, 49/60 tuberculosis signatures are for tuberculosis diagnosis, while 8/60 are for monitoring the response to tuberculosis treatment and 3/60 are for monitoring tuberculosis disease progression. In addition, there have been 15 unique genes that have been reported in more than 10 tuberculosis signatures (Figure 2.4). The most frequent genes are APOL6, GBP5, GBP6, C1QB, DHRS9, ETV7, CD274, SERPING1, FCGR1A, SEPT4, FCGR1B, ANKRD22, BATF2, C1QC, and SCARF1.

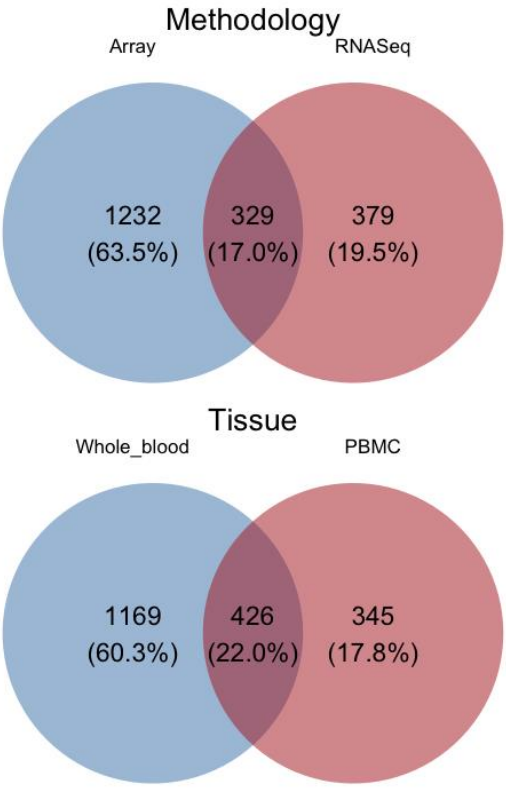


Figure 2.3. Venn Diagram depicting the comparisons of methodology and tissue sample in tuberculosis signature presentation

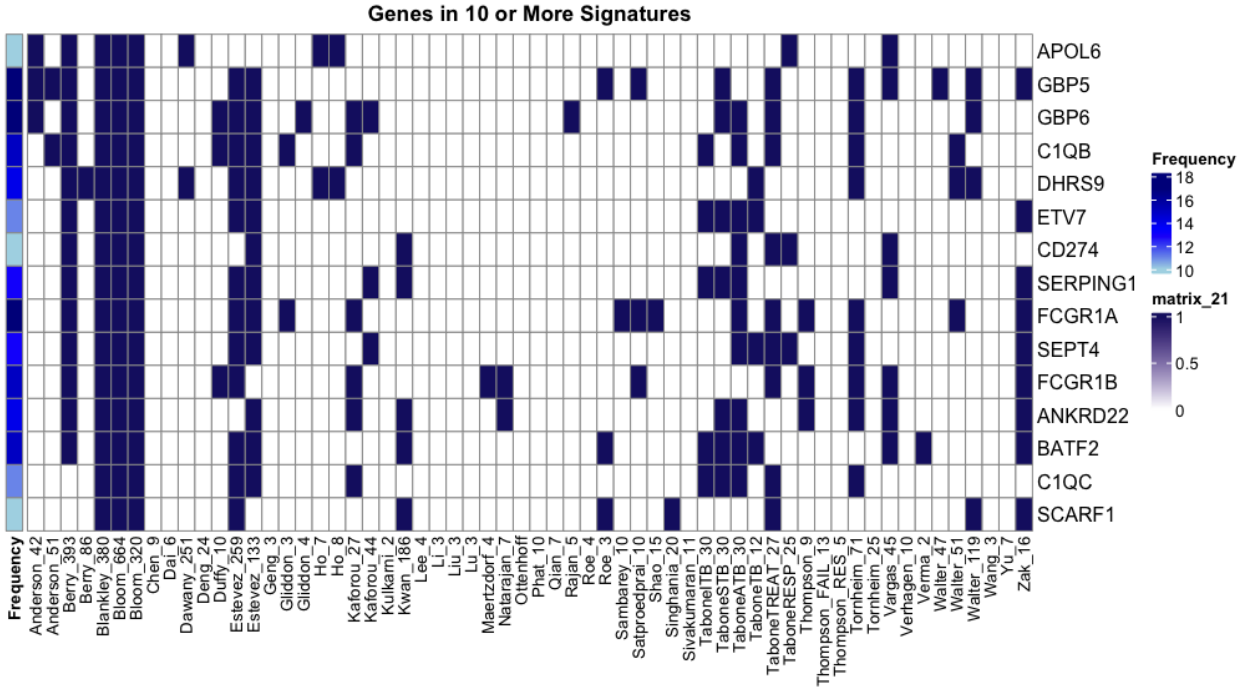


Figure 2.4. Heatmap depicting the genes reported in 10 or more tuberculosis signature

Table 2.4. Tissue Sample Overlap List

ACTA2	MYL9	IFI44	ZNF540	CXCL10	SCARF1	FFAR2	HNMT	MMP9	GOLGA8A/GOLGA8B
APOL6	NLRC4	OSM	ADAM28	KCNJ15	SIGLEC16	UBE2L6	HSPA6	KLF12	HOXA9
CARD16	P2RY10	KIF1B	ADCY3	LIN7A	SLAMF8	PRRG4	IL18R1	CLYBL	IFIT1
GBP5	PFKFB2	GNG10	ANO9	ETV7	SLC2A14	CASP4	IL1B	RSAD2	IRAK3
GBP6	SLC6A12	IL1RN	AQP10	CLEC12A	ST3GAL4	APOL1	LEPR	OAS1	ITGB5
LRRN3	YME1L1	DDX60	ARG1	TIMM10	SYTL2	GK	LOC93432	PLSCR1	KCNJ2
PASK	AK4	SUCNR1	ASPRV1	SOD2	TFPI	CHMP5	MAP7	PGLYRP1	KLHDC8B
RAP1A	C2	GZMK	BANK1	ISG15	TLR8	TIFA	MGAM	FCGBP	KLHL3
TGIF1	CASP1	TNFAIP6	BST1	IFI44L	TMEM144	STAT1	MIR600HG	PARP9	LCK
	CCR1	SERPING1	C1QA	CDK5RAP2	TRIM6	STAT2	MSRB3	EPB41L3	LTF
C1QB	CEACAM8	IFIH1	CCDC65	IFIT5	VNN1	SIGLEC5	ODF3B	CMPK2	LY6E
CD79A	CRISPLD2	WDFY3	CD19	ZAK	VPS9D1	FCGR1A	OPLAH	BCL6	MARCO
CEACAM1	CXCR5	DYSF	CD248	XAF1	XK	ATF3	PDE9A	CASP5	MCTP1
F2RL1	DEFA1 (includes others)	ADM	CD96	GAS6	ACKR3	SEPT4	PF4V1	CCR6	MEGF9
GBP3	DSC2	ASPHD2	CHPT1	SIPA1L2	ACSL1	LACTB	PMEPA1	CACNA1E	METTL7B
KREMEN1	F5	ZDHHC19	CLIC3	ANXA3	AFF3	FCGR1B	PNKD	TNFSF13B	MMP8
PDCD1LG2	FAM20A	IFI16	CLUHP3	HIST2H2BF	ALAS2	TRIM22	PSG9	FCAR	MS4A1
SMARCD3	FCGR3A/FCGR3B	HPSE	CNIH4	ABLIM1	ALPK1	PSTPIP2	PVRL2	FAIM3	MT1G
VAMP5	FYB	EPSTI1	CTTN	FAM26F	AP5B1	AIM2	RAB24	CD5	MUC1
NAIP	GBP1P1	RAB20	CXCR3	QPCT	ASAP2	FBXO6	REPS2	IL15	NAMPT
FAM102A	GM2A	IFI35	DDX60L	SERPINA1	AXIN2	LHFPL2	RHOT1	GPR141	NCR3
OASL	HCAR2	SAMD9L	EBF1	GADD45G	BACH2	GBP1	SAMD14	PML	NOD2
CD151	HCAR3	PARP14	EPG5	TMEM51	BPI	ANKRD22	SAMD4A	CREB5	NUDT16P1

CR1	HPCAL4	GCH1	FAM159A	CD274	CA4	PLAUR	SH2D1B	EPHA4	OSBPL10
SPOCK2	HRK	LMNB1	FCRL2	LILRA5	CACNA2D3	BATF2	SH3BGRL2	ZBP1	PSG3
SOCS3	IL23A	IFIT2	FLNB	HERC5	CAMK2N1	GBP2	SMA4	CACNA1I	ROPN1L
DHRS9	KLRB1	LAP3	GPR68	OAS3	CARNS1	SORT1	SNX10	SELM	SELP
P2RY14	LCN2	TLR5	GPR97	IL18RAP	CD8B	WARS	SPATS2L	FRMD3	SMCO4
SOCS1	LRRK2	TRAFD1	GRIN3A	LOC653610	CEACAM6	FLVCR2	SPIB	GPR84	STEAP4
FCRLA	MCTP2	SCO2	GUCY1A3	IFI6	CFB	DUSP3	SULT1B1	SLC26A8	STK3
ALDH1A1	MGST1	TNFSF10	GUSBP1	TCN2	CLEC4E	APOL2	TLR4	C9orf72	SYTL4
ID3	MYLK	DTX3L	H2AFJ	IGF2BP3	COBLL1	BRSK1	TRIM69	IFITM3	TGFA
CD38	NEAT1	HIST2H2AC	HIP1R	DHRS12	CREG1	JAK2	TSPYL2	NELL2	TGM2
CLEC4D	NMT2	ZNF438	HIST1H2BE	TCF7	CTDSPL	GBP4	VNN2	LPCAT2	TMEM140
TNFRSF25	OLIG1	MAPK14	HIST1H4H	SLC22A4	ELANE	PSMB9	VPREB3	BLK	TMEM158
ASGR2	PLOD2	RTP4	HIST2H2AB	LIMK2	FAS	MTHFD2	IRF1	IFIT3	TREML1
BMX	PROS1	TAP2	HIST2H2BE	IRF7	FPR2	STX11	IER3	PFKFB3	USP32
GYG1	CSF2RB	HP	ARL4C	MCEMP1	KIAA0319L	ITGB3	ANAPC1	CALD1	FUCA2
CCR2	FCGR3B	MAR1	GP9	MYOF	TLR6	RNF213	KIAA1370	CARD17	SLPI
FCRL3	SPARC	CAMP	MSRB2	TDRD9	VNN3	S100A12	ZNF91	CETP	MT2A
PRCP	C6orf25	CD36	CMTM5	C1QC	CDKN2D	TYMP	SMTNL1	GPR183	KCNH7
TNFRSF14	FCGR2C	FAM198B	SEPT5	DISC1	INSL3	ABCB1	RNF19A	HIST1H2BD	CAQB
HIST1H3D	LY96	HIST2H2AA3/HIST 2H2AA4	CLEC7A	ITGA2B	ANKRD44				

Table 2.5. Methodology Overlap List

NAIP	CFB	BATF2	SEMA6B	EPSTI1	KLHDC8A	CEACAM6	FCGBP	TMEM25	IRAK3
OASL	ELANE	GBP5	SIGLEC1	RAB20	LIPM	OPLAH	BCL6	TRAF4	NLRC4
SPOCK2	HOXA9	GBP2	AHRR	IFI35	LYPD5	INSL3	CASP5	TRIM47	B4GALT5
SOCS3	METTL7B	SORT1	NEIL3	SAMD9L	MAP6	CEACAM8	CACNA1E	USP54	SECTM1
DHRS9	MMP8	PSME2	FBXO39	LMNB1	MYZAP	FAM20A	FCAR	VEGFB	NAMPT
P2RY14	CD96	FLVCR2	AXL	IFIT2	NEURL3	MPO	CD5	ANXA8	CARD17
SOCS1	GRIN3A	DUSP3	LGALS2	LAP3	NFXL1	AAK1	IFITM1	ARHGEF17	GP9
TLR2	REPS2	JAK2	RUFY4	TLR5	NRCAM	PGA5	PML	ARHGEF37	ACSL1
BMX	SH3BGRL2	GBP4	LGALS3BP	TRAFD1	NRN1	HBD	ZBP1	AZU1	HIST2H2AB
CXCL10	CD177	GYG1	EXOC3L1	SCO2	OLR1	DEFA1B	LILRB4	BEST3	CMTM5
KCNJ15	CLEC7A	VAMP5	COL23A1	CEACAM1	PCOLCE2	DEFA3	FRMD3	C17orf105	ITGA2B
ETV7	NRG1	APOL6	MT2A	ZNF438	PRRT4	RAP1A	GPR84	C3orf84	TREML1
TIMM10	LIMK1	POLB	SCT	MAPK14	PRTN3	PDCD1LG2	SLC26A8	CDCP1	PROS1
ISG15	HK3	LTF	MSLN	RTP4	PXT1	PTK2	IFITM3	CLDN18	CA4
IFI44L	RAB13	KLHDC8B	CCDC144A	FFAR2	RAB3IL1	PPBP	NELL2	CLEC5A	HIST1H2BE
XAF1	RBBP8	FCGR1C	SPACA3	UBE2L6	SCG5	C2	IFIT3	CORIN	ODF3B
SIPA1L2	CYP4F3	IRF1	HIST1H4A	FCER1G	SPATC1	GBP1P1	OSM	CTSE	SCARF1
ANXA3	SLPI	IER3	HIST1H1B	PRRG4	TCTEX1D1	BPI	IL1RN	CTSG	BACH2
HIST2H2BF	PRKCB	CSF2RB	HIST1H4F	APOL1	TMEM52B	HIST1H4C	SUCNR1	CXorf36	ASAP2
FAM26F	IFNGR2	MBOAT2	NXPH3	GK	WNT9A	MTRNR2L1	TNFAIP6	DDIT4L	C1QC
TMEM51	GSK3B	NOD2	HIST1H4B	TIFA	ADAMTSL4	EXOC3L4	SERPING1	DOC2B	MGAM
CD274	APOL4	FCGR3B	ZBED6	STAT1	ATP8B4	VWA3B	WDFY3	DUSP13	ROR1
IFI6	ARHGEF9	VNN1	HSPA12B	FCGR1A	CC2D2A	SLC8A2	DYSF	DZIP1L	CAMP
TCN2	ARNTL2	SLC2A14	TRAJ4	SEPT4	CHI3L1	RHOV	HIST2H2AA3	ELOVL3	ASPRV1
IGF2BP3	BDH1	SPARC	TAS2R3	FCGR1B	IGF2R	AOC1	ADM	EPB42	SLC6A12
C1QB	CCDC120	LRRK2	HTRA1	PSTPIP2	ITGAM	KCNMA1	ASPHD2	ERG	VNN3
IRF7	COL4A4	LCN2	GALNT4	AIM2	KCNH7	KCNJ10	GBP6	GLDN	ERLIN1

MMP9	CTSB	TGM2	HIST1H1D	FBXO6	PADI4	SDC3	ZDHHC19	HTRA3	C1QA
SMARCD3	ICAM1	HP	HIST1H1E	LHFPL2	MTRNR2L10	BAK1	RARRES3	LIPA	PLA2G4A
RSAD2	KCNC4	CD19	HIST1H3C	GBP1	CCL2	GRAMD1C	RP11-476D10.1	CHMP2B	MBOAT1
PLSCR1	PAIP2B	C6orf25	TICAM2	TAP1	HESX1	FCGR1CP	ARPC5	RAB5A	CAQB
PGLYRP1	SMYD5	PF4V1	TAS2R60	ANKRD22	PCGF2	EFCAB2	ACSL4	GABARAPL2	LY96
KREMEN1	SPHK1	FCGR2C	CH17-296N19.1	C16orf7	LCN8	RP11-468E2.5	PLD4		

2.3.5 Publicly Available Datasets Used

Gene Expression Omnibus (GEO) publicly available tuberculosis transcriptomic datasets were compiled and analyzed, which include both microarray and RNA sequencing (RNA-Seq) technologies through all the papers that were included in the PRISMA search. A total of 45 datasets were identified (Table 2.6). There were 15 publicly available RNA-seq datasets while there are 30 publicly available microarray datasets. Whole blood was the predominant sample type with 39 datasets, while 6 datasets utilized PBMCs. The datasets were either used as test, training or validation cohort for tuberculosis biomarker discoveries, 8/43 studies did not provide GEO accession numbers, or they uploaded datasets in a different database.

Four super series were identified in the dataset analysis. Super series GSE39941 comprises GSE39939 and GSE39940[126]. Super series GSE42834 includes GSE42825, GSE42826, and GSE42830[132]. Super series GSE19491 encompasses GSE19444, GSE19442, GSE19439, GSE19443, and GSE19435[106]. Lastly, super series GSE107995 consists of GSE107991, GSE107992, GSE107993, and GSE107994[111].

These publicly available datasets were derived from cohorts from 15 unique countries, showcasing a diverse geographic distribution. These countries include Brazil, China, Ethiopia, The Gambia, Germany, India, Indonesia, Kenya, Malawi, South Africa, Taiwan, Uganda, the United Kingdom, the United States of America, and Venezuela.

Most frequently used datasets with more than 10 citations included GSE37250 (14 references), GSE19444 (14 references), GSE19442 (13 references), GSE19439 (13 references), GSE39940 (11 references), GSE42825 (10 references), GSE42826 (10 references), GSE42830 (10 references), GSE39939 (10 references), which are all whole blood microarray datasets. RNA-seq datasets, while fewer in number, have been increasingly utilized over time in more recent studies GSE79362 (6 references) and GSE107991(4 references), which are both whole-blood samples. The rarest publicly available dataset identified was GSE112104 (1 reference) with the combination of RNA-seq methodology with PBMC samples.

Table 2.6. Usage Trends of Public Transcriptomic Datasets in Tuberculosis Biomarker Discovery Studies

Dataset	Country	Sample	Technology	Frequency Used	PMID
GSE39939	Kenya	Whole Blood	Microarray	10 [126,127,133–140]	24785206
GSE39940	South Africa, Malawi	Whole Blood	Microarray	11 [126,127,134–142]	24785206
GSE54992	China	PBMC	Microarray	3 [133,136,139]	24647646
GSE37250	South Africa, Malawi	Whole Blood	Microarray	14 [100,111,125,127,128,133–136,139,142–145]	24167453
GSE31348	South Africa	Whole Blood	Microarray	4 [133,134,139,145]	22872737
GSE36238	South Africa	Whole Blood	Microarray	3 [133,134,139]	22872737
GSE42825	United Kingdom	Whole Blood	Microarray	10 [99,100,111,127,128,133,134,139,143,146]	23940611
GSE42826	United Kingdom	Whole Blood	Microarray	10 [99,100,111,127,128,133,134,139,143,146]	23940611
GSE42830	United Kingdom	Whole Blood	Microarray	10 [99,100,111,127,128,133,134,139,143,146]	23940611
GSE40553	United Kingdom, South Africa	Whole Blood	Microarray	6 [100,118,133,134,139,147]	23056259
GSE56153	Indonesia	Whole Blood	Microarray	4 [133,139,146,148]	23029268
GSE34608	Germany	Whole Blood	Microarray	3 [133,139,146]	22547807
GSE28623	The Gambia	Whole Blood	Microarray	4 [133,139,146,149]	25895988
GSE19444	United Kingdom	Whole Blood	Microarray	14 [100,106,118,127,133,134,136,139,143,144,146,149–151]	20725040
GSE19442	South Africa	Whole Blood	Microarray	13 [100,106,118,127,133,134,139,143,144,146,149–151]	20725040
GSE19439	United Kingdom	Whole Blood	Microarray	13 [100,106,118,127,133,134,139,143,144,146,149–151]	20725040

GSE19443	United Kingdom	Whole Blood	Microarray	7 [106,127,134,143,144,149,151]	20725040
GSE19435	United Kingdom	Whole Blood	Microarray	8 [106,118,127,134,143,144,149,151]	20725040
GSE27984	China	PBMC	Microarray	1 [121]	21904626
GSE41055	Venezuela	Whole Blood	Microarray	2 [139,152]	23375113
GSE50834	South Africa	PBMC	Microarray	2 [118,139]	24587128
GSE62525	Taiwan	PBMC	Microarray	3 [122,139,149]	26818387
GSE73408	United States of America	Whole Blood	Microarray	2 [139,153]	26582831
GSE103188	China	PBMC	Microarray	1 [154]	29248507
GSE79362	South Africa, The Gambia	Whole Blood	RNA-Seq	6 [99,100,111,134,139,155]	27017310
GSE107991	United Kingdom	Whole Blood	RNA-Seq	4 [99,111,139,145]	29921861
GSE107992	South Africa	Whole Blood	RNA-Seq	2 [99,111]	29921861
GSE107993	United Kingdom	Whole Blood	RNA-Seq	3 [99,111,139]	29921861
GSE107994	United Kingdom	Whole Blood	RNA-Seq	3 [111,139,145]	29921861
GSE107104	Uganda	Whole Blood	RNA-Seq	2 [112,135]	29764370
GSE89403	South Africa	Whole Blood	RNA-Seq	5 [99,104,134,139,145]	29050771
GSE162164	India	Whole Blood	RNA-Seq	1 [135]	33692804
GSE157657	United Kingdom	Whole Blood	RNA-Seq	2 [99,139]	34491266
GSE101705	India	Whole Blood	RNA-Seq	3 [99,139,145]	29559120
GSE193777	India	Whole Blood	RNA-Seq	1 [156]	36713386
GSE181143	India, Brazil	Whole Blood	RNA-Seq	1 [145]	37173394
GSE29536	United Kingdom	Whole Blood	Microarray	1 [139]	24069364
GSE62147	Germany	Whole Blood	Microarray	1 [139]	26043170
GSE69581	South Africa	Whole Blood	Microarray	1 [139]	29339504
GSE83456	United Kingdom	Whole Blood	Microarray	1 [139]	27706152
GSE84076	Brazil	Whole Blood	RNA-Seq	1 [139]	27826286
GSE116014	South Africa	Whole Blood	Microarray	1 [139]	30135583
GSE94438	South Africa, Ethiopia, Uganda, The Gambia	Whole Blood	RNA-Seq	2 [100,139]	29624071
GSE112104	Brazil	PBMC	RNA-Seq	1 [139]	32090859
GSE67589	South Africa	Whole Blood	Microarray	1 [139]	26351358

2.4 Discussion

This scoping review of transcriptomic studies in tuberculosis biomarker research highlights the increasing utilization of transcriptomic technologies, such as microarrays and RNA sequencing, to identify novel gene signatures associated with tuberculosis. By synthesizing findings from 43 studies, this analysis provides insights into gene expression profiling methodologies, most common samples used, and demographic characteristics that shape tuberculosis transcriptomic research.

2.4.1 Geographic Diversity of Transcriptomic Studies

The geographic diversity of the included studies reflects a global effort to address tuberculosis, with contributions spanning endemic and non-endemic regions across 21 countries (Figure 2.2). This underscores the importance of context-specific research to address the heterogeneity in tuberculosis presentations and the host genetic and exposures background that govern immune responses. However, the geographic distribution of public datasets, primarily clustered in countries like the United Kingdom, South Africa, and China, reveals potential biases in available data, limiting representation from regions with the highest tuberculosis burdens. As of 2023, India, Indonesia, China, Philippines, Pakistan, Nigeria, Bangladesh and the Democratic Republic of the Congo account for 67% of tuberculosis burden[8]. The presentation of tuberculosis can vary depending on factors such as genetics, comorbidities (e.g., HIV), and socioeconomic conditions. Therefore, future studies representing high tuberculosis burden countries and socioeconomic factors are needed.

2.4.2 Microarray and RNA-Seq comparisons

Gene expression profiling methodological approaches varied significantly, with microarray techniques as the more common choice, despite RNA sequencing gaining attention in recent years. While the use of microarrays may have been more practical and cost-effective, as evidenced by the predominant use in 2010s, they are limited due to their reliance on pre-designed probes, which restrict their ability to detect novel transcripts,

splice variants, or low-abundant genes[157]. RNA-Seq on the other hand, can provide a comprehensive approach to transcriptomic analysis, with the ability to also detect non-coding RNAs[157,158]. Additionally, there have been studies of RNA-Seq reporting more differentially expressed genes compared to microarrays[110,113,114]. There are 1232 unique genes for microarray, and 379 genes for RNA-seq (Figure 2.3), however this is potentially due to the possibility that the former methodology was the most used and its public availability (Table 2.6). Nevertheless, the overlap of 329 unique genes between microarray and RNA-seq datasets demonstrates consistency in gene discovery but also highlights the advantages of integrating methodologies to enhance biomarker validation. The implementation of RNA-seq for synthesizing tuberculosis gene signatures with the use of microarray datasets or real-time polymerase chain reaction (RT-qPCR) has become the standard in modern transcriptomic studies[123].

2.4.3 Tissue Sample comparisons

Tissue sample selection further influenced gene discovery, with whole-blood samples being overwhelmingly preferred over PBMCs (31 vs 9). This preference reflects the accessibility of whole-blood samples, the need to use samples that require less technical steps or highly specialized training and equipment, and their suitability for high-throughput transcriptomic analysis[159]. Studies show that the use of whole blood samples report more genes and with higher expression[159–161], 1169 genes are unique to whole blood and 345 genes for PBMC samples while it is possible that the higher reported gene in whole blood is due to its diverse cell population, it is potentially also because whole-blood samples are more easily accessible and more readily used. PBMC samples on the other hand requires more labor-intensive steps for isolation, directly reflecting to its low use in public datasets (Table 2.6). Studies have shown that technical differences with regards to tissue sample isolation, handling and storage in addition to the sample type does affect gene expression profiling[161]. Nonetheless, there are 426 genes that have been shown to be common in both whole blood and PBMC tissue samples. We excluded sputum samples, but the utility of

such samples and proximity to the responses in the respiratory tract may be of value to provide additional validation for the findings in the blood.

2.4.4 Potential Biomarkers

The identification of 15 frequently reported genes across more than 10 tuberculosis gene signatures, including apolipoprotein L6 (APOL6), guanylate-binding protein 5 (GBP5), guanylate-binding protein 6 (GBP6), complement C1q B chain (C1QB), dehydrogenase /reductase 9 (DHRS9), ETS variant transcription factor 7 (ETV7), cluster of differentiation 274 (CD274, also known as programmed death-ligand 1 or PD-L1), serpin family G member 1 (SERPING1), Fc gamma receptor Ia (FCGR1A), septin 4 (SEPT4), Fc gamma receptor Ib (FCGR1B), ankyrin repeat domain 22 (ANKRD22), basic leucine zipper transcription factor 2 (BATF2), complement C1q C chain (C1QC), and scavenger receptor class F member 1 (SCARF1) highlights potential candidates for robust tuberculosis biomarkers identification across different populations (Figure 2.4). These genes have either been reported to tuberculosis diagnosis, progression, monitoring treatment and response. Notably, all genes have been consistently expressed across different methodologies (microarray vs RNA-seq) and tissue sample (whole-blood vs PBMC) which highlights their reproducibility in transcriptomic studies for tuberculosis (Figure 2.3).

Several of these key genes play a role in immune response and inflammation in tuberculosis. Particularly, the C1QB and C1QC are part of the complement system cascade and plays a role in the immune response to tuberculosis[162]. C1QB and C1QC were reported to have higher expression in active tuberculosis disease compared to health controls and latent tuberculosis infection[163,164]. SERPING1 gene encodes the C1-inhibitor that is involved in the regulation of the complement system pathway[165]. While no evidence of clearance of *M. tuberculosis*, SERPING 1 plays a role in modulating inflammation and preventing excessive complement activation and has been reported increased expression in tuberculosis[166,167].

GBP5 is an interferon-induced GTPase that contributes to the inflammasome activation and innate immunity against intracellular bacteria like *M. tuberculosis*[168,169]. While also reportedly expressed in tuberculosis biomarkers, the GBP6 gene however have limited studies in the context of *M. tuberculosis* defense. SCARF1 that plays a role in clearance of apoptotic cells, as well as regulating an immune response to tuberculosis[166,170]. Specifically, to the immune response, it modulates neutrophil accumulation, inflammation and formation of granulomas[166]. Studies shown that expression of the SCARF1 gene is reported in tuberculosis progressor cohorts, implicating that this biomarker is involved in tuberculosis progression[100,155,166].

The FCGR1A and FCGR1B both encode high-affinity Fc-gamma receptors that mediate macrophage-driven phagocytosis and immune signaling, which are essential for immunity against tuberculosis[171,172]. Studies suggests that upregulation of CD274 or PD-L1 is primarily observed in neutrophils which implies a role in an immune response to tuberculosis[173]. This expression is significantly increased in active tuberculosis compared to health controls and latent tuberculosis infection[173]. Additionally, CD274 is also expressed within granulomas that are formed during *M. tuberculosis* infection suggesting its association with tuberculosis progression[21]. SEPT4 is involved in apoptosis and have been implied to have a role in defense against tuberculosis infection[166,174].

APOL6 has been suggested to have an association to defense response and the interferon signaling pathway, though its specific role in tuberculosis remains unclear[175]. Similarly, ETV7 is involved with regulating interferon-stimulated genes immune response and apoptosis[176,177]. In contrast, the functions of ANKRD22 and the DHRS9 in host immunity and its involvement with tuberculosis are not well characterized. Overall, APOL6, ETV7, ANKRD22, and DHRS9 have been consistently expressed in individuals with tuberculosis. However, their role in immunology against tuberculosis in the host is unclear.

Among these, the BATF2 gene stands out as a promising biomarker. It has been utilized as a standalone marker and as a part of a minimal 2 gene signature associated with tuberculosis[112,178,179]. The BATF2 plays a role in host inflammatory responses against *M. tuberculosis* infection, particularly the regulation of macrophage response[180,181]. Therefore,

pathway analysis exploration on BATF2 gene and the rest of the frequently reported genes and their association with tuberculosis would further solidify its relevance and validation as a biomarker. Their consistent expression across varying methods and sample types enhances the potential for tuberculosis biomarker application in clinical settings, suggesting that these genes could be the foundation of standardized biomarker panels for effective diagnosis, monitoring and management.

2.4.5 Publicly Available Datasets

Public datasets, such as those in the GEO, have played a pivotal role in advancing tuberculosis transcriptomic research. The compilation of 45 datasets, dominated by microarray methodologies and whole blood samples, underscores the reliance on public resources for training, testing, and validation of biomarkers. However, the scarcity of RNA-seq datasets, particularly those using PBMC samples, limits opportunities to explore the full potential of next-generation sequencing technologies in tuberculosis research. The increasing citation of RNA-seq datasets like GSE79362 in recent studies signals a shift toward more comprehensive approaches, but the underutilization of datasets such as GSE112104 reveals gaps in leveraging available resources.

Additionally, the recruitment timelines and the publication dates of these datasets – many of which predate the COVID-19 pandemic which could pose as a concern about their relevance to modern tuberculosis research. The changes and classifications of the tuberculosis spectrum, addition of incipient, subclinical and minimal tuberculosis disease, along with updated tuberculosis diagnostics, and treatment regimens may necessitate updated public datasets to ensure that the findings remain applicable to current definitions[37,38]. This highlights the crucial need for new datasets that reflects modern recruitment processes and methodologies for tuberculosis transcriptome studies.

2.4.6 Novel Profiling Approaches and Current Limitations of the Findings

While microarray and RNA-seq remain the gold standard of tuberculosis transcriptomic research, emerging technologies such as single-cell RNA sequencing (scRNA-seq), NanoString platform profiling, and microRNA (miRNA) profiling have shown promise in tuberculosis biomarker discovery[102,182–186]. These novel approaches offer unique advantages, such as improved resolution of cellular heterogeneity and enhanced sensitivity[186–192]. However, they also come with limitations, including increased technical complexity, and challenges in data standardization compared to the more established microarray and RNA-seq platforms[186,187,190,192,193]. Continued exploration of these advanced technologies, alongside the refinement of existing methods, will be essential for novel insights into tuberculosis transcriptomics.

Despite the substantial progress made in identifying potential tuberculosis biomarkers, several limitations remain in this scoping review. First, the search strategy did not explicitly account for tuberculosis-associated comorbidities, such as HIV and diabetes, which could significantly influence biomarker expression as well additional tuberculosis biomarker discovery not included in the search. Similarly, drug-resistant tuberculosis was not included due to its unique characteristics related to clinical isolates and its interaction with the host, potentially overlooking biomarkers associated with these challenging cases. Second, the screening, full-text review, and data extraction were conducted by a single reviewer. Although eligibility criteria were applied consistently, this approach carries the risk of selection bias. Third, the literature search was limited to peer-reviewed articles indexed in selected databases; grey literature sources (e.g., conference abstracts, dissertations, preprints) were not included. Manual reference-list screening of included articles was also not performed.

Fourth, technical differences in sample processing, ranging from sample collection protocols to variations in bioinformatics pipelines were not considered, which could affect the comparability of findings across studies. Variability in the recruitment processes and genetic background of each cohort, particularly in culturally diverse countries like the USA and UK were not fully examined, limiting the ability to fully contextualize the findings.

Finally, the review highlights broader research gaps, including the underrepresentation of pediatric populations, limited inclusion of cohorts from both under-studied high and low tuberculosis burden settings, the relatively small number of RNA-seq based studies, and the scarcity of PBMC-based studies. Addressing these methodological, demographic, and technical gaps through diverse cohort inclusion, standardized protocols, and multi-modal profiling, will be crucial for advancing the discovery and validation of robust, clinically relevant tuberculosis biomarkers.

2.5 Conclusion

This scoping review highlights significant progress in tuberculosis biomarker discovery through transcriptomic studies, emphasizing the contributions of microarray and RNA sequencing methodologies across diverse populations. The identification of 15 frequently reported genes offers promising candidates for robust biomarkers, but the findings also reveal gaps, including underrepresentation of pediatric populations, and limited public RNA-seq datasets. Future research should focus on integrating methodologies, and diversifying study populations, to develop clinically applicable and globally representative tuberculosis biomarkers.

CHAPTER III: GENE EXPRESSION PROFILE OF TUBERCULOSIS DISEASE AMONG PEOPLE LIVING WITH HIV

3.1 Introduction

Host blood transcriptomics and gene expression profiling has emerged as a powerful tool for unraveling the complex host-pathogen interactions in tuberculosis and HIV coinfection[97,194,195]. By examining transcriptional changes in immune cells and tissues, researchers have identified potential biomarkers and pathways associated with disease progression, immune activation, and treatment outcomes[99,100,148]. However, the unique gene expression signatures in tuberculosis in PLHIV unreproducible, particularly in diverse clinical settings and populations[194,196].

This study aims to 1) examine the gene expression profile of tuberculosis in PLHIV, and 2) investigate the molecular mechanisms and signaling pathways that contribute to the interactions of tuberculosis and HIV. This knowledge could help identify new biomarkers and lead to more thorough understanding of the syndemic interactions between tuberculosis and HIV which could in turn advance future diagnostic and treatment strategies.

3.2 Methods

3.2.1 Participants

Participants >18 years old from Medellin, Colombia were enrolled between September 2016 and December 2018 (Table 3.1). Participants non-infected (n = 13) and people diagnosed with tuberculosis (n = 10) were enrolled in two male prisons. Additional details about recruitment process, inclusion and exclusion criteria for clinical tuberculosis and non-infected participants can be found and supplemented by Herrera et al.[197].

People diagnosed with HIV alone (n =12) cohorts were individuals hospitalized in Medellin, Colombia at the Hospital Universitario San Vicente Fundacion and through

private HIV practice at Clinica SOMA. Inclusion criteria included >18 years old and serologically diagnosed with HIV that had a documented viral load. Additional details about recruitment process, inclusion and exclusion criteria can be found and supplemented by Head et al.[198], and Rodriguez-Sabogal et al.[199].

3.2.2 Published cohort sequences

The sample size was primarily determined by the number of participants in the parent study which was further complemented by whole-blood publicly available RNA sequences (GSE107991, GSE107104, GSE162164)[111,112,135]. The raw data sequences were searched from the public database, NCBI-GEO. Raw reads RNA sequences in fastq file format were downloaded from The European Nucleotide Archive (ENA)[200]. Cohorts included a tuberculosis group, people living with HIV, and people diagnosed with both tuberculosis and HIV. Information regarding the sequences can be found in Table 3.1.

3.2.3 Sample Processing

For the Colombia cohorts, blood samples were collected and PBMCs were isolated via density gradient with Ficoll (Sigma-Aldrich, Missouri, US), and preserved at -121ºC in DMSO, bovine fetal serum, and RNA later® (Ambion, Texas, US) until RNA extraction. PBMC RNA Extraction was performed using the RNeasy® Plus Mini Kit (Qiagen, Hilden, Germany), with the modified protocol described in Appendix 2. Additional information about PBMC storage procedures can be found in Herrera et al.[197].

Paired-end cDNA libraries were prepared using the TruSeq Stranded mRNA Library Kit (Illumina, California, USA), and sequencing was performed by Macrogen Inc. (Seoul, Korea) on the NovaSeq system (Illumina, California, USA), based on the methodology described in Herrera et al.[197].

Of the samples, 21 were processed as part of the 2022 study by Herrera et al.[197], and an additional 2 non-infected cohort samples were processed in 2023 for inclusion in the present analysis. Sample processing information on all cohorts can be found in Table 3.2.

Table 3.1. Study design and recruitment characteristics of cohorts

	United Kingdom[A]	Uganda[B]	India[C]	Colombia[D]	
Cohort Conditions	**TB**	**TB in PLHIV**	**TB in PHIV and HIV alone**	**TB, and Non-infected**	**HIV**
Recruitment Sites	St. Mary's and Hammersmith Hospitals, Imperial College, London	Mulago National Referral Hospital and Infectious Diseases Institute, Makerere University	BJGMC and Sassoon General Hospitals, India	Medellin male prisons	Hospital San Vicente Fundacion, Clinica SOMA
Recruitment Period	~2007 (Not specified)	March – December 2013	January 2018 – June 2019	September 2016 - December 2018	November 2016 - December 2018
Sex	Male (n = 13) Female (n = 8)	Male (n = 9) Female (n = 8)	Male (n = 23) Female (n = 7)	Male (n = 23)	Male (n = 12)
Inclusion	TB confirmation, > 18 y/o, before start of TB treatment	TB, HIV confirmation, > 18 y/o CD4 count of ≤ 100 cells/uL	> 18 y/o, HIV, advanced HIV, ART-naïve and ART experienced	TB: Smear positive, culture positive, <5 days of TB treatment non-infected: (-) TST	> 18 y/o, serological confirmation with documented viral load
Exclusion	Pregnancy, immunosuppression, diabetes, autoimmune status, HIV positive	more than 2 days of anti-TB medication	TB history, anti-TB medication prior to enrolment	Live vaccines before TST administration, adverse reaction to TST, TB history, less than 2 years of	hospitalized during the last 2 weeks, recent antibiotic exposure, COPD, other immunosuppression, chronic lung disease
TB Confirmation	Sputum / BAL Culture	Smear positive or culture	Symptom Screen, GeneXpert MTB/RIF, smear and culture	Sputum smear and culture	None
HIV Confirmation	None	Serological	Not Specified	None	Serological
Opportunistic Infections	None	None	Not reported	None	Yes
Ethics Consent	Written Consent	Written Consent	Written Consent	Written Consent	Written Consent
Accession Number	GSE107991	GSE107104	GSE162164	Not available	Not available
Key References	Berry et al., Singhania et al.	Verma et al.	Kulkarni et al.	Herrera et al.	Head et al.

[A] Information retrieved from Berry et al. & Singhania et al.[106,111] ; [B] Information retrieved from Verma et al.[112]
[C] Information retrieved from Kulkarni et al.[135] ; [D] Information retrieved from Herrera et al. & Head et al. [197,198]

Table 3.2. Sample and RNA processing information on all cohorts

	GSE107991 (United Kingdom)	GSE107104 (Uganda)	GSE162164 (India)	Colombia (Herrera et al.)
Sample Type	Whole blood	Whole blood	Whole blood	PBMCs
Extraction Kit/Method	MagMAX™ for Stabilized Blood Tubes RNA Isolation Kit (Applied Biosystems/Thermo Fisher Scientific); HT RNA Assay Reagent Kit (Perkin Elmer);	PAXgene Blood RNA Kit (Qiagen);	PAXgene Blood RNA Kit (Qiagen, catalog # 762165)	RNeasy Mini Kit (Qiagen, Hildsen, Germany); RNeasy-Free Water
RNA Quantity/Quality Assessment	NanoDrop™ 8000 Spectrophotometer for quantity and purity; LabChip GX Bioanalyzer (Caliper Life Sciences/Perkin Elmer) for quality.	Not explicitly stated for initial RNA, but implied for amplified RNA. MessageAmp™ II aRNA Amplification Kit (ThermoFisher Scientific); Ribo-zero rRNA removal kit (Epicenter, Applied Systems)	Qubit RNA HS Assay (Invitrogen, Cat # Q32852); RNA purity by QIAxpert; RNA integrity by TapeStation using RNA HS ScreenTapes (Agilent, Cat# 5067-5579).	NanoDrop™ 2000c (Thermo Fisher, Massachusetts, US); RNA Integrity Number (RIN) by TapeStation
RNA Extract Method	Total RNA-Seq	Total RNA-Seq	Total RNA-Seq	Total RNA-Seq
Library	cDNA	cDNA	cDNA	cDNA
Sequence Platform	Illumina HiSeq 4000	Illumina HiSeq 2000	Illumina HiSeq X Ten	Illumina

[A] GSE107104 information can be retrieved from Verma et al.[112]

[B] GSE162164 information can be retrieved from Kulkarni et al.[135]

[C] GSE107991information can be retrieved from Singhania et al.[111]

[D] Colombia cohort information can be retrieved from Herrera et al.[197]

3.2.4 RNA-Seq Processing

Sequences were cleaned and pre-processed using the Galaxy Project platform server. The sequences were subjected to quality control using FastQC v.0.11.9 (Babraham Bioinformatics), and the adapters and low-quality sequences (i.e. Phred score <30) were trimmed by Trimmomatic program v0.38.1[201]. The filtered reads were aligned to the reference *Homo sapiens* genome GRCh38 using HiSAT2 v2.2.1[202]. Then, aligned reads were quantified to obtain the gene-level counts using featureCounts v2.0.1[203]. Information of the RNA-Seq processing steps can be found on Appendix 3.

3.2.5 Bioinformatics Analysis

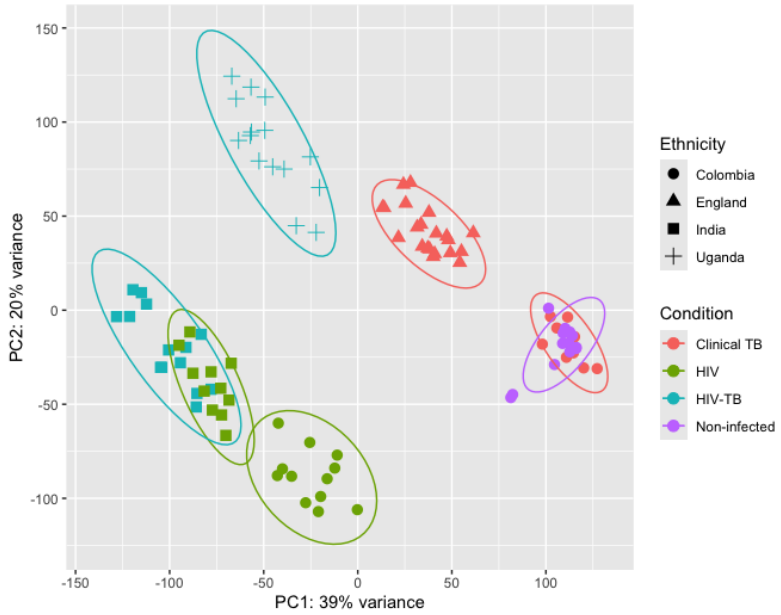
Gene expression profile statistical analysis and visualization were performed by R version studio 4.4.1, using the packages ggplot2 and DESeq2[204]. Combat-Seq was applied to adjust for batch effects associated with collection site (country) and tissue sample (Figure 3.1 – 3.3)[205]. Differentially expressed genes (DEGs) are considered significant using the following parameters: adjusted p-value ≤ 0.05 and fold change = ±1.5.

Functional enrichment of the gene list was analyzed by using, clusterProfiler R package that performs an overrepresentation analysis[206,207]. The hypergeometric test and Benjamini-Hochberg multiple testing correction was employed (q-value ≤ 0.05). Details on data analysis and visualization can be found on Appendix 4.

3.2.6 Identifying Potential Gene Biomarkers

A scoping review was conducted to identify published articles reporting tuberculosis gene signatures. The list of identified signatures is provided in Chapter II, Table 2.3. From this list, genes that appeared in 10 or more signatures were selected for further analysis. Their normalized expression levels were compared across all study conditions, and statistical significance was evaluated using Wilcoxon test. The potential gene biomarkers were then further examined using Enrichr, specifically utilizing the Reactome pathway database[208,209].

[A] Before Combat-Seq Correction



[B] After Combat-Seq Correction

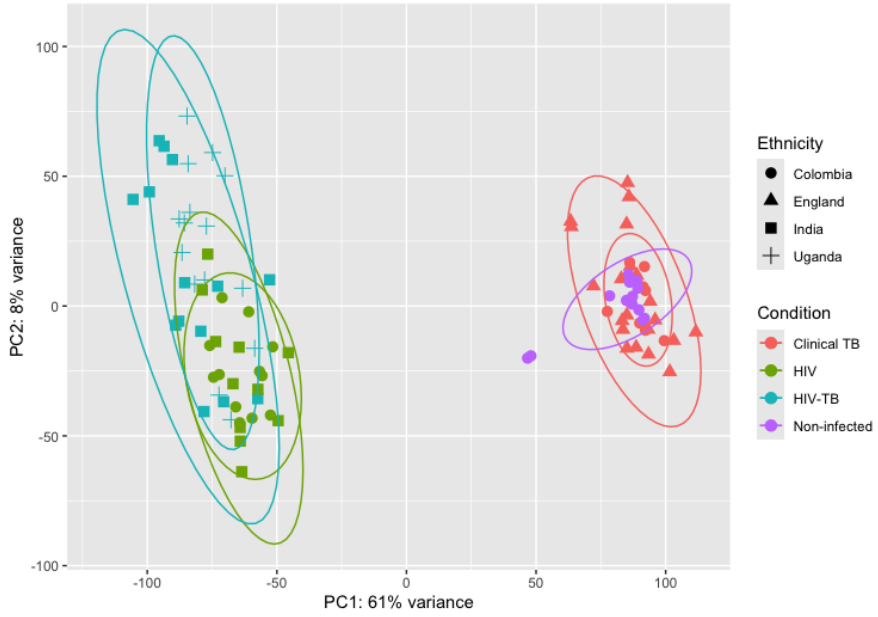


Figure 3.1. Principal Component Analysis of all 4 cohorts. A) Before correction B) After correction

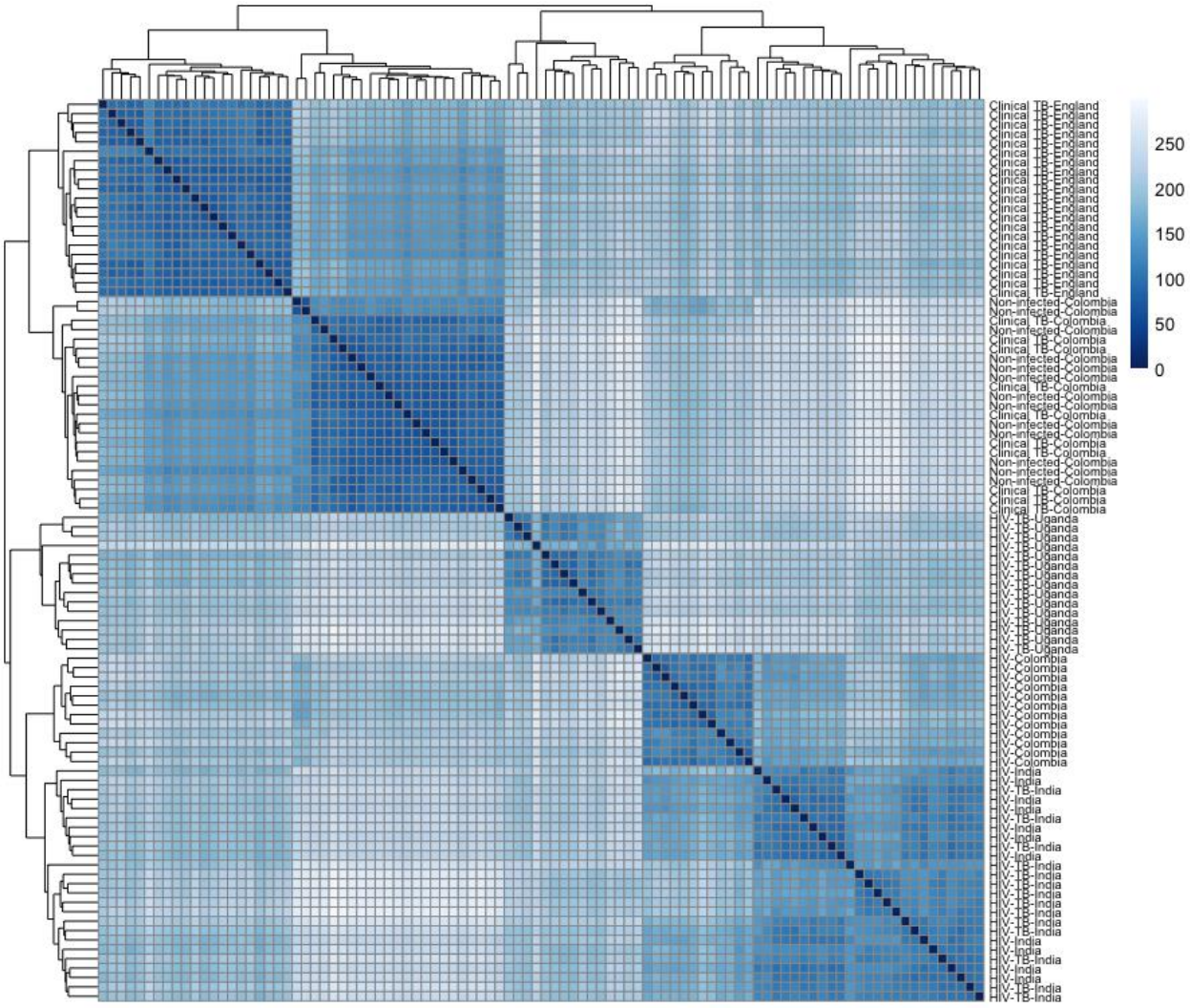


Figure 3.2. Hierarchal heatmap of the sample-to-sample distances before Combat-Seq correction

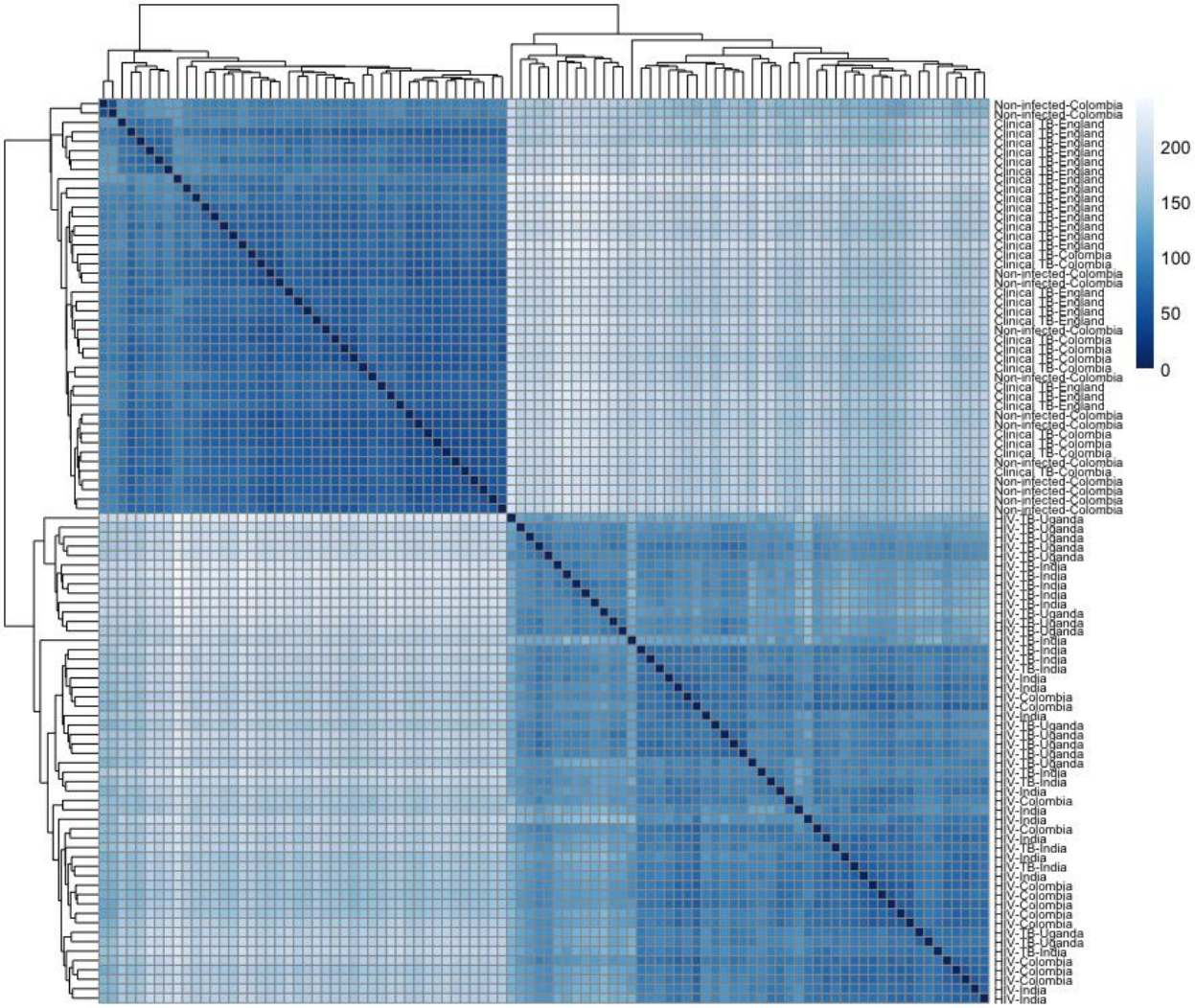


Figure 3.3. Hierarchal heatmap of the sample-to-sample distances after Combat-seq correction

3.2.7 Ethics Declaration

This research was approved by the ethics committees of the University of Manitoba (HS19804 [H2016:218]), Universidad Pontificia Bolivariana (July 15, 2015), and Universidad de Antioquia (approval number 007/2016) in Medellín, Colombia. For the prison cohort, the project received approval from the Instituto Nacional Penitenciario y Carcelario (INPEC) and the directors of each participating prison. Additionally, Hospital Universitario San Vicente Fundación (#16-2016) and Clínica SOMA (#57-2017) approved the study for patients recruited at these institutions.

All study participants provided written informed consent, and sample transportation complied with regulations set by the Ministerio de Salud y Protección Social de Colombia. Individuals diagnosed with tuberculosis and HIV received appropriate treatment and were monitored according to Colombian national guidelines for these diseases.

3.3 Results

3.3.1 Cohort Description

A total of 96 participants were included in the study (Table 3.2), distributed across four cohorts as follows: individuals diagnosed with tuberculosis disease (n =31), HIV (n = 23), tuberculosis among PLHIV (n=29), and non-HIV/non-tuberculosis (n =13). The non-infected group consists of only the Colombia cohort (n =13) with all participants being male, with median age of 32 years. The group diagnosed with HIV (HIV infection without tuberculosis) included participants from both the Colombia cohort (n=12) and India cohort (n=11), with overall sex distribution of 83% male and 17% female, and a median age of 40 years. The group diagnosed with only tuberculosis disease consisted of participants from the Colombia cohort (n = 10) and the United Kingdom cohort (n=21), with an overall sex distribution of 74% male and 26% female, and a median age of 39 years. The group diagnosed with tuberculosis disease and HIV coinfection, included participants from the India cohort (n=14) and the Uganda cohort (n =15), with an overall sex distribution of 58% male and 42% female, and a median age of 41 years.

3.3.2 Differentially Expressed Genes

A total of 10,308 differentially expressed genes were found between all four cohorts (Figure 3.4) with 6,562 upregulated and 3,746 downregulated genes (adjusted p-value < 0.05 & fold change = ±1.5) (Figure 3.4). A total of 3 differential gene comparisons were performed: tuberculosis in PLHIV vs. non-infected, tuberculosis in PLHIV vs. HIV alone, and tuberculosis in PHIV vs tuberculosis alone (Figure 3.5). A total of 246 up-regulated and 196 down-regulated genes were unique to tuberculosis in PLHIV vs. non-infected. 45 up-regulated and 141 down-regulated genes were unique to tuberculosis in PLHIV vs. HIV alone. Lastly, there are 1520 up-regulated and 424 down-regulated genes unique to tuberculosis in PLHIV vs tuberculosis alone comparisons.

3.3.3 Enrichment Analysis

Gene Ontology analysis was performed to investigate the functional roles of significant DEGs and were ranked based on number of genes associated and q-value ≤ 0.05 (Appendix 5 - 7). Among the comparison between tuberculosis PLHIV vs. tuberculosis alone, the most enriched biological processes (BP) included 'muscle contraction', 'cytoplasmic translation'. The top molecular functions (MF) were 'passive transmembrane transporter activity' and 'channel activity', while the most enriched cellular components (CC) included the 'transporter complex' and the 'monoatomic ion channel complex' (Figure 3.6A). For DEGs compared between tuberculosis in PLHIV and HIV alone, key biological processes involved 'regulation of inflammatory response', 'leukocyte migration' and the 'defense response to bacterium'. The most prominent molecular functions were 'peptidase regulator activity' and 'antigen binding', while enriched cellular components included the 'plasma membrane signaling receptor complex' and the 'T cell receptor complex' (Figure 3.6B). Lastly the comparisons between tuberculosis in PLHIV vs. Non-infected, the most enriched biological processes were 'cytoplasmic translation' and 'nucleosome organization'. Molecular function analysis highlighted 'protein heterodimerization activity', 'small GTPase binding, and 'GTPase activator activity,' while cellular component enrichment was involved the 'ribosome' and 'ribosomal subunit' (Figure 3.6C).

Table 3.3. Baseline characteristics of people diagnosed with HIV and/or tuberculosis compared to healthy controls

	TB in PLHIV	HIV	TB	Non-Infected
Sample Size	29	23	31	13
Country	Uganda and India	Colombia and India	Colombia and U.K.	Colombia
Median Age [Range]	41 [18 - 60]	40 [18 - 63]	39 [18 - 78]	32 [19 - 50]
Sex [%]	Male [58%] Female [42%]	Male [83%] Female [17%]	Male [74%] Female [26%]	Male [100%] Female [0%]
HIV Status	Positive	Positive	Negative	Negative
TB Status	Positive	Negative	Positive	Negative
Median CD4 Count (cells/mm3) [IQR]	Uganda: 23 [4 - 105] India: 48 [31 - 65]	Colombia: 261 [38 - 408.75] India: 53 [32 - 75]	~	~
Median Viral Load (Log10 copies/mL) [IQR]	Uganda: not reported India: 5.50 [4.97 - 5.87]	Colombia: 3.95 [3.25 - 5.24] India: 4.92 [4.24 - 5.77]	~	~
Diabetes	Not reported	Colombia: 0 India: not reported	3% [1 out of 31]	0
Smoking	Uganda: not reported India: 5	Colombia: 4 India: 4	Colombia: 5/10 U.K: not reported	Yes: 5 Unknown: 2
BMI median [IQR]	Uganda: not reported India: 17.6 [16.4 - 19.9]	Colombia: 23.2 [20.51 - 25.5] India: 20.0 [16.8 - 21.4]	Colombia: 20.8 [20.1-23.4] UK: not reported	22.6 [21.3–24.9]
BCG [%]	Not reported	Not reported	Yes [74%] No [7%] Unknown [19%]	Yes [82%]
ATTB	No ATTB	~	Colombia: < 5 days of TB	~
ART	Naïve + Experienced	Naïve	~	~

[A] GSE107104 information can be retrieved from Verma et al.[112]

[B] GSE162164 information can be retrieved from Kulkarni et al.[135]

[C] GSE107991information can be retrieved from Singhania et al.[111]

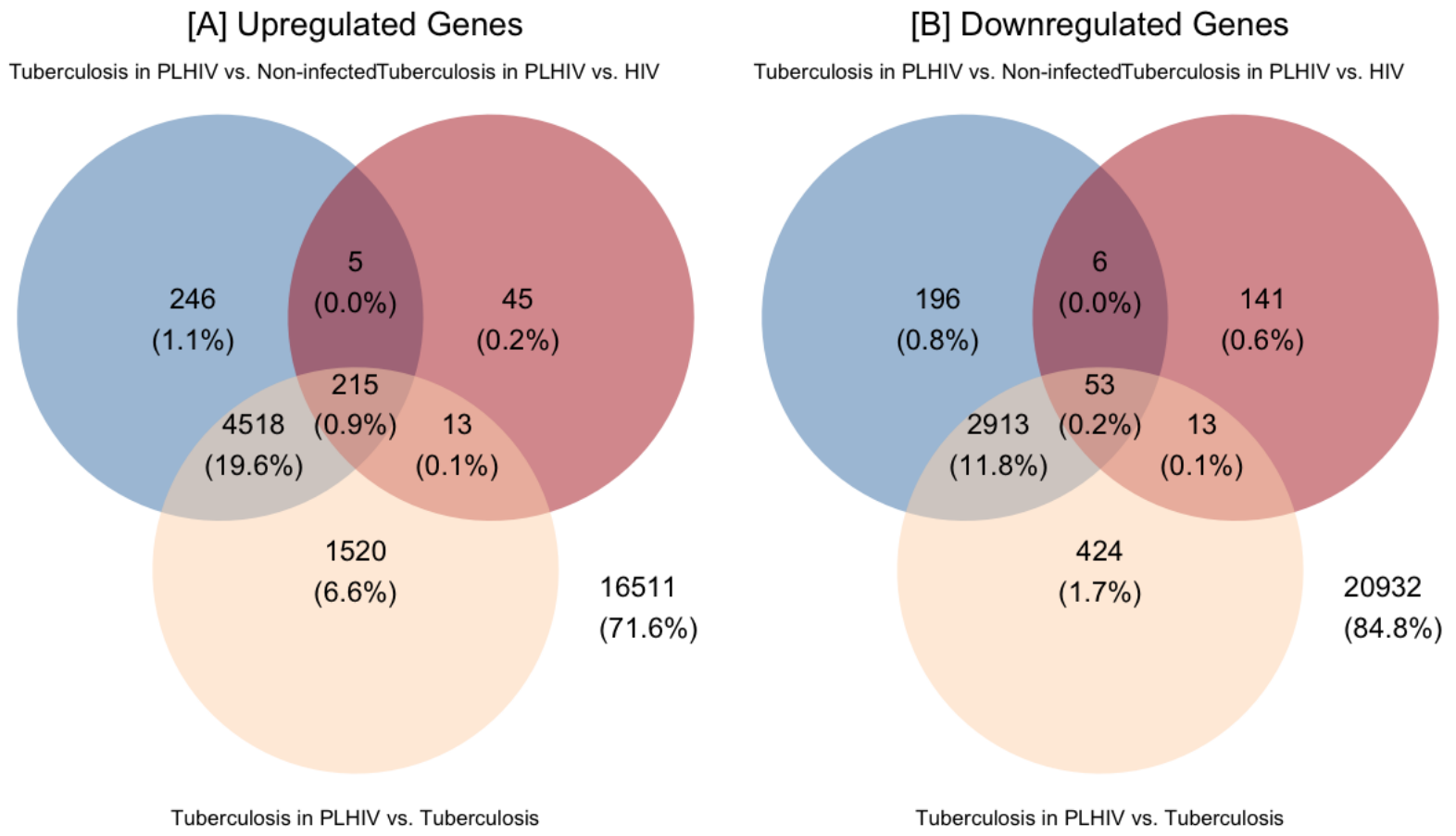


Figure 3.4. Venn diagram depicting the differentially expressed genes of people diagnosed with tuberculosis alone, HIV alone, tuberculosis among PLHIV, and non-HIV/non-tuberculosis cohorts. Participants were recruited from Medellin, Colombia, and retrieved from publicly available data from the United Kingdom, Uganda, and India (GSE107991, GSE107104 and GSE162164)

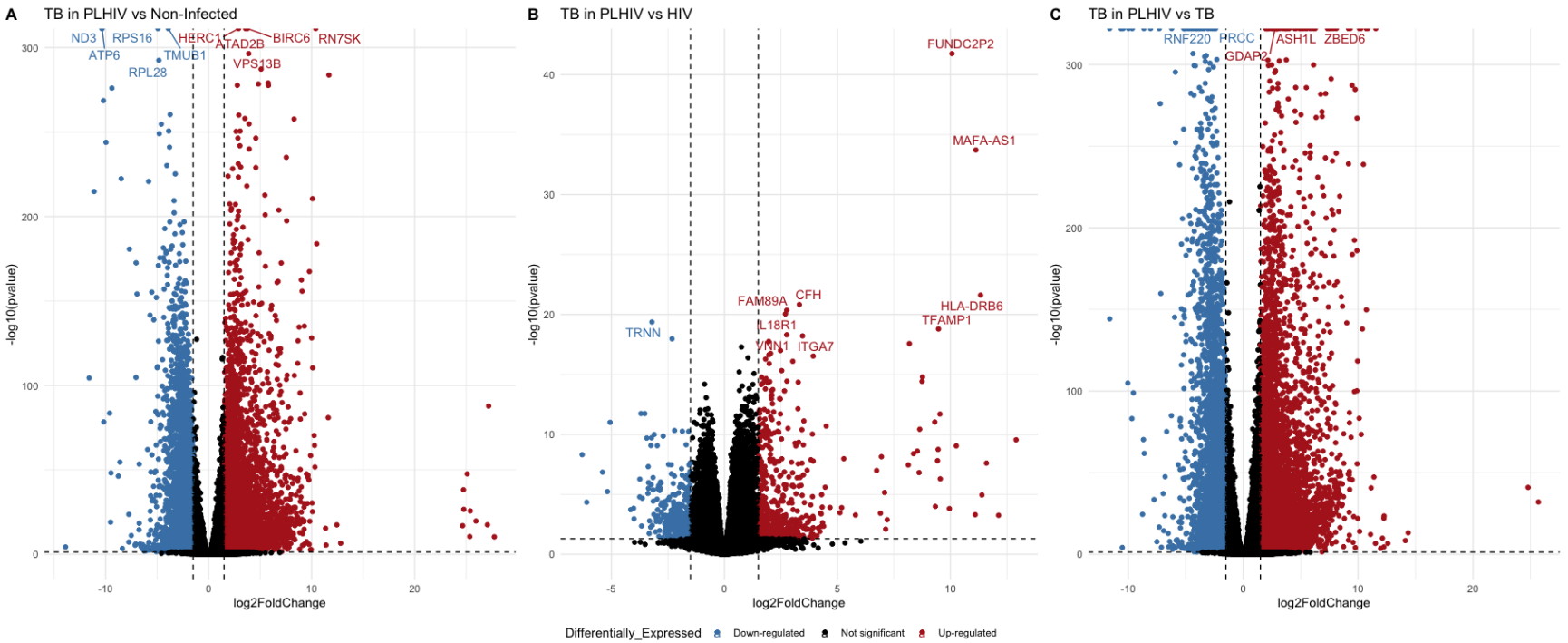


Figure 3.5. Volcano plot depicting differentially expressed genes. [A] Depicts comparison between tuberculosis in people living with HIV and non-infected cohort. [B] Depicts comparison between tuberculosis in people living with HIV and people with HIV alone cohorts. [C] Depicts comparison between tuberculosis in people living with HIV and people diagnosed with tuberculosis alone cohorts. The labelled genes are the top differentially expressed genes based on parameters logFC ± 1.5 and adjusted p value of ≤ 0.05

3.3.4 Candidate Gene Biomarkers for Tuberculosis in PLHIV

To identify genes consistently associated with tuberculosis, the presence of each gene that was shared across all conditions were analyzed across multiple published gene signatures. A total of six genes; GBP6, DHRS9, GBP5, CD274, FCGR1A, and ANKRD22, were found in at least 10 tuberculosis associated gene signatures (Figure 3.7). Notably, GBP6, GBP5, and FCGR1A were the most frequently identified genes, appearing in over 15 signatures, whereas DHRS9, CD274, and ANKRD22 were present in at least 10 signatures.

Assessment of normalized gene expression levels showed that all 6 genes were overexpressed in the tuberculosis in PLHIV cohort compared to the other 3 cohorts (Figure 3.8). Reactome pathway enrichment analysis of the candidate gene biomarkers (Table 3.4) revealed a dominant interferon-driven immune signature, with interferon gamma signaling and interferon signaling (GBP5, GBP6, FCGR1A) as the most significantly enriched pathways. Additional enrichment was observed in cytokine signaling in the immune system and broader immune system pathways. CD274 was linked to immune regulatory pathways, including PD-1 signaling, while FCGR1A was associated with antigen cross-presentation. DHRS9 was enriched in retinoid metabolism pathways.

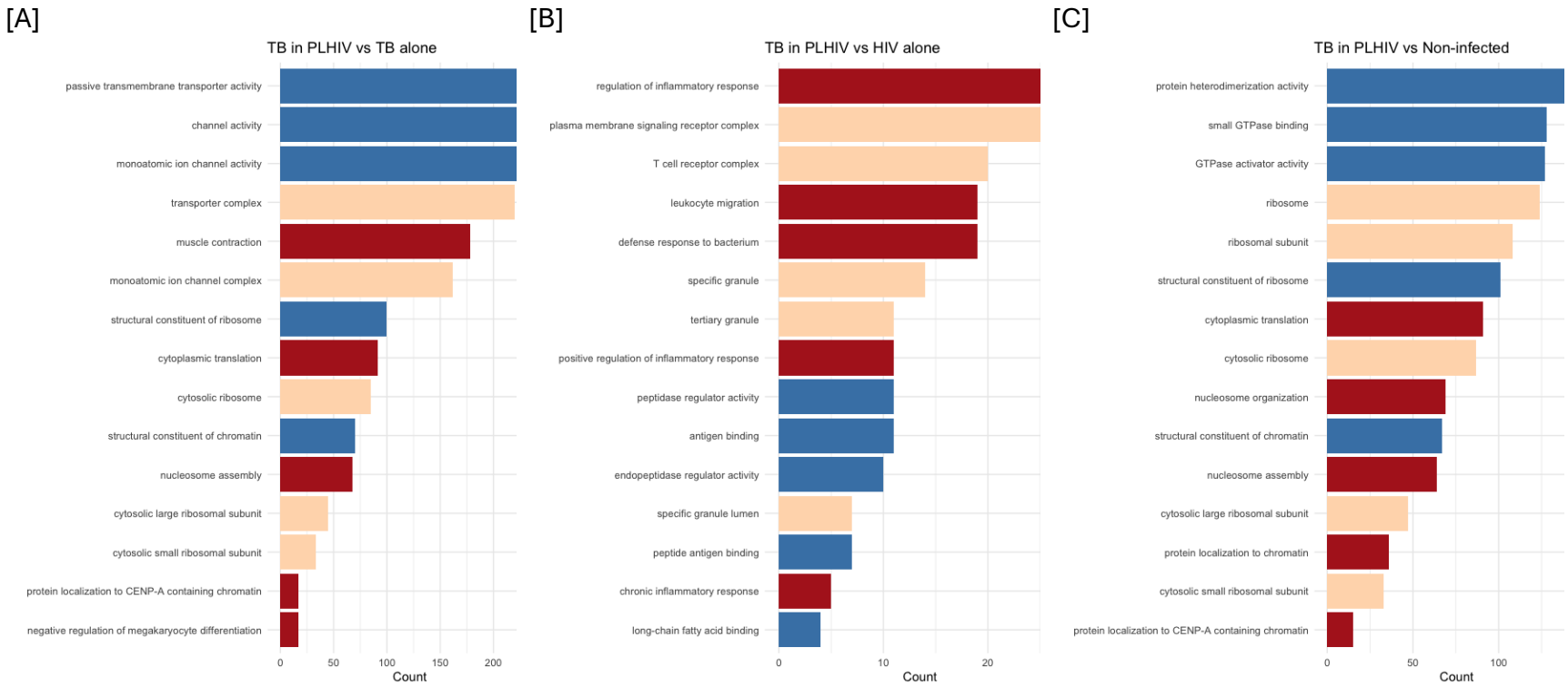


Figure 3.6. Gene Ontology enrichment analysis of DEGs shared across study cohorts. (A) tuberculosis in PLHIV vs. tuberculosis alone, (B) Tuberculosis in PLHIV vs. HIV alone, and (C) tuberculosis in PLHIV vs. non-infected. The x-axis represents the number of genes associated with each GO term, and the y-axis lists the significantly enriched GO terms.

*[BP] Biological Process; [CC] Cellular Component; [MF] Molecular Function

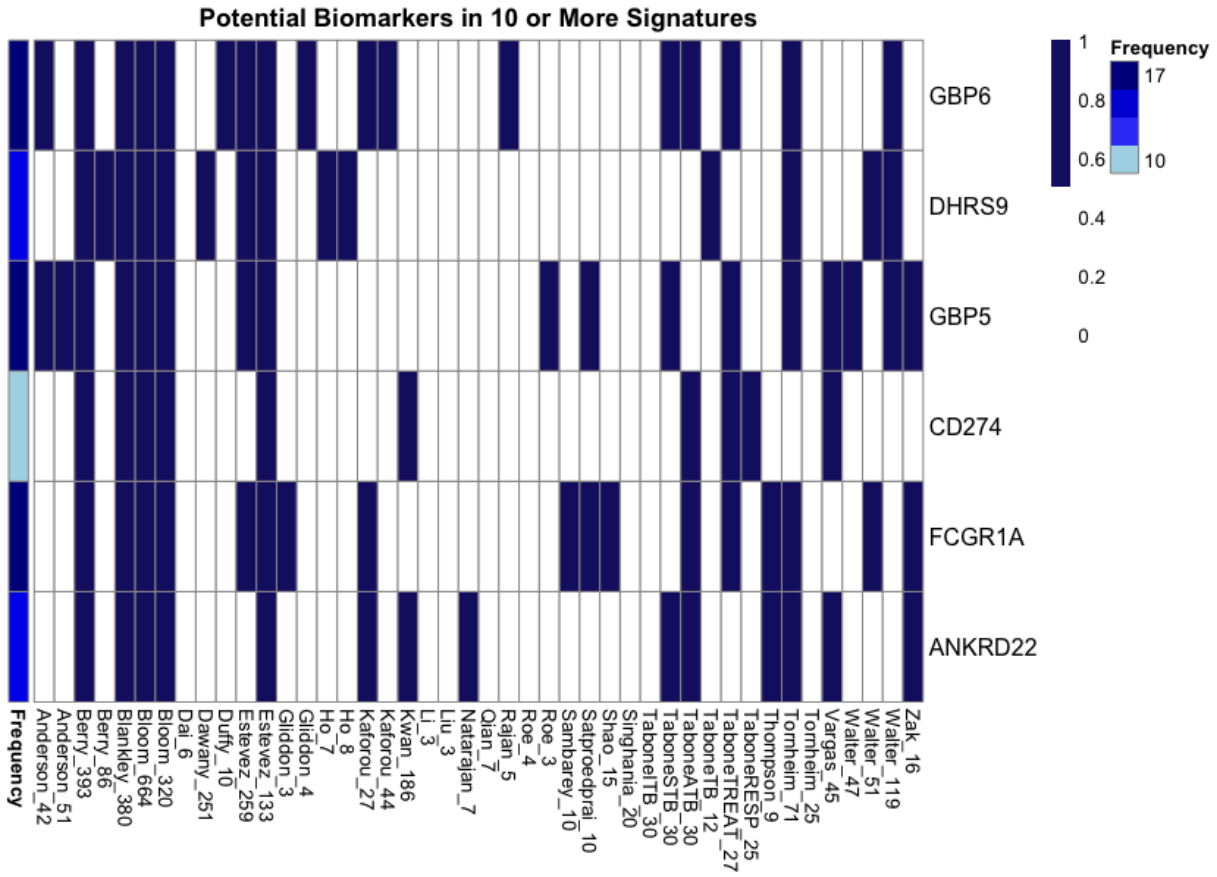


Figure 3.7. Consensus biomarkers identified in 10 or more tuberculosis gene signatures

Table 3.4. Top 10 Reactome pathways enrichment analysis of candidate gene biomarkers

Genes	Name	Adjusted p-value
GBP5, GBP6, FCGR1A	Interferon Gamma Signaling	7.68E-05
GBP5, GBP6, FCGR1A	Interferon Signaling	0.000868
GBP5, GBP6, FCGR1A	Cytokine Signaling in Immune System	0.01172
GBP5, GBP6, FCGR1A, CD274	Immune System	0.01378
CD274	STAT3 Nuclear Events Downstream of ALK Signaling	0.02175
DHRS9	The Canonical Retinoid Cycle in Rods (Twilight Vision)	0.03103
DHRS9	RA Biosynthesis Pathway	0.03103
CD274	Signaling by ALK	0.03288
CD274	PD-1 Signaling	0.03288
FCGR1A	Cross-presentation of Soluble Exogenous Antigens (Endosomes)	0.03647

*Adjusted p-value is calculated via Benjamini Hochberg method

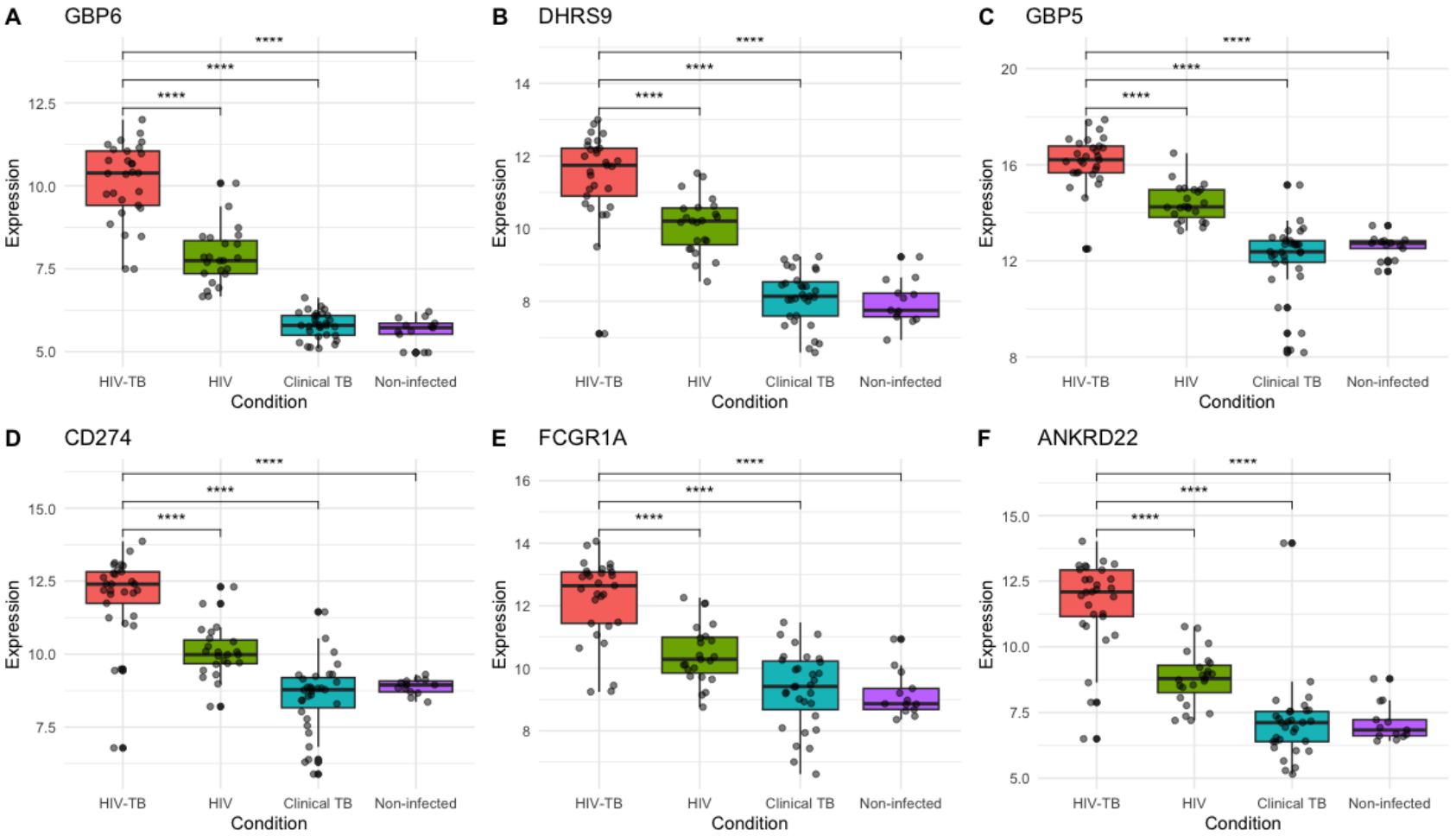


Figure 3.8. Gene expression of potential tuberculosis biomarkers across conditions.
*Statistical comparisons via Wilcox test: [ns]: p > 0.05, [*]: p ≤ 0.05, [**]: p ≤ 0.01, [***]: p ≤ 0.001, [****]: p ≤ 0.0001

3.4 Discussion

In this study, we investigated gene expression differences across individuals with tuberculosis disease in PLHIV, HIV alone, tuberculosis disease, and non-infected controls. Our cohorts in Colombia, were supplemented by previously published datasets: GSE107991, GSE107104, and GSE162164. Our findings investigated the transcriptional profiles associated with each condition, revealing both shared and unique DEGs using DESeq2 for differential expression analysis and ggplot package for visualization. Gene enrichment analyses and systematic biomarker identification provided insights into the molecular pathways underlying tuberculosis disease in PLHIV.

3.4.1 Differential Expression and Enrichment Analysis

Our analysis identified 10,308 DEGs across all conditions (Figure 3.4), with notable differences between tuberculosis in PLHIV and the other cohorts (adjusted p-value < 0.05 & fold change = ±1.5). The greatest number of unique DEGs was found in the comparison of tuberculosis in PLHIV versus tuberculosis alone with 1520 up-regulated and 424 down-regulated genes (Figure 3.4). This suggests that HIV infection significantly alters the host response to *M. tuberculosis,* potentially explaining the increased susceptibility and disease progression in co-infected individuals.

Enrichment analyses further highlighted key biological processes involved in disease pathogenesis (Figure 3.6). The tuberculosis disease in PLHIV vs. HIV aimed to examine the impact of tuberculosis disease on individuals living with HIV. Immune-related pathways were significantly enriched, including regulation of inflammatory response, leukocyte migration, and defense response to bacteria. These findings suggest that tuberculosis infection in PLHIV induces a shift in immune system activation, possibly counteracting HIV-driven immune dysregulation. The purpose of comparing tuberculosis disease in PLHIV vs. non-infected is to investigate the interaction of HIV and tuberculosis which highlighted biological processes related to cytoplasmic translation and nucleosome organization, as well as molecular functions related in GTPase activity, which may reflect broader systemic immune activation in response to tuberculosis.

3.4.2 Identification of Candidate Gene Biomarkers

To identify potential biomarkers of tuberculosis in PLHIV, we assessed the presence of DEGs across multiple published gene signatures. Six genes: GBP6, DHRS9, GBP5, CD274, FCGR1A, and ANKRD22 were found in at least 10 tuberculosis-associated gene signatures (Figure 3.7). Among these, GBP6, GBP5, and FCGR1A were the most frequently reported, appearing in over 15 signatures.

The normalized gene expression of the 6 candidate genes shows up-regulation of these genes compared to the other 3 cohorts: tuberculosis disease alone, HIV alone, and non-infected (Figure 3.8). Interestingly, the 6 genes were not significantly up-regulated in tuberculosis disease cohorts, however in the context of HIV coinfection, they were up-regulated. This implies that HIV plays a role in the expression of these genes in people with tuberculosis disease.

GBP6 and GBP5 play a role in innate immunity against intracellular pathogens by eliciting pro-inflammatory responses, mainly IFNs[169]. A study showed that GBP5 interferes with HIV viral replication, and high GBP5 levels in host macrophage correlates to low infectivity of HIV[210]. CD274 or PD-L1 is a key immune checkpoint molecule, known to play a significant role in HIV infection and T cell exhaustion[211,212]. FCGR1A has been associated with monocyte and macrophage activation, which is critical for pathogen clearance[213]. DHRS9 have been reported as a marker for human regulatory macrophages[214]. ANKRD22 expression has been linked to chronic HIV infection in both macrophages and T cells[215]. ANKRD22 and DHRS9 have been associated with immune response however further exploration in their roles to tuberculosis and HIV interactions is needed.

Reactome pathway enrichment of the candidate biomarkers (Table 3.5) shows that GBP5, GBP6, FCGR1A, and CD274 cluster within interconnected pathways, including interferon and cytokine signaling in the immune system – indicating they form a coordinated immune response module. In this network, GBP5, GBP6, and FCGR1A contribute to macrophage activation and antimicrobial responses, while CD274 provides an immune checkpoint mechanism that may restrain excessive inflammation. In contrast, DHSR9 was enriched in retinoic acid metabolism pathways, and ANKRD22 showed

minimal overlap with the interferon-driven module, suggesting that these two genes act largely independently from the four interferon-driven genes, contributing metabolic and tissue-specific modulatory functions.

In summary, four of the identified biomarkers (GBP5, GBP6, FCGR1A, and CD274) form an interferon-mediated immune module, while DHRS9 and ANKRD22 appear to function more independently in supporting or modulatory roles.

3.5.3 Limitations

Despite the strengths of this study, several limitations should be considered when interpreting the findings. First, the sample size was limited, particularly for the non-infected cohort, which consisted only of participants from the Colombia cohort. This may impact the generalizability of the findings to broader populations.

Second, while batch effects related to ethnicity and genetic background were controlled using ComBat-Seq, and tissue type was accounted for in the DESeq2 model, some residual variability may remain. These adjustments reduce confounding, but subtle population-specific differences in immune responses or gene expression, potentially arising from unmeasured genetic ancestry, may still influence the findings.

Additionally, the datasets for the different groups (tuberculosis in PLHIV, tuberculosis only, HIV only and non-infected cohorts) were largely non-overlapping in terms of collection site and period. This lack of overlap may introduce bias, as differences between groups could partially reflect geographic, or cohort-specific factors that may influence gene expression independently of disease status. Moreover, differences in the time and context of sample collection across cohorts may have contributed to variability in gene expression. For example, United Kingdom samples, were collected in 2007, whereas Uganda, India and Colombia samples were collected in the later years, in 2013, 2018-2019, and 2016-2018, respectively. Such time differences also reflect a difference in diagnostic practices, and public health interventions over time. Furthermore, factors such as antiretroviral therapy regiments, viral load, bacterial load, and tuberculosis treatment

protocols likely varied across sites and collection periods, further contributing to biological variability that could not be fully accounted for in the analysis.

Third, this study focused solely on gene expression analysis without incorporating protein expression. While the identified gene biomarkers are consistently associated with tuberculosis across multiple published signatures, further studies are needed to assess their functional relevance and potential clinical utility.

3.5 Conclusion

Our study provides a comprehensive transcriptomic analysis of tuberculosis in PLHIV, identifying key differentially expressed genes, enriched biological pathways, and potential biomarkers. The upregulation of genes such as GBP6, DHRS9, GBP5, CD274, FCGR1A, and ANKRD22 suggests a distinct immune activation state in tuberculosis in PLHIV, which could serve as a basis for future tuberculosis biomarker diagnostics. These findings contribute to a growing body of evidence highlighting the complex interplay between tuberculosis and HIV and highlights the need for further research on tuberculosis and HIV pathogenesis.

CHAPTER IV: FINAL DISCUSSION AND FUTURE DIRECTIONS

4.1 Final Discussion

This Masters project combines a scoping review of tuberculosis host blood RNA biomarkers with a primary transcriptomic analysis of tuberculosis in PLHIV. The scoping review identified 60 tuberculosis gene signatures comprising a total 1,939 genes overall, with 15 genes frequently appearing across multiple studies. The review highlighted methodological differences between RNA-Seq and microarray-based studies, the predominance of whole blood samples, and the underrepresentation of diverse populations especially in high tuberculosis burden countries in biomarker discovery.

In the primary study, transcriptomic data from four cohorts—tuberculosis in PLHIV, tuberculosis alone, HIV alone, and non-infected individuals—revealed 10,308 DEGs. Six genes (GBP6, DHRS9, GBP5, CD274, FCGR1A, and ANKRD22) were consistently associated with tuberculosis in PLHIV and overlapped with at least 10 previously published gene signatures. Functional enrichment analysis revealed pathways linked to immune activation and inflammatory responses, further reinforcing their potential as biomarkers. The integration of these findings suggests that while transcriptomic biomarkers hold promise for tuberculosis diagnostics, key challenges remain, particularly in methodology standardization, cohort diversity, and validation across different populations.

4.1.1 Potential Biomarkers

The identification of 15 frequently reported genes in the scoping review paper and the 6 frequently reported genes in the primary paper further reinforces the argument for potential diagnostic biomarker utility. The six genes GBP6, DHRS9, GBP5, CD274, FCGR1A, and ANKRD22 were both reported in our findings in both the review and primary paper. GBP5 and GBP6 help trigger immune responses through interferon activation, which plays a key role in immune response to tuberculosis. CD274 (PD-L1) is involved in immune suppression and could impact how tuberculosis progresses in people living with HIV.

FCGR1A, a high-affinity Fc receptor, is linked to the body's immune reaction to tuberculosis, making it a promising biomarker for detecting and tracking the disease.

4.1.2 Connecting the Goals of the Scoping Review and Primary Paper

The scoping review and primary study are connected, being able to complement and reinforce each other in multiple ways. The scoping review provided a broad analysis of tuberculosis host blood RNA biomarkers, identifying 60 gene signatures and highlighting gaps in methodological approaches, cohort diversity, and validation. A key research gap identified in the review was the predominance of microarray-based studies and the lack of representation from high tuberculosis burden countries and from Latin American countries, particularly in biomarker discovery.

The primary gene expression analysis addressed these gaps by utilizing RNA-Seq data from geographically diverse cohorts, including Colombia, and previously published cohorts from Uganda, India, and the United Kingdom.

From the primary study, six genes (GBP6, DHRS9, GBP5, CD274, FCGR1A, and ANKRD22) were consistently differentially expressed in tuberculosis in PLHIV cases and overlapped with at least 10 previously identified gene signatures from the scoping review. This overlap reinforces the reproducibility of transcriptomic biomarkers across different datasets and methodologies.

4.1.3 Adjusting for Cohort and Geographic Effects

The cohorts included in this study were selected to capture tuberculosis and HIV immune responses across different geographic regions and likely genetic backgrounds, ensuring a broader understanding of disease-associated transcriptional changes. The Colombian cohorts encompassed tuberculosis, HIV, and non-infected individuals, enabling comparisons within a single population. The Indian HIV cohorts provided additional insights into HIV-associated immune responses in a distinct regional setting[135]. The Ugandan cohorts, which included tuberculosis and HIV co-infected individuals, were critical for examining immune dysregulation in a high-burden population[112]. The United

Kingdom tuberculosis cohort, from the Berry et al. study that identified the 393-gene tuberculosis transcript[106,111], was included as a reference for tuberculosis-associated gene expression in a lower-burden setting. The Berry study also incorporated a diverse participant pool, making it particularly valuable for investigating transcriptional responses across different ancestries[106].

Because geographic origin can be associated with both genetic background and technical variation, cross-cohort comparisons risk confounding from "site effect" that are unrelated to disease biology. ComBat-Seq, which applies an empirical Bayes framework[205], was used to adjust for batch differences linked to collection site, which may also reflect demographic or ancestry-related variation, while retaining disease-specific signals. This approach improved cross-cohort comparability and ensured that observed gene expression differences were more reflective of tuberculosis and HIV pathogenesis rather than site-related or demographic differences. By integrating geographically diverse cohorts and reducing site- and ancestry-correlated effects, this study enhances the generalizability of transcriptomic findings in tuberculosis and HIV research.

4.1.4 Addressing the Hypothesis

The findings of my Master's thesis project provide strong support for the initial hypothesis that a distinct set of genes is involved in tuberculosis progression in PLHIV, including previously identified genes such as GBP5 and BATF2. The scoping review confirmed the presence of commonly identified biomarkers across multiple studies, reinforcing their potential utility in tuberculosis biomarkers in diagnostics. Additionally, the transcriptomic analysis identified differentially expressed genes and enriched pathways unique to tuberculosis in PLHIV, supporting the notion that there are both shared and unique molecular mechanisms at play in co-infected individuals. The first aim, to review tuberculosis gene biomarker studies, was successfully addressed by identifying common tuberculosis-associated biomarkers across RNA-Seq and microarray studies, highlighting both methodological differences and the need for standardized approaches in transcriptomic biomarker research. The second aim, identifying the gene expression profile

of tuberculosis in PLHIV, was met through the discovery of six key genes consistently differentially expressed in tuberculosis in PLHIV cases, some of which overlapped with previous studies. The third aim, analyzing gene functions and pathways associated with tuberculosis in PLHIV, was addressed by pathway enrichment analysis. Key findings included upregulation of inflammatory response pathways, leukocyte activation, and T-cell receptor signaling, which are indicative of active immune engagement. Together, these findings support the study's hypothesis and highlight the potential for transcriptomic biomarkers in tuberculosis diagnostics.

4.1.5 Combining Whole-Blood and PBMC Samples for Gene Expression Analysis

Gene expression profiling of tuberculosis PLHIV requires approaches that account for both systemic immune responses and cell-type-specific mechanisms. Whole-blood and PBMC RNA-Seq can offer complementary insights into host immune responses, with each sample type capturing distinct immune cell populations and transcriptional profiles. Integrating these approaches may enhance diagnostic accuracy, improves biomarker validation, and provides a more comprehensive understanding of tuberculosis and HIV coinfection immunopathogenesis.

Whole-blood RNA-seq captures transcriptional signatures from all circulating immune cells, including granulocytes and platelets, which are excluded in PBMC isolation. This broad immune coverage is critical for detecting systemic inflammation and innate immune activation patterns, which play a central role in tuberculosis and HIV coinfection[112,144]. In contrast, PBMC RNA-seq focuses on lymphocytes and monocytes, key mediators of adaptive immunity, providing a more refined view of T-cell and macrophage dysfunction[120,154,216], and potentially including HIV-driven CD4+ T cell depletion and tuberculosis-specific immune exhaustion.

4.1.6 Overall Limitations of the Masters Project

This Masters project offers important insights in transcriptomics and biomarker discovery studies associated with tuberculosis; however, some limitations are needed to be considered when interpreting the findings.

The scoping review (Chapter II) did not specifically address comorbidities like HIV and diabetes, which may impact biomarker expression, nor did it include drug-resistant tuberculosis, potentially missing key biomarkers. Additionally, the search: (screening, full-text review and data extraction) was conducted by a single reviewer, which may have introduced selection bias during study screening and data extraction despite efforts to apply eligibility criteria consistently. The search strategy was limited to peer-reviewed literature indexed in selected databases; no grey literature sources (e.g. conference proceedings, dissertations, preprints) were included, potentially excluding relevant unpublished or non-indexed studies. Furthermore, manual reference list screening of included articles was not performed, which may have led to omission of additional eligible studies cited in the literature. These factors could limit the comprehensiveness and completeness of the evidence base capture in this review.

In the primary study (Chapter III), the small sample size, especially for the non-infected group, may affect the generalizability of results. Although batch effects related to cohort and tissue type were adjusted for, some variability may remain. Importantly, the absence of genotype data prevented precise adjustment for genetic ancestry. This means that some observed differences in gene expression could partly reflect population structure or ancestry-related immune response differences rather than disease effects alone. A further limitation is that the datasets for the four groups: tuberculosis in PLHIV, tuberculosis only, HIV only, and non-infected, were largely non-overlapping in both collection site and period. This lack of overlap introduces potential bias, as differences in gene expression may partly reflect geographic, cohort-specific, or time factors rather than true disease-related expressions. For instance, United Kingdom samples were collected in roughly in 2007, whereas samples from Uganda, India, and Colombia were obtained between 2013 and 2019. These differences in collection periods coincide with changes in

diagnostic practices, public health interventions, antiretroviral therapy regimens, and tuberculosis treatment protocols, which could influence gene expression patterns.

Finally, this Masters project focused solely on transcriptomic data without incorporating protein-level validation. While the identified gene biomarkers are consistently associated with tuberculosis across multiple published signatures, further research including proteomic and functional studies is needed to confirm their biological relevance and assess their potential clinical utility.

4.1.6 Strengths of the Masters Project

Despite the limitations, this Masters project has several notable strengths. The scoping review (Chapter II) synthesized evidence on transcriptomic biomarkers for tuberculosis across diverse study designs, populations, and analytical platforms. By mapping findings from multiple geographic regions and methodological approaches, the review identified recurrent gene signatures and highlighted gaps and opportunities for future tuberculosis biomarker development.

In the primary study (Chapter III), the use of RNA sequencing data from well-characterized cohorts allowed for a rigorous assessment of gene expression patterns across multiple groups. The inclusion of both whole-blood and PBMC datasets provided broader coverage of immune cell-specific and systemic transcriptional responses. The utilization of DESeq2 and ComBat-Seq, helped minimize technical variability and ensure comparability between datasets.

A key strength is that several of the differentially expressed genes identified in this study were also consistently reported in over ten independent studies, including those describing the 6 candidate biomarkers (Chapter III). This strong consistency with prior literature enhances confidence in the biological relevance of these findings and suggests that they are robust across diverse populations and study designs.

Finally, the combined approach of a scoping review and primary transcriptomic analysis offers a unique integration of evidence synthesis and original data generation. This

dual strategy not only contextualizes the study findings within the broader biomarker literature but also provides a more nuanced understanding of the biological and clinical relevance of the identified genes.

4.2 Future Directions

Future transcriptomic studies focusing on recruitment of cohorts on high tuberculosis burden countries such as India, Indonesia, China, Philippines, Pakistan, Nigeria, Bangladesh and the Democratic Republic of the Congo are needed, while keeping the COVID-19 pandemic in mind to stay up-to-date and relevance with tuberculosis biomarkers research. The expansion of population diversity in tuberculosis biomarker research could improve the applicability and generalizability of biomarkers across different ethnic groups and genetic backgrounds.

Tuberculosis is now defined as a spectrum, with the additional classification of incipient, minimal, and subclinical tuberculosis disease, which should be considered in future diagnostic studies. The findings in the scoping review (Chapter II) presses for guidelines for data preprocessing, normalization, and differential expression analysis to be established to facilitate cross-study comparisons. Furthermore, studies should report key technical details, such as RNA extraction methods and sequencing depth, to enhance reproducibility and transparency.

To strengthen the approach used in the primary study (Chapter III), future work could integrate overlapping datasets for each phenotype, thereby reducing potential bias introduced by non-overlapping cohorts and enabling more robust within-subject comparisons. Increasing the sample size for underrepresented phenotypes, such as tuberculosis in PLHIV, and non-infected cohorts, would improve the statistical power. Incorporating longitudinal sampling could further reveal dynamic gene expression changes through disease progression and treatment.

The six candidate genes identified in this study (GBP6, DHRS9, GBP5, CD274, FCGR1A, and ANKRD22) were consistently reported in previous transcriptomic studies, highlighting their potential biological relevance. However, their diagnostic utility should be validated in larger and more diverse populations, including individuals from different geographic regions and genetic backgrounds. The identified genes should be tested in combination as part of a transcriptomic signature for tuberculosis detection in PLHIV. Additionally, machine learning approaches could identify the predictive power of the signature in other previously published datasets to further strengthen the validity of these genes. Experimental validation using targeted assays such as qRT-PCR, should also be pursued to complement computational findings.

Ultimately, the goal of transcriptomic biomarkers is to develop a rapid, blood-based diagnostic tests suitable for clinical and low-resource settings. The integration of diverse cohorts, rigorous validation, and translational application will be critical to advancing these biomarkers toward clinical implementation.

CHAPTER V: REFERENCES

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CHAPTER VI: APPENDIX

Appendix 1. Scoping review codes (R script)

```
World Map Code
setwd("~/Desktop/Review Paper")

library(ggplot2)
library(rworldmap)
library(dplyr)
library(sf)

# Get a world map as an sf (simple features) object
world_map <- st_as_sf(getMap(resolution = "low"))

# Merge your study data with the world map data
data <- read.csv('Map_data.csv')

map_data <- world_map %>%
 left_join(data, by = c("NAME" = "Country"))

# Plot the map
ggplot(map_data) +
          geom_sf(aes(fill = Frequency)) +  # Fill countries by study frequency
          scale_fill_gradient(low = "peachpuff", high = "firebrick", na.value = "white") +
          labs(fill = "Study Frequency", title = "Geographical Frequency of Host Blood
         Gene Biomarker Studies for Tuberculosis") +
          theme_minimal() +
          theme(axis.text = element_blank(), axis.ticks = element_blank(), panel.grid =
         element_blank())

Venn Diagram
setwd("~/Desktop/Review Paper")

library(VennDiagram)
library(ggvenn)
library(ggplot2)
library(ggsignif)
library(ggpubr)

# Step 1: Load your CSV file
# Replace 'your_file.csv' with the path to your dataset
Microarray_list <- read.csv("Microarray.csv", header = TRUE, stringsAsFactors = FALSE)
RNA_seq_list <- read.csv("RNA-Seq.csv", header = TRUE, stringsAsFactors = FALSE)
```

```
Whole_blood_list <- read.csv( "Whole-blood.csv" , header = TRUE, stringsAsFactors =
FALSE)
PBMC_list <- read.csv("PBMC.csv", header = TRUE, stringsAsFactors = FALSE)

# Step 2: Combine all genes from the dataset into a single unique list
Array_unique_genes <- unique(unlist(Microarray_list))
Seq_unique_genes <- unique(unlist(RNA_seq_list))
Whole_unique_genes <- unique(unlist(Whole_blood_list))
PBMC_unique_genes <- unique(unlist(PBMC_list))


Methodology <- list(Array = Array_unique_genes, RNASeq = Seq_unique_genes)

v1 <- ggvenn(Methodology,
         fill_color = c("steelblue", "firebrick"),
         stroke_color = "transparent",
         set_name_size = 4.5,
         text_size = 6) +
        ggtitle( "Methodology" ) +
        theme(plot.title = element_text(size = 20, hjust = 0.5))

Tissue <- list(Whole_blood = Whole_unique_genes, PBMC = PBMC_unique_genes)

v2 <- ggvenn(Tissue,
         fill_color = c("steelblue", "firebrick"),
         stroke_color = "transparent",
         set_name_size = 4.5,
         text_size = 6) +
         ggtitle("Tissue") +
         theme(plot.title = element_text(size = 20, hjust = 0.5))

venn <- ggarrange(v1, v2,
             ncol = 1, nrow = 2, common.legend = TRUE, legend= "bottom")
venn

# Overlap between Array and RNASeq
overlap_list1 <- intersect(Methodology$Array, Methodology$RNASeq)
overlap_methodology <- as.data.frame(overlap_list1) # Genes common to Array and
RNASeq

# Overlap between Whole blood and PBMC
overlap_list2 <- intersect(Tissue$Whole_blood, Tissue$PBMC)
overlap_tissue <- as.data.frame(overlap_list2) # Genes common to Array and RNASeq
```

```
# Saving overlap files in csv for supplemental
write.csv(overlap_methodology, "overlap_methodology.csv", row.names = FALSE)
write.csv(overlap_tissue, "overlap_tissue.csv", row.names = FALSE)

Binary Matrix
setwd("~/Desktop/Review Paper")

# Load necessary libraries
library(tidyr)
library(dplyr)
library(ggplot2)
library(pheatmap)
library(tibble)

#Binary matrix
# Step 1: Load your CSV file
# Replace 'your_file.csv' with the path to your dataset
data <- read.csv("Sample.csv", header = TRUE, stringsAsFactors = FALSE)

# Step 2: Combine all genes from the dataset into a single unique list
unique_genes <- unique(unlist(data))

# Step 3: Remove empty entries or NAs from the unique gene list
unique_genes <- unique_genes[unique_genes != "" & !is.na(unique_genes)]

# Step 4: Create a binary matrix
binary_matrix <- sapply(data, function(column) {
  as.integer(unique_genes %in% column)  # Check if each unique gene is in the column
})

# Step 5: Assign row names (unique genes) and column names
rownames(binary_matrix) <- unique_genes
colnames(binary_matrix) <- colnames(data)

# Step 6: Convert to a data frame (optional)
binary_matrix_df <- as.data.frame(binary_matrix)

# Step 7: Save the binary matrix to a CSV file (optional)
write.csv(binary_matrix_df, "binary_matrix.csv", row.names = TRUE)

# Step 8: View the result
print(binary_matrix_df)

#heatmap ####
```

```
# Assume 'binary_matrix' is your binary dataset
# Rows are genes, columns are signatures (0 or 1)

# Calculate gene frequency
gene_frequency <- rowSums(binary_matrix)

# Filter genes listed in 10 or more signatures
filtered_genes <- names(gene_frequency[gene_frequency >= 10])
filtered_binary_matrix <- binary_matrix[filtered_genes, ]

# Create a data frame for annotation
row_annotation <- data.frame(Frequency = gene_frequency[filtered_genes])
rownames(row_annotation) <- filtered_genes

# Define custom colors for frequency
annotation_colors <- list(
          Frequency = colorRampPalette(c("lightblue", "blue",
         "darkblue"))(max(row_annotation$Frequency)))

# Create a heatmap with row annotations
pheatmap(filtered_binary_matrix,
      color = c( "white" , "midnightblue" ),
      cluster_rows = FALSE,
      cluster_cols = FALSE,
      main = "Genes in 10 or More Signatures",
      annotation_row = row_annotation, # Add annotation
      annotation_colors = annotation_colors, # Custom color
      fontsize_row = 12,
      fontsize_col = 10)

view(filtered_genes)
```

Appendix 2. PBMC Extraction Protocol

1. **OBJECTIVE:** The objective of this experiment is to perform total RNA extraction in human PBMC samples.

2. **PURPOSE:** RNA carries all the genetic information in host and pathogens. Performing total RNA extraction would isolate all RNA from the samples, which can then be used for RNA sequencing analysis.

3. **LABORATORY SAFETY:** RNAs are extremely sensitive and exerting extra precaution is crucial to make sure RNA does not degrade due to the presence of RNase everywhere
   - All work with RNA must be done in the biosafety cabinet that is properly cleaned (refer to procedure A)
   - Gloves and lab coats must be worn at all times
     - Gloves must be disinfected with ethanol and/or RNAZap before handling RNA samples

4. **MATERIALS AND EQUIPMENTS:**

<u>Materials</u>

- Water Bath
- Small and large racks
- Microcentrifuge
- Vortex
- RNAZap
- Microchem
- 70% ethanol
- Pipettes
  - (1-10 µL; 20-200 µL; 100-1000 µL)
- Tubes (1.5 mL; 0.6 mL)
- Falcon (50 mL [waste]; 15 mL [reagents])
- Biohazard waste container to discard tips
- Cleaning paper
- Gloves
- Markers – pens
- Chronometer
- Ice box for transporting samples
- Prepared DNase
- Parafilm paper

<u>Commercial kits</u>

- RNeasy plus mini kit, QIAGEN
- DNase, RNase-free, QIAGEN
- Qubit, RNA Quantification, high sensitivity (4-200 ng)
- RNA ScreenTape Analysis

5. **PROCEDURE**

   a. **CLEANING**

   Clean all work surfaces, supplies (externally), and instruments using the following:

   1) Michrochem, leave for 5 minutes
   2) 70% ethanol
   3) RNaseZap

After cleaning and before starting the procedure, label all the materials needed to perform the extraction. E.g. two 1.5 mL vials and one RNAeasy column for each sample to be extracted.

b. **REAGENT PREPARATION**

All reagents must be prepared in a clean biosafety extraction cabinet

- Buffer RLT plus: add 10 µL β-mercaptoethanol for every 1 mL of Buffer RLT plus
    - To prepare for 50 samples (700 µL) à mix 400 µL β-mercaptoethanol + 40 mL Buffer RLT plus.
- DNase: the DNase must be previously reconstituted following the manufacturer's recommendations (stock DNase)
    - To prepare for 10 samples à 700 µL Buffer RDD + 100 µL DNase stock
    - This is called prepared DNase

Note: DNase cannot be vortexed nor centrifuges, must be gently mixed by pipetting

c. **RNA LATER REMOVAL**

- Remove PBMCs from liquid nitrogen (stored in: 2 mL PBMCs + RNA later+ DMSO + FBS), and immediately start processing
- Put in a bain-marie at 37°C for 2 minutes. Verify that the PBMCs are completely thawed by inversion mixing
- Take 750 µL of PBMCs in each of the 1.5 mL vials. (each sample is processed in duplicates)
- Centrifuge 8000 rpm (5000 g) for 5 minutes
- Remove the supernatants (RNA later + DMSO) completely using a tip
- Use the cell button in the extraction procedure as described below

d. **RNA EXTRACTION**

- Add 350 µL of Buffer RLT plus ($<5x10^6$ cell/mL) to the button of cells
- Set chronometer/stopwatch for 10 min, vortex until the button is removed, and leave incubating at room temperature until the time is up. Vortex occasionally
- Add 500 µL of 70% ethanol (1Vol), then mix by pipetting
- Incubate 5 min at room temperature
- Transfer 700 µL (including precipitates) to the RNeasy column
- Centrifuge at 12000 rpm (>8000 g) for 15 seconds, then discard the filtrate and reuse the waste tube. Repeat until all sample is finished
- Add 350 µL Buffer RW1 to the RNeasy column
- Centrifuge at 12000 rpm (>8000 g) for 15 seconds. Discard the filtrate and reuse the waste collection tube
- Add 80 µL of the prepared DNase. Incubate 15 minutes at room temperature
- Add 350 µL Buffer RW1 to the RNeasy column
- Centrifuge at 12000 rpm (>8000 g) for 15 seconds. Discard the filtrate and reuse the waste collection tube
- Add 500 µL of Buffer RPE to the RNeasy column

- Centrifuge at 12000 rpm (>8000 g) for 15 seconds. Discard the filtrate and reuse the waste collection tube
- Add 500 µL of Buffer RPE to the RNeasy column
- Centrifuge at 12000 rpm (>8000 g) for 2 minutes. Discard the filtrate and reuse the waste collection tube
- Centrifuge at maximum speed (14000 rpm) for 1 minute. Discard waste collection tube
- Put the RNeaasy column in a 1.5 mL tube provided by the commercial kit. Mark this tube with the consecutive number assigned to the sample (Mark the tubes)
- Add 30 µL of RNase-free water (provided by the commercial kit)
- Centrifuge at 12000 rpm (>8000 g) for 1 minute. In this step, eluted RNA is obtained
- Separate 8 µL of eluted RNA in a 0.6 mL tube to perform quality control
- Cover the eluted RNA very well and seal using parafilm paper (caution: transfer immediately to ice
- Always transport on ice and store at -80 °C

e. **PERFORM RNA QUALITY CONTROL**

- Measure in NanoDrop: Concentration and ratio 260/280 using 1 µL of sample
- Measure in Qubit: Concentration in ng/mL, using 1 µL of sample
- Measure on TapeStation: Integrity using RIN, 28S/18S ratio

f. **PREPARATION OF SAMPLES FOR SENDING TO MACROGEN – RNAseq**

- The eluted RNA tube contains 22 µL of RNA after removing 8 µL for QC
- Add 2.2 µL of 3M Sodium Acetate + 48.4 µL of 100% ethanol to the eluted RNA tube, according to Macrogen recommendations (store at -20°C)
- Cover very well and seal using parafilm
- Mix well and store at -20°C)
- Send as soon as possible for sequencing, packing the 1.5 mL tubes into 50 mL Falcon tubes; trim excess space with napkins

Appendix 3. Galaxy Project Protocol

1. In the upper left corner, select upload data and choose all the desired files that needed to be uploaded
    - Files must be in fastq.gz format

2. Once all the files have been uploaded, click on the search tool and type "FASTQC"
    - Under the "raw read data from your current history", click multiple files and select all the files that was uploaded.
    - Keep the rest of the categories in their default setting
    - Press execute

3. Click on "FastQC data: webpage" and analyze the summary report

4. Click on the search tool and type "trimmomatic"
    - Under the category "single-end or paired-end reads?" select **paired-ends (two separate input files)**
    - Under "input FASTQ file" make sure to select the paired files in order.
        - E.g. R1 à 02_037_0_2_1
        - E.g. R2 à 02_037_0_2_2
    - Keep the rest of the categories in the default setting
    - Press execute

5. Once the trimmomatic processing is done. Search "FastQC" for quality control again
    - Under the category "raw read data from your current history" select all the trimmomatic fastq.gz files
    - The purpose of this step is to see any differences from the previous quality report to the current quality report
    - Keep the rest of categories listed as default
    - Press execute

6. Click on "FastQC data: webpage" and analyze the summary report

7. Once done analyzing the quality report. Search "HISAT2"
    - Under the category "select a reference genome", choose **Human (Homo sapiens) (b38): hg38**

- Under the category “is this a single or paired library, choose **paired-end**
- Under the FASTA/Q file #1 & #2, select the appropriate trimmomatic fastq.gz files
- Press execute

8. Once HISAT2 is done processing, the format will be converted into BAM files and the title of the files needs to be renamed back to their sample names
   - Click on the edit attributes (pen symbol) and type in the designated sample to each file samples
   - Click save

9. After the HISAT2 and renaming is done. Search and click “FeatureCounts”
   - Under the category “alignment file” select all the HISAT2 BAM files for processing
   - Under the “gene annotation file”, select **featureCounts built-in**
   - Under “select built-in genome”, select **hg38**
   - Keep the remaining categories as “default”
   - Press execute

10. Once featureCounts is done processing, the BAM files will be converted into tabular files and once again has to be renamed to their designated sample name
    - Click on the counts file and select “edit attributes” (pen symbol) and rename the file to the designate sample name
    - Click save

11. R studio accepts csv file format. The tabular files provided by featureCounts must then be converted to csv format.
    - In the same file, after renaming, go to the “convert” tab. Under the “target datatype” category, select csv (using ‘tabular-to-csv’)

12. Once the files are converted, it will generate a new file on the left side of the screen. It will need renaming again.
    - Once renaming is complete. Save the file (floppy disk symbol) to a designated folder

Appendix 4. Primary transcriptomic profiling codes (R script)

```
setwd("~/Desktop/Primary Paper")

# DESeq ####
#Constructing a  DESeqDataSet Object
# Convert Condition to a factor with three levels
Col_data$Condition <- factor(Col_data$Condition, levels = c( "HIV-TB" , "HIV" , "Clinical TB" , "Non-infected" ))

dds <- DESeqDataSetFromMatrix(countData = read_counts,
                              colData = Col_data,
                              design = ~ Condition)

# Keep genes with at least 5 reads across all samples
keep <- rowSums(counts(dds)) >= 10
dds <- dds[keep, ]

# run DESeq function
dds <- DESeq(dds)

#plot dispersion estimates to examine normalization
plotDispEsts(dds)

# checking results
res <- results(dds)
res
resultsNames(dds)

# SVA Combat Seq ####
read_counts # counts data
Col_data # col-data
sample_info <- Col_data

combat_counts <- ComBat_seq(as.matrix(read_counts), batch = sample_info$Ethnicity, group = sample_info$Condition)
read_counts
view(combat_counts)

dds <- DESeqDataSetFromMatrix(countData = combat_counts, colData = sample_info, design = ~ Condition + Tissue)

keep <- rowSums(counts(dds)) >= 10
dds <- dds[keep, ]
```

```
dds <- DESeq(dds)

res <- results(dds)
res

# Clean up results file ####
res <- res[order(res$padj),]
res <- na.omit(res)
res <-as.data.frame(res)

# Contrasting Conditions ####
resHIVTB <- results(dds, contrast = c( " Condition" , "HIV-TB" , "Non-infected" ))
resHIV <- results(dds, contrast = c( "Condition" , "HIV" , "Non-infected" ))
resTB <- results(dds, contrast = c( "Condition" , "Clinical TB" , "Non-infected" ))

resHIVTB_TB <-results(dds, contrast = c( "Condition" , "HIV-TB" , "Clinical TB" ))
resHIVTB_HIV <- results (dds, contrast = c( "Condition" , "HIV-TB" , "HIV" ))

# Setting the parameters based on fold change and adjusted p value ####
logFC = 1.5
padjust = 0.05


# Significant results up and down regulated ####
# sig HIVTB
{
 up_resHIVTB <- resHIVTB[which(resHIVTB$padj <= padjust &
resHIVTB$log2FoldChange >= logFC), ]
 up_resHIVTB_df <- as.data.frame(up_resHIVTB)
 down_resHIVTB <- resHIVTB[which(resHIVTB$padj <= padjust &
resHIVTB$log2FoldChange <= -logFC), ]
 down_resHIVTB_df <- as.data.frame(down_resHIVTB)

 #Combining both upregulated and downregulated
 sig_HIVTB <- dplyr::full_join(up_resHIVTB_df, down_resHIVTB_df)
 HIVTB_genelist <- sig_HIVTB$Symbol
 up_HIVTB_list <- up_resHIVTB_df$Symbol
 down_HIVTB_list <- down_resHIVTB_df$Symbol
}

# sig HIVTB vs HIV
{
```

```
 up_resHIVTB_HIV <- resHIVTB_HIV[which(resHIVTB_HIV$padj <= padjust &
resHIVTB_HIV$log2FoldChange >= logFC), ]
 up_resHIVTB_HIV_df <- as.data.frame(up_resHIVTB_HIV)
 down_resHIVTB_HIV <- resHIVTB_HIV[which(resHIVTB_HIV$padj <= padjust &
resHIVTB_HIV$log2FoldChange <= -logFC), ]
 down_resHIVTB_HIV_df <- as.data.frame(down_resHIVTB_HIV)

 #Combining both upregulated and downregulated
 sig_HIVTB_HIV <- dplyr::full_join(up_resHIVTB_HIV_df, down_resHIVTB_HIV_df)
 HIVTB_vs_HIV_genelist <- sig_HIVTB_HIV$Symbol
 up_HIVTB_vs_HIV_list <- up_resHIVTB_HIV_df$Symbol
 down_HIVTB_vs_HIV_list <- down_resHIVTB_HIV_df$Symbol
}

# sig HIVTB vs TB
{
 up_resHIVTB_TB <- resHIVTB_TB[which(resHIVTB_TB$padj <= padjust &
resHIVTB_TB$log2FoldChange >= logFC), ]
 up_resHIVTB_TB_df <- as.data.frame(up_resHIVTB_TB)
 down_resHIVTB_TB <- resHIVTB_TB[which(resHIVTB_TB$padj <= padjust &
resHIVTB_TB$log2FoldChange <= -logFC), ]
 down_resHIVTB_TB_df <- as.data.frame(down_resHIVTB_TB)

 #Combining both upregulated and downregulated
 sig_HIVTB_TB <- dplyr::full_join(up_resHIVTB_TB_df, down_resHIVTB_TB_df)
 HIVTB_vs_TB_genelist <- sig_HIVTB_TB$Symbol
 up_HIVTB_vs_TB_list <- up_resHIVTB_TB_df$Symbol
 down_HIVTB_vs_TB_list <- down_resHIVTB_TB_df$Symbol
}

#unique to TB in PLHIV ####
unique_HIVTB <- setdiff(HIVTB_genelist, union(HIVTB_vs_HIV_genelist,
HIVTB_vs_TB_genelist))
unique_HIVTB <- as.data.frame(unique_HIVTB)
unique_HIVTB <- unique_HIVTB %>% dplyr:: rename(Symbol = unique_HIVTB)

#unique to TB in PLHIV vs HIV ####
unique_HIVTB_vs_HIV <- setdiff(HIVTB_vs_HIV_genelist, union(HIVTB_genelist,
HIVTB_vs_TB_genelist))
unique_HIVTB_vs_HIV <- as.data.frame(unique_HIVTB_vs_HIV)
unique_HIVTB_vs_HIV <- unique_HIVTB_vs_HIV %>% dplyr:: rename(Symbol =
unique_HIVTB_vs_HIV)

#unique to TB in PLHIV vs TB ####
```

```
unique_HIVTB_vs_TB <- setdiff(HIVTB_vs_TB_genelist, union(HIVTB_genelist,
HIVTB_vs_HIV_genelist))
unique_HIVTB_vs_TB <- as.data.frame(unique_HIVTB_vs_TB)
unique_HIVTB_vs_TB <- unique_HIVTB_vs_TB %>% dplyr:: rename(Symbol =
unique_HIVTB_vs_TB)

# Potential markers  ####
shared_HIVTB_TB <- intersect(HIVTB_genelist, HIVTB_vs_TB_genelist) # shared between
HIVTB and TB
shared_HIVTB_TB <- setdiff(shared_HIVTB_TB, HIVTB_vs_HIV_genelist)

shared_HIVTB_TB_df <- as.data.frame(shared_HIVTB_TB)
shared_HIVTB_TB_df <- shared_HIVTB_TB_df %>% dplyr:: rename(Symbol =
shared_HIVTB_TB)

shared_HIVTB_HIV <- intersect(HIVTB_genelist, HIVTB_vs_HIV_genelist) # shared
between HIVTB and TB
shared_HIVTB_HIV <- setdiff(shared_HIVTB_TB, HIVTB_vs_TB_genelist)

shared_HIVTB_HIV_df <- as.data.frame(shared_HIVTB_HIV)
shared_HIVTB_HIV_df <- shared_HIVTB_HIV_df %>% dplyr:: rename(Symbol =
shared_HIVTB_HIV)

# Run GO enrichment analysis for HIVTB vs HIV  #####
HIVTBvsHIV_ego <- enrichGO(gene = HIVTB_vs_HIV_genelist,
          universe = Background_genes,
          keyType = "SYMBOL",
          OrgDb = org.Hs.eg.db,
          ont = "ALL",
          pAdjustMethod = "BH",
          qvalueCutoff = 0.05,
          readable = TRUE)

clustered_HIVTBvsHIV<- data.frame(HIVTBvsHIV_ego)
view(clustered_HIVTBvsHIV)
{
 # Select top terms from each category
 top_terms <- clustered_HIVTBvsHIV %>%
  group_by(ONTOLOGY) %>%
  arrange(qvalue, desc(Count)) %>%  # Rank by q-value (ascending) and Count
(descending)
  slice_head(n = 5) %>%  # Select top 5 for each category
  ungroup()
```

```
 # Rename categories for plotting
 top_terms$ONTOLOGY <- factor(top_terms$ONTOLOGY, levels = c( "BP" , "CC" , "MF" ))

 # Order by count
 top_terms <- top_terms[order(top_terms$Count, decreasing = TRUE), ]
}
# Create bar plot
ggplot(top_terms, aes(x = reorder(Description, Count), y = Count, fill = ONTOLOGY)) +
 geom_bar(stat = "identity") +
 coord_flip() +  # Horizontal bars
 scale_fill_manual(values = c("BP" = "firebrick", "CC" = "peachpuff", "MF" = "steelblue"))
+  # Colors
 labs(title = "TB in PLHIV vs HIV alone",
     x = "",
     y = "Count",
     fill = "GO Category") +
 theme_minimal()

# Run GO enrichment analysis for HIVTB vs TB  #####
HIVTBvsTB_ego <- enrichGO(gene = HIVTB_vs_TB_genelist,
                  universe = Background_genes,
                  keyType = "SYMBOL",
                  OrgDb = org.Hs.eg.db,
                  ont = "ALL",
                  pAdjustMethod = "BH",
                  qvalueCutoff = 0.05,
                  readable = TRUE)

clustered_HIVTBvsTB<- data.frame(HIVTBvsTB_ego)
view(clustered_HIVTBvsTB)
{
 # Select top terms from each category
 top_terms <- clustered_HIVTBvsTB %>%
  group_by(ONTOLOGY) %>%
  arrange(qvalue, desc(Count)) %>%  # Rank by q-value (ascending) and Count
(descending)
  slice_head(n = 5) %>%  # Select top 5 for each category
  ungroup()

 # Rename categories for plotting
 top_terms$ONTOLOGY <- factor(top_terms$ONTOLOGY, levels = c( "BP" , "CC" , "MF" ))

 # Order by count
 top_terms <- top_terms[order(top_terms$Count, decreasing = TRUE), ]
```

```
}
# Create bar plot
ggplot(top_terms, aes(x = reorder(Description, Count), y = Count, fill = ONTOLOGY)) +
 geom_bar(stat = "identity") +
 coord_flip() +  # Horizontal bars
 scale_fill_manual(values = c("BP" = "firebrick", "CC" = "peachpuff", "MF" = "steelblue"))
+  # Colors
 labs(title = "TB in PLHIV vs TB alone",
     x = "",
     y = "Count",
     fill = "GO Category") +
 theme_minimal()

# Run GO enrichment analysis for HIVTB vs Non-infected  #####
HIVTB_ego <- enrichGO(gene = HIVTB_genelist,
                      universe = Background_genes,
                      keyType = "SYMBOL",
                      OrgDb = org.Hs.eg.db,
                      ont = "ALL",
                      pAdjustMethod = "BH",
                      qvalueCutoff = 0.05,
                      readable = TRUE)

clustered_HIVTB<- data.frame(HIVTB_ego)
view(clustered_HIVTB)
{
 # Select top terms from each category
 top_terms <- clustered_HIVTB %>%
  group_by(ONTOLOGY) %>%
  arrange(qvalue, desc(Count)) %>%  # Rank by q-value (ascending) and Count
(descending)
  slice_head(n = 5) %>%  # Select top 5 for each category
  ungroup()

 # Rename categories for plotting
 top_terms$ONTOLOGY <- factor(top_terms$ONTOLOGY, levels = c( "BP" , "CC" , "MF" ))

 # Order by count
 top_terms <- top_terms[order(top_terms$Count, decreasing = TRUE), ]
}
# Create bar plot
ggplot(top_terms, aes(x = reorder(Description, Count), y = Count, fill = ONTOLOGY)) +
 geom_bar(stat = "identity") +
 coord_flip() +  # Horizontal bars
```

```
  scale_fill_manual(values = c("BP" = "firebrick", "CC" = "peachpuff", "MF" = "steelblue"))
+  # Colors
  labs(title = "TB in PLHIV vs Non-infected",
       x = "",
       y = "Count",
       fill = "GO Category") +
  theme_minimal()
```

Appendix 5. Enrichment analysis of tuberculosis in PLHIV vs. tuberculosis alone via clusterProfiler

Ontology	ID	Description	p.adjust	qvalue	geneID	Count
BP	GO:0002181	cytoplasmic translation	3.95E-03	3.86E-03	DHX36/CPEB3/NCBP1/CPEB4/DHX29/MCTS2/NEMF/CPEB2/LIN28A/IGF2BP1/RBM24/RPS16/RPL28/RPS3/RPS28/RPS15/MIF4GD/RPL29/RPL8/RPL10/RPL18A/EIF3K/RPL18/RPL27/RPL7A/RPL13/RPS2/RPL14/RPL27A/RPL3/RPS21/EIF3F/RPS19/RPL12/RPL36/EIF3G/RPL15/DRG2/RPL37A/RPL13A/RPL19/RPL10A/RPS13/RPL23A/RPLP2/FAU/RPSA/RPL37/RPL35/RACK1/RPS5/RPS27A/RPLP1/RPS4X/RPL22/FTSJ1/RPL38/RPL6/RPS29/RPS8/RPL32/ZNF385A/RPS14/RPLP0/RPS23/RPL35A/RPS20/RPS25/RPS6/RPL4/RPL5/RPS26/RPL24/RPL23/RPL11/PARP16/EIF3CL/RPS27/RPL41/RPS11/RPL39/RPL9/RPS12/RPL26/RPL21/RPL34/RPS3A/EIF3C/RPS18/RPS17/RPS9	91
BP	GO:0061644	protein localization to CENP-A containing chromatin	6.27E-03	6.13E-03	H4C4/H4C5/H4C3/H2AC8/H4C16/H2BC11/H4C2/H4C8/H4C9/H4C6/H4C13/H2AC4/H4C1/H4C12/H4C14/H4C11/H4C15	17
BP	GO:0006334	nucleosome assembly	6.95E-03	6.79E-03	H2BC4/H3C4/SHPRH/H4C4/H4C5/H4C3/H2BC15/H2BC6/H2BC8/ATRX/RSF1/H4C16/KAT6A/H2BC11/H1-2/H1-3/H1-4/H4C2/H3C10/H2BC9/H2BC7/H3C8/H2BC3/H2BC13/H1-6/H4C8/SMARCA5/BAZ1A/H3C12/H4C9/H2BC17/H2BC10/H4C6/H3C2/H4C13/H1-5/H3C13/H2BC14/H3C3/H3C6/H2BC21/H3C7/H3C11/H1-1/H4C1/H3C1/H3C15/H4C12/TSPYL6/H4C14/TSPY26P/H4C11/H3C14/SOX9/H4C15/H3-4/CHRAC1/H1-10/POLE3/ANP32B/NAA60/H2AX/MACROH2A2/TSPYL2/DAXX/BRD2/NAP1L3/H2AB3	68
BP	GO:0006936	muscle contraction	8.67E-03	8.47E-03	TTN/HTR2B/AKAP9/PIK3C2A/UTRN/PDE5A/PIK3CG/NUP155/SLMAP/TMOD3/ROCK2/PLN/DOCK5/SLC8A1/KCNE1/DOCK4/MIR21/ADCY10/TACR1/ROCK1/PPP1R12B/CHUK/KCNJ2/PIK3CA/GUCY1A1/VPS54/ASPH/CERT1/MYOF/ZDHHC21/PTGS2/TACR2/SCN3B/MYLK/DSC2/ITGA2/ACTA2/CHRNB2/HOMER1/MYOT/TMOD2/PRKG1/CKMT2/CHRNG/MAP2K6/CALD1/GRIP2/CACNB2/ACE2/ARHGAP42/CACNA1D/KCNE3/RYR3/SSPN/EDN1/APBB2/TMOD1/CD38/CSRP3/FGF13/CHRNA1/NEDD4L/PKP2/SLC8A3/PLCE1/DMD/GJC1/PROK2/CHRND/STAC/MIR30E/LMOD2/SPX/NPNT/ANK2/CTTN/EDNRB/NOS1AP/ABCC9/CACNA2D1/RYR2/FGF12/MYOCD/KLHL41/COMP/	178

					PRKD1/GLRA1/HCN4/KCNN2/TBX20/GATA4/CACNG1/HTR2A/MYH2/EDNRA/KCNJ3/TRDN/DSG2/KCNMA1/CHRM3/CACNA1S/GHSR/CTNNA3/TNNI1/CALCA/SSTR2/MYH13/SCN1A/SCN7A/MYH4/KBTBD13/KCNA1/SULF1/TBX3/HTR1D/NOS1/MYH1/GDNF/CACNA1G/KCND2/ADRA1A/ADRA1B/TBX2/MYH8/MYH7/P2RX3/KCNJ5/EMD/TAFAZZIN/VEGFB/DMPK/CALM3/CACNB1/BIN1/TPM2/GAMT/GRK2/GSTM2/MYL6B/PPP1R13L/SNTA1/APBB1/SMAD7/NMUR1/MYL5/PABPN1/KCNIP2/PRKACA/C12orf57/CACNA1H/FXYD1/TNNI2/ADA/NR4A1/STAC3/TCAP/ALDOA/NPPA/SLC9A1/DCANP1/CCDC78/UCN/SGCA/TNNC1/CLCN1/TRPM4/SCN4B/MYOM2/JUP/JSRP1/KCNH2/ACTA1/MYL9/CASQ1/DES/KCNA5/MYBPH/LMOD1	
BP	GO:0045653	negative regulation of megakaryocyte differentiation	1.48E-02	1.45E-02	H4C4/H4C5/H4C3/H4C16/H4C2/H4C8/GABPA/H4C9/H4C6/H4C13/H4C1/H4C12/H4C14/H4C11/H4C15/CIB1/PRMT1	17
BP	GO:0050804	modulation of chemical synaptic transmission	1.54E-02	1.50E-02	BTBD9/NF1/USP8/CDKL5/BRAF/LRRK2/GRIK1/STAU2/DISC1/STXBP5/PLCL2/SYNE1/RAB5A/CPEB3/JAK2/LRRTM2/PREPL/MCTP1/RNF19A/VPS35/KIF5B/RAPGEF2/TACR1/MCTP2/KRAS/UBE3A/GUCY1A1/MIR421/PTEN/OPHN1/SIPA1L1/CALB1/RAB3GAP1/RTN4/PSEN1/MYOF/MAPK1/ITGB1/TRIO/SLC1A3/PRKCE/LRRC4/GRIN3A/PTGS2/TACR2/ZDHHC2/SLC12A2/SLC30A1/GUCY1B1/SLC38A2/P2RY1/SLC7A11/CHRNB2/HOMER1/STX3/MAP1B/SLC6A4/DYSF/MME/BDNF/EPHB1/PRKAR2B/HIP1/SRGN/AKAP12/CNTN2/SHISA7/MIR320C1/CCR2/EDN1/CD38/TSHZ3/ADCY1/DGKI/SLC8A3/RIMS2/MIR545/CACNB4/CA2/SLC24A2/PPP1R9A/CPLX2/CDH11/SNCA/FER1L5/DCC/CNTN4/SV2C/SHISA6/DLGAP1/GRIA3/TNR/SLC4A10/CHRNA5/TMEM108/MIR320D1/GRIA4/NLGN1/NGF/GRIN2A/GRM8/RELN/MIR320A/HTR2A/CAMK2A/GRIN2B/NLGN4X/PHF24/CDH2/SLC1A1/GRIA1/ERC2/NALCN/GHSR/OTOF/FLOT1/GABRR1/SHANK2/NTNG1/SYT1/PPFIA2/GRM5/GRID2/ADCY8/SORCS3/NRXN1/CPLX4/IGSF11/PTPRD/LRRC4C/NR2E1/CNTNAP4/RIMS1/SLC6A1/SYT4/SCGN/EPHA7/CLSTN2/CBLN1/DRD5/GRIA2/FRRS1L/ADRA1A/GRM6/SCTR/NRG3/GPR158/RIMS4/GRIK3/P2RX3/CALB2/CHRNA6/CACNA1B/VAMP2/PFN1/RNF167/ATF4/CLN3/ZDHHC12/GIT1/GIPC1/KAT2A/DLGAP4/MIR142/DVL1/ANAPC2/MAPK3/DMPK/DGKZ/PNKD/RGS14/NSMF/STX1A/NCDN/GNAI2/PICK1/S1PR2/ARF1/SY	235

					NGR1/TYROBP/FBXO2/PPFIA3/KCTD13/RAB3A/RARA/NLGN2/DLGAP3/TBC1D24/PRKACA/ARRB2/PRKAR1B/ADGRB1/NEURL1/TMEM25/DLG4/PDE9A/BRSK1/SYN1/BAIAP2/CPLX3/DBN1/IQSEC2/CPLX1/PRRT2/UCN/NSG1/ASIC1/STX1B/MAPK8IP2/MPP2/BEGAIN/BGLAP/DNM1/NGFR/BAIAP3/GRM2/CYP46A1/ARC/WNT7A/NOG/SHISA8/APBA2/MIR324/SHANK1/AGER/APOE/NEFL/TUBB2B/HRAS/CCL2/NFATC4/SYNGAP1/VGF/SNCG/HTR1B	
BP	GO:0099177	regulation of trans-synaptic signaling	1.58E-02	1.54E-02	BTBD9/NF1/USP8/CDKL5/BRAF/LRRK2/GRIK1/STAU2/DISC1/STXBP5/PLCL2/SYNE1/RAB5A/CPEB3/JAK2/LRRTM2/PREPL/MCTP1/RNF19A/VPS35/KIF5B/RAPGEF2/TACR1/MCTP2/KRAS/UBE3A/GUCY1A1/MIR421/PTEN/OPHN1/SIPA1L1/CALB1/RAB3GAP1/RTN4/PSEN1/MYOF/MAPK1/ITGB1/TRIO/SLC1A3/PRKCE/LRRC4/GRIN3A/PTGS2/TACR2/ZDHHC2/SLC12A2/SLC30A1/GUCY1B1/SLC38A2/P2RY1/SLC7A11/CHRNB2/HOMER1/STX3/MAP1B/SLC6A4/DYSF/MME/BDNF/EPHB1/PRKAR2B/HIP1/SRGN/AKAP12/CNTN2/SHISA7/MIR320C1/CCR2/EDN1/CD38/TSHZ3/ADCY1/DGKI/SLC8A3/RIMS2/MIR545/CACNB4/CA2/SLC24A2/PPP1R9A/CPLX2/CDH11/SNCA/FER1L5/DCC/CNTN4/SV2C/SHISA6/DLGAP1/GRIA3/TNR/SLC4A10/CHRNA5/TMEM108/MIR320D1/GRIA4/NLGN1/NGF/GRIN2A/GRM8/RELN/MIR320A/HTR2A/CAMK2A/GRIN2B/NLGN4X/PHF24/CDH2/SLC1A1/GRIA1/ERC2/NALCN/GHSR/OTOF/FLOT1/GABRR1/SHANK2/NTNG1/SYT1/PPFIA2/GRM5/GRID2/ADCY8/SORCS3/NRXN1/CPLX4/IGSF11/PTPRD/LRRC4C/NR2E1/CNTNAP4/RIMS1/SLC6A1/SYT4/SCGN/EPHA7/CLSTN2/CBLN1/DRD5/GRIA2/FRRS1L/ADRA1A/GRM6/SCTR/NRG3/GPR158/RIMS4/GRIK3/P2RX3/CALB2/CHRNA6/CACNA1B/VAMP2/PFN1/RNF167/ATF4/CLN3/ZDHHC12/GIT1/GIPC1/KAT2A/DLGAP4/MIR142/DVL1/ANAPC2/MAPK3/DMPK/DGKZ/PNKD/RGS14/NSMF/STX1A/NCDN/GNAI2/PICK1/S1PR2/ARF1/SYNGR1/TYROBP/FBXO2/PPFIA3/KCTD13/RAB3A/RARA/NLGN2/DLGAP3/TBC1D24/PRKACA/ARRB2/PRKAR1B/ADGRB1/NEURL1/TMEM25/DLG4/PDE9A/BRSK1/SYN1/BAIAP2/CPLX3/DBN1/IQSEC2/CPLX1/PRRT2/UCN/NSG1/ASIC1/STX1B/MAPK8IP2/MPP2/BEGAIN/BGLAP/DNM1/NGFR/BAIAP3/GRM2/CYP46A1/ARC/WNT7A/NOG/SHISA8/APBA2/MIR324/SHANK1/	235

					AGER/APOE/NEFL/TUBB2B/HRAS/CCL2/NFATC4/SYNGAP1/VGF/SNCG/HTR1B	
BP	GO:0042391	regulation of membrane potential	2.91E-02	2.84E-02	INSYN2B/AKAP9/LRRK2/NDUFS1/GRIK1/NUP155/SLMAP/MFN1/SYNE1/PLN/NNT/SLC8A1/KCNE1/KIF5B/ADCY10/TACR1/KCNC1/SEZ6/KCNJ2/PTEN/GCLM/KCNH7/RAB3GAP1/NEDD4/PSEN1/GABRR2/SPART/GRIN3A/ZMPSTE24/SCN3B/DSC2/USP53/ANK3/CHRNB2/SLC6A4/SOD2/SLC39A8/CHRNG/CACNB2/P2RX7/CACNA1D/GNAQ/KCNE3/TRPC5/KCNH6/CHRNA2/MIR29B1/SLC4A4/SLC26A3/EDN1/CXADR/SCN8A/SLC26A5/FGF13/CHRNA1/NEDD4L/PKP2/SLC8A3/GNA14/DMD/RIMS2/GJC1/CHRND/CACNB4/SNCA/ANK2/CLDN19/NOS1AP/ABCC9/GRIA3/KCNJ9/CACNA2D1/RYR2/FGF12/TBX18/CHRNA5/GLRA2/TMEM108/INSYN1/ZACN/GRIA4/GLRA1/NLGN1/HCN4/KCNN2/GABRA4/GRIN2A/KCNMB2/PTPN3/RELN/CNGB1/ABCB5/GRIN2B/KCNJ3/NLGN4X/TRDN/DSG2/KCNMA1/GRIA1/KCNC2/GABRA2/NALCN/GABRB1/CTNNA3/GLRA3/GABRR1/KCNK3/SCN1A/HCN1/MIR181B1/GRM5/GRID2/PIEZO2/NRXN1/GABRE/IGSF11/TBX5/KCNA1/GABRG2/BEST2/CLIC1/RIMS1/ACTN2/RGS7BP/CBLN1/GLRB/CHRFAM7A/HTR3E/PHOX2B/KCNJ11/GRIA2/GABRG3/CACNA1G/KCND2/ADRA1A/GABRA5/KCNK16/GABRG1/BVES/RIMS4/GABRB2/GRIK3/P2RX3/CHRNA6/KCNJ5/BAX/CLN3/TUSC2/KCNAB2/DVL1/ATP5IF1/DMPK/CALM3/KCNK6/RACK1/UCP2/BIN1/CRTC1/STX1A/S1PR2/HCN2/CACNB3/MTLN/NPFF/SNTA1/GPR35/SMAD7/HSH2D/GSK3A/NLGN2/KCNN4/TBC1D24/KCNIP2/BOK/ARRB2/CACNA1H/FXYD1/SRC/PRKAR1B/POPDC2/MLLT11/PIEZO1/P2RX5/GNA11/ABCD1/NPPA/TMEM25/DLG4/SLC9A1/YWHAE/BAIAP2/SLC4A3/TCL1A/GNA15/ASIC1/CACNA1I/KCNH3/STX1B/SLC29A1/MAPK8IP2/MPP2/SLC1A7/CLCN1/TRPM4/WNT7A/SCN4B/KCNK17/JUP/PID1/SHANK1/KCNH2/KCNK10/KCNA5/HTR3A	214
BP	GO:0008015	blood circulation	3.07E-02	3.00E-02	TTN/LNPEP/HTR2B/AKAP9/PIK3C2A/PDE5A/PIK3CG/NUP155/ROCK2/PLN/DOCK5/SLC8A1/KCNE1/DOCK4/ZEB2/MDM2/MIR21/ERAP1/ADCY10/ITGA1/TACR1/ROCK1/STAT1/KCNJ2/PIK3CA/GUCY1A1/GCLM/CHD7/WNK1/MYOF/KCNG2/PTPRJ/GPR37L1/SUCNR1/ZDHHC21/PTGS2/TACR2/ZMPSTE24/GNA13/SCN3B/MEF2A/CEACAM1/DSC2/F5/GUCY1B1/ACTA2/P2RY1/KL/PRKG1/SLC6A4/F2RL1/SOD2/CYSLTR1/MAP2K6/G	242

					RIP2/MYLK3/CACNB2/BMP6/OCLN/ACE2/EXT1/ARHGAP42/CACNA1D/KCNE3/TBC1D8/AVPR1A/DDAH1/AKAP12/KCNH6/PDE3A/PPARG/CXCR2/THRB/C2CD4A/GCH1/EDN1/NPR3/EMILIN2/TMIGD3/ATP2B2/CD38/KNG1/CSRP3/CXADR/FGF13/SMTNL1/NEDD4L/PKP2/NR2F2/SLC8A3/AR/HSD11B2/DMD/WNK4/GJC1/SERPING1/TAC4/AGTR1/MIR30E/SPX/ANK2/ANGPT1/EDNRB/NOS1AP/ABCC9/BRS3/TEK/FERMT2/FOXC1/DLL4/VEGFC/SGCG/CACNA2D1/RYR2/FGF12/TBX18/COMP/MIR199A1/CYP11B1/HCN4/KCNN2/FGA/KCNMB2/TBX20/GATA4/CPS1/HTR2A/EDNRA/FOXN4/KCNJ3/FGB/TRDN/OR51E2/DSG2/SLC1A1/KCNMA1/CHRM3/CASR/GPR4/TGFB2/CTNNA3/TNNI1/OLR1/CALCA/SCN1A/ADRA1D/ABCC8/LPA/TBX5/AGT/HTR1D/NOS1/MIR27B/MYL7/ATP2B3/DRD5/CACNA1G/KCND2/ADRA1A/CYP11B2/ADRA1B/GCGR/ACTC1/SOD3/SH3GL2/FGG/BVES/TBX2/MYH7/AVPR1B/HSPB7/NPPB/COL1A2/KCNJ5/UMOD/TAFAZZIN/VEGFB/KLF2/CTNNBIP1/DMPK/CALM3/KCNK6/TGFB1/CYB5R3/BIN1/E2F4/ATP2A3/GRK2/GSTM2/PLOD3/KCNMB1/PPP1R13L/FAAH/SNTA1/SMAD7/FGFBP3/SREBF1/GSK3A/KCNIP2/PRKACA/CACNA1H/FXYD1/SRC/SCNN1A/TNNI2/POPDC2/SCNN1D/ADA/AGTRAP/TCAP/GNA11/ADM5/NPPA/SLC9A1/YWHAE/DBH/SLC4A3/PDGFB/TJP3/UCN/EPO/PLVAP/S100A1/TNNC1/GNB3/XCL2/CORO2B/TRPM4/SCN4B/JUP/HBB/AGER/KLK1/KCNH2/APOE/DES/KCNA5/APLN/TAC3/IER3/SERPINF2/HTR1B	
BP	GO:0003018	vascular process in circulatory system	3.28E-02	3.21E-02	HTR2B/PIK3C2A/ROCK2/DOCK5/SLC8A1/ATP8A1/DOCK4/ZEB2/LEPR/MIR21/ITGA1/SLC5A3/TACR1/ROCK1/GUCY1A1/SLC2A13/ABCC4/GCLM/SLC22A1/SLC16A7/SLC1A3/PTPRJ/ZDHHC21/PTGS2/TACR2/SLC12A2/CEACAM1/ACTA2/TFRC/SLC38A2/P2RY1/SLC6A20/PRKG1/SLC6A4/F2RL1/SOD2/CYSLTR1/GRIP2/MYLK3/BMP6/OCLN/ACE2/EXT1/ARHGAP42/AVPR1A/SLC16A12/DDAH1/AKAP12/PDE3A/CXCR2/C2CD4A/SLC4A4/GCH1/EDN1/SLC6A13/LRP2/CD38/KNG1/SLC24A3/SLC1A2/SMTNL1/SLC7A2/AGTR1/ABCG2/ANGPT1/EDNRB/ABCC9/TEK/FERMT2/FOXC1/COMP/SLC5A1/FGA/KCNMB2/CPS1/HTR2A/EDNRA/FGB/SLC1A1/KCNMA1/CHRM3/CASR/GPR4/CALCA/ADRA1D/ABCC8/AGT/SLCO2B1/HTR1D/NOS1/SLC6A1/SLC38A3/DRD5/SLC6A17/SLC22A2/ADRA1A/ADRA1B/SOD3/SH3GL2/FGG/AVPR1B/NPPB/NHERF1/KLF2/CTNNBIP	136

					1/TGFB1/SLC29A2/SLC27A1/ATP2A3/LRP3/PLOD3/KCNMB1/FAAH/SNTA1/FGFBP3/SRC/SLC5A6/SLC5A5/NPPA/DBH/SLC4A3/TJP3/SLC7A5/SLC7A8/UCN/SLC29A4/SLC29A1/PLVAP/TRPM4/HBB/AGER/APOE/KCNA5/SERPINF2/HTR1B/SLC7A3	
CC	GO:0022626	cytosolic ribosome	4.15E-11	3.78E-11	LTN1/HBS1L/ASCC3/DHX29/NEMF/GSPT1/RPL10L/RPS16/RPL28/RPS3/RPS28/RPS15/RPL29/RPL8/RPL10/RPL18A/ZNF598/RPL18/RPL27/RPL7A/RPL13/RPS2/RPL14/RPL27A/RPL3/RPS21/SNU13/RPS19/RPL12/RPL36/RPL15/RPL37A/RPL13A/RPL19/RNF25/RPL10A/RPS13/RPL23A/RPLP2/FAU/RPSA/RPL37/RPL35/RACK1/NHP2/RPS5/RPS27A/RPLP1/RPS4X/RPL22/RPL38/RPL6/RPS29/RPS8/RPL32/RPS14/RPLP0/RPS23/RPL35A/RPS20/RPS25/RPS6/RPL4/RPL5/RPS26/RPL24/RPL23/RPL11/RPS27/RPL41/RPS11/RPL39/RPL9/RPS12/RPL26/RPL21/RPL34/RPS3A/RPSA2/RPL39L/RPS18/RPS17/RPS4Y2/RPS9/RPS4Y1	85
CC	GO:0022625	cytosolic large ribosomal subunit	7.74E-07	7.05E-07	RPL10L/RPL28/RPL29/RPL8/RPL10/RPL18A/RPL18/RPL27/RPL7A/RPL13/RPL14/RPL27A/RPL3/SNU13/RPL12/RPL36/RPL15/RPL37A/RPL13A/RPL19/RPL10A/RPL23A/RPLP2/RPL37/RPL35/NHP2/RPLP1/RPL22/RPL38/RPL6/RPL32/RPLP0/RPL35A/RPL4/RPL5/RPL24/RPL23/RPL11/RPL41/RPL39/RPL9/RPL26/RPL21/RPL34/RPL39L	45
CC	GO:1990351	transporter complex	6.98E-06	6.36E-06	AKAP9/ATP11C/TMEM30A/NDUFS1/GRIK1/ATP8B1/KCNS1/STXBP5/PLN/ATP10D/ATP8A1/KCNE1/ANO6/ATP6V1A/ATP8B4/BEST1/SLC5A3/CACNA1E/ATP11B/KCNC1/ERGIC2/PEX13/KCNJ2/GABRR2/SCN9A/ATP11A/PKD1L3/KCNG2/GRIN3A/SCN3B/LRRC8B/CHRNB2/KCNIP4/CLIC4/ATP6V1C1/CACNB2/ATP4B/CACNA1D/ANO2/CNGB3/TRPC5/RYR3/C2CD6/SHISA7/CHRNA2/KCNV2/CLCA3P/KCNS2/SCN8A/CHRNA1/ABCG5/HSPA2/ATP10B/SCN3A/CHRND/CACNB4/CNGA1/UNC80/TRPC6/TMEM262/SHISA6/ABCC9/GRIA3/LRRC8E/CACNA2D1/RYR2/BEST3/CHRNA5/GLRA2/KCNG3/VWC2L/GRIA4/GLRA1/HCN4/GABRA4/GRIN2A/ATP1B4/KCNMB2/CNGB1/CACNG1/GRIN2B/KCNJ3/KCNMA1/ABCG8/CACNA1S/ATP12A/GRIA1/KCNC2/GABRA2/CNTNAP2/GABRB1/GLRA3/GABRR1/SLC17A8/SCN1A/KCNV1/HCN1/SCN7A/GRID2/DPP10/ABCC8/KCNJ16/KCNJ6/GABRE/KCNA1/GABRG2/CATSPERD/BEST2/CLIC1/ANO1/GLRB/CHRFAM7A/VWC2/HTR3E/KCNJ11/GRIA2/GABRG3/CACNA1G/KCND2/CNGA3/DPP6/GABRA5/G	220

					ABRG1/KCNIP1/GABRB2/GRIK3/CHRNA6/CACNA1B/KCNIP3/KCNJ5/ATP6V1F/ND2/ND3/ND4L/ND6/ND5/CYTB/NDUFA11/COX1/NDUFA7/NDUFB7/PTPA/NDUFS7/NDUFS8/NDUFB11/CLIC3/CYC1/KCNAB2/NDUFB10/NDUFS6/PORCN/NDUFS3/TIMM13/CALM3/ORAI1/ERGIC3/NDUFC1/NDUFA13/ABCB8/KCNK6/CLCN7/PEX14/CACNB1/NDUFV1/ND1/KCNAB3/ABCD4/KCNC3/NDUFB9/ND4/NDUFAB1/ATP6V0C/CACNA2D4/HCN2/CACNB3/TIMM9/ABHD12/FKBP1A/BCS1L/KCNMB1/NDUFB2/TTYH2/NDUFA12/KCNN4/KCNIP2/PRKACA/CNIH2/CACNA1H/FXYD1/SCNN1A/TTYH3/SCNN1D/STAC3/CACNA1F/CATSPER1/CLCN2/DLG4/PKD1/SLC9A1/LRRC26/CACNA2D2/KCNG1/TMEM249/CACNA1I/TMEM30B/OLFM2/CLCN1/TRPM4/SCN4B/SHISA8/CACNG6/CACNA2D3/KCNH2/KCNA5/TRPV6/HTR3A/EFCAB9/NDUFA3/SLC17A7/CPT1C	
CC	GO:0022627	cytosolic small ribosomal subunit	7.76E-06	7.06E-06	DHX29/RPS16/RPS3/RPS28/RPS15/RPS2/RPS21/RPS19/RPS13/FAU/RPSA/RACK1/RPS5/RPS27A/RPS4X/RPS29/RPS8/RPS14/RPS23/RPS20/RPS25/RPS6/RPS26/RPS27/RPS11/RPS12/RPS3A/RPSA2/RPS18/RPS17/RPS4Y2/RPS9/RPS4Y1	33
CC	GO:0034702	monoatomic ion channel complex	1.76E-05	1.60E-05	AKAP9/GRIK1/KCNS1/STXBP5/KCNE1/ANO6/BEST1/SLC5A3/CACNA1E/KCNC1/KCNJ2/GABRR2/SCN9A/PKD1L3/KCNG2/GRIN3A/SCN3B/LRRC8B/CHRNB2/KCNIP4/CLIC4/CACNB2/CACNA1D/ANO2/CNGB3/TRPC5/RYR3/C2CD6/SHISA7/CHRNA2/KCNV2/CLCA3P/KCNS2/SCN8A/CHRNA1/HSPA2/SCN3A/CHRND/CACNB4/CNGA1/UNC80/TRPC6/TMEM262/SHISA6/ABCC9/GRIA3/LRRC8E/CACNA2D1/RYR2/BEST3/CHRNA5/GLRA2/KCNG3/VWC2L/GRIA4/GLRA1/HCN4/GABRA4/GRIN2A/KCNMB2/CNGB1/CACNG1/GRIN2B/KCNJ3/KCNMA1/CACNA1S/GRIA1/KCNC2/GABRA2/CNTNAP2/GABRB1/GLRA3/GABRR1/SLC17A8/SCN1A/KCNV1/HCN1/SCN7A/GRID2/DPP10/ABCC8/KCNJ16/KCNJ6/GABRE/KCNA1/GABRG2/CATSPERD/BEST2/CLIC1/ANO1/GLRB/CHRFAM7A/VWC2/HTR3E/KCNJ11/GRIA2/GABRG3/CACNA1G/KCND2/CNGA3/DPP6/GABRA5/GABRG1/KCNIP1/GABRB2/GRIK3/CHRNA6/CACNA1B/KCNIP3/KCNJ5/PTPA/CLIC3/KCNAB2/PORCN/CALM3/ORAI1/ABCB8/KCNK6/CLCN7/CACNB1/KCNAB3/KCNC3/CACNA2D4/HCN2/CACNB3/ABHD12/FKBP1A/KCNMB1/TTYH2/KCNN4/KCNIP2/PRKACA/CNIH2/CACNA1H/SCNN1A/TTYH3/SCNN1D/STAC3/CACNA1F/CATSPER1/CLCN2/DLG4/PKD1/	162

					LRRC26/CACNA2D2/KCNG1/TMEM249/CACNA1I/OLFM2/CLCN1/TRPM4/SCN4B/SHISA8/CACNG6/CACNA2D3/KCNH2/KCNA5/TRPV6/HTR3A/EFCAB9/SLC17A7/CPT1C	
CC	GO:0000786	nucleosome	1.83E-05	1.66E-05	H2BC18/H2BC4/H3C4/SHPRH/H2AC20/H4C4/H4C5/H4C3/H2BC15/H2BC6/H2BC8/H2AC6/H2AC17/H2AC11/SLF1/EPC2/H2AC8/H4C16/H2AC15/TRRAP/H2AC13/KAT6A/H2BC11/KDM1B/H1-2/H1-3/H2BC5/H1-4/H4C2/H3C10/H2BC9/H2BC7/H3C8/H2BC3/H2BC13/H1-6/H4C8/H2BC12/H3C12/H2AC16/H2BC26/H4C9/H2AC21/H2BC17/H2BC10/H4C6/H3C2/H4C13/H1-5/H3C13/H2BC14/H2AC4/H2AC12/H3C3/H3C6/H2BC21/H3-5/H3C7/H3C11/H2AC7/H1-1/H4C1/H3C1/H3C15/H4C12/H4C14/H4C11/H3C14/TGM2/H4C15/H3-4/H1-10/DMAP1/H2AX/SPHK2/MACROH2A2/H2AB3	77
CC	GO:0044391	ribosomal subunit	1.83E-05	1.66E-05	NSUN3/DHX29/RPL10L/RPS16/RPL28/MRPL38/RPS3/MRPL12/RPS28/MRPS2/RPS15/RPL29/RPL8/RPL10/RPL18A/RPL18/RPL27/MRPL4/RPL7A/RPL13/RPS2/MRPS34/RPL14/RPL27A/RPL3/RPS21/SNU13/RPS19/RPL12/RPL36/MRPL9/MRPL52/MRPL41/RPL15/MRPL43/RPL37A/MRPL10/RPL13A/MRPL34/RPL19/MRPL54/MRPL2/RPL10A/RPS13/RPL23A/MPV17L2/GADD45GIP1/RPLP2/FAU/MRPL11/IMP3/RPSA/MRPS12/RPL37/MRPS21/RPL35/RACK1/NHP2/MRPL55/RPS5/RPS27A/MRPS26/RPLP1/MRPL24/RPS4X/AURKAIP1/RPL22/MRPS15/RPL38/RPL6/MRPL53/RPS29/RPS8/RPL32/MRPL37/RPS14/RPLP0/RPS23/RPL35A/RPS20/RPS25/RPS6/RPL4/RPL5/RPS26/RPL24/RPL23/RPL11/MRPL48/RPS27/RPL41/RPS11/MRPS6/RPL39/RPL9/RPS12/RPL26/RPL21/RPL34/MRPL23/RPS3A/RPSA2/RPL39L/RPS18/RPS17/RPS4Y2/RPS9/RPS4Y1	108
CC	GO:1902495	transmembrane transporter complex	1.83E-05	1.66E-05	AKAP9/NDUFS1/GRIK1/KCNS1/STXBP5/PLN/KCNE1/ANO6/ATP6V1A/BEST1/SLC5A3/CACNA1E/KCNC1/KCNJ2/GABRR2/SCN9A/PKD1L3/KCNG2/GRIN3A/SCN3B/LRRC8B/CHRNB2/KCNIP4/CLIC4/ATP6V1C1/CACNB2/ATP4B/CACNA1D/ANO2/CNGB3/TRPC5/RYR3/C2CD6/SHISA7/CHRNA2/KCNV2/CLCA3P/KCNS2/SCN8A/CHRNA1/ABCG5/HSPA2/SCN3A/CHRND/CACNB4/CNGA1/UNC80/TRPC6/TMEM262/SHISA6/ABCC9/GRIA3/LRRC8E/CACNA2D1/RYR2/BEST3/CHRNA5/GLRA2/KCNG3/VWC2L/GRIA4/GLRA1/HCN4/GABRA4/GRIN2A/ATP1	204

					B4/KCNMB2/CNGB1/CACNG1/GRIN2B/KCNJ3/KCNMA1/ABCG8/CACNA1S/ATP12A/GRIA1/KCNC2/GABRA2/CNTNAP2/GABRB1/GLRA3/GABRR1/SLC17A8/SCN1A/KCNV1/HCN1/SCN7A/GRID2/DPP10/ABCC8/KCNJ16/KCNJ6/GABRE/KCNA1/GABRG2/CATSPERD/BEST2/CLIC1/ANO1/GLRB/CHRFAM7A/VWC2/HTR3E/KCNJ11/GRIA2/GABRG3/CACNA1G/KCND2/CNGA3/DPP6/GABRA5/GABRG1/KCNIP1/GABRB2/GRIK3/CHRNA6/CACNA1B/KCNIP3/KCNJ5/ATP6V1F/ND2/ND3/ND4L/ND6/ND5/CYTB/NDUFA11/COX1/NDUFA7/NDUFB7/PTPA/NDUFS7/NDUFS8/NDUFB11/CLIC3/CYC1/KCNAB2/NDUFB10/NDUFS6/PORCN/NDUFS3/CALM3/ORAI1/NDUFC1/NDUFA13/ABCB8/KCNK6/CLCN7/CACNB1/NDUFV1/ND1/KCNAB3/ABCD4/KCNC3/NDUFB9/ND4/NDUFAB1/ATP6V0C/CACNA2D4/HCN2/CACNB3/ABHD12/FKBP1A/BCS1L/KCNMB1/NDUFB2/TTYH2/NDUFA12/KCNN4/KCNIP2/PRKACA/CNIH2/CACNA1H/FXYD1/SCNN1A/TTYH3/SCNN1D/STAC3/CACNA1F/CATSPER1/CLCN2/DLG4/PKD1/SLC9A1/LRRC26/CACNA2D2/KCNG1/TMEM249/CACNA1I/OLFM2/CLCN1/TRPM4/SCN4B/SHISA8/CACNG6/CACNA2D3/KCNH2/KCNA5/TRPV6/HTR3A/EFCAB9/NDUFA3/SLC17A7/CPT1C	
CC	GO:0043505	CENP-A containing nucleosome	1.40E-04	1.27E-04	H4C4/H4C5/H4C3/H2AC8/H4C16/H2BC11/H4C2/H4C8/H4C9/H4C6/H4C13/H2AC4/H4C1/H4C12/H4C14/H4C11/H4C15	17
CC	GO:0061638	CENP-A containing chromatin	1.40E-04	1.27E-04	H4C4/H4C5/H4C3/H2AC8/H4C16/H2BC11/H4C2/H4C8/H4C9/H4C6/H4C13/H2AC4/H4C1/H4C12/H4C14/H4C11/H4C15	17
CC	GO:0034506	chromosome, centromeric core domain	7.52E-04	6.85E-04	H4C4/H4C5/H4C3/H2AC8/H4C16/H2BC11/H4C2/H4C8/H4C9/H4C6/H4C13/H2AC4/H4C1/H4C12/H4C14/H4C11/H4C15	17
CC	GO:0005840	ribosome	9.00E-04	8.20E-04	LINC01004/LTN1/NUFIP2/NSUN3/HBS1L/ASCC3/DHX29/EIF2AK2/NEMF/GSPT1/RPL13AP3/RPL10L/HULC/RPS16/RPL28/MRPL38/RPS3/MRPL12/RPS28/MRPS2/RPS15/RPL29/RPL8/RPL10/RPL18A/NDUFA7/ZNF598/RPL18/RPL27/MRPL4/RPL7A/RPL13/RPS2/MRPS34/RPL14/RPL27A/RPL3/RPS21/SNU13/RPS19/RPL12/RPL36/MRPL9/MRPL52/MRPL41/RPL15/APEX1/SF1/MRPL43/RPL37A/MRPL10/RPL13A/MRPL34/RPL19/MRPL54/MRPL2/RNF25/RPL10A/RPS13/RPL23A/MPV17L2/GADD45GIP1/RPLP2/FAU/MRPL11/IMP3/RPSA/MRPS12/RPL37/M	125

					RPS21/RPL35/RACK1/NHP2/MRPL55/RPS5/RPS27A/MRPS26/RPLP1/MRPL24/RPS4X/AURKAIP1/RPL22/MRPS15/RPL38/RPL6/MRPL53/RPS29/RPS8/RPL32/MRPL37/RPS14/RPLP0/RPS23/RPL35A/RPS20/RPS25/RPS6/RPL4/RPL5/RPS26/RPL24/RPL23/MTG1/RPL11/MRPL48/BTF3/RPS27/RPL41/RPS11/MRPS6/RPL39/RPL9/RPS12/RPL26/RPL21/RPL34/MRPL23/RPS3A/RPSA2/RPL39L/RPS18/RPS17/RPS4Y2/RPS9/RPS4Y1	
CC	GO:0097060	synaptic membrane	1.39E-03	1.26E-03	AKAP9/UTRN/GRIK1/ITSN2/STRN/SYNE1/ZNRF2/LRRTM2/ADAM10/CTNNB1/FCHO2/KCNC1/KCNJ2/PICALM/DNM3/SYNJ1/ITGB3/PSEN1/SLC16A7/GABRR2/ITGB1/ZDHHC17/LRRC4/GRIN3A/FARP1/LIN7A/LRRC7/SLC30A1/P2RY1/ANK3/CHRNB2/STX3/CHRM5/SLC6A4/DNAJC6/CHRNG/RAP2A/GRIP2/PDLIM4/LHFPL4/HIP1/CNTN2/MUSK/SHISA7/CHRNA2/SSPN/ATP2B2/STX19/SCN8A/SLC1A2/CHRNA1/ADCY1/DGKI/DMD/RIMS2/CHRND/ANK2/DCC/KCTD16/SHISA6/NRXN3/GRIA3/KCNJ9/CHRNA5/GLRA2/CDH9/GRIA4/ERBB4/GLRA1/NLGN1/GABRA4/GRIN2A/GABBR2/HTR2A/GRIN2B/KCNJ3/NLGN4X/KCNMA1/CHRM3/GRIA1/KCNC2/ERC2/GABRA2/IL1RAPL1/CNTNAP2/GHSR/OTOF/GABRB1/DGKB/GLRA3/CDH8/GABRR1/SHANK2/NTNG1/SNAP91/HCN1/ITGA8/PTPRT/LRRTM4/LRRTM3/SYT1/CDH10/PPFIA2/GRM5/GRID2/ADCY8/SORCS3/NRXN1/GABRE/KCNA1/GABRG2/PTPRD/LRRC4C/CNTNAP4/RIMS1/SRPX2/SLC6A1/ACTN2/OPRK1/RGS7BP/TENM2/ADGRB3/CLSTN2/CBLN1/SLC6A7/GLRB/ATP2B3/CNTN5/GRIA2/GABRG3/KCND2/GPR158/GABRA5/GABRG1/RIMS4/FLRT3/GABRB2/CNTN1/GRIK3/CHRNA6/SLC6A11/KCTD8/TMUB1/NDUFS7/SIGMAR1/ABHD17A/NIPSNAP1/ADGRL1/LRFN4/FXYD6/PPP1R9B/LRFN3/KCNC3/STX1A/PICK1/FBXO2/SNTA1/NINJ1/NLGN2/CNIH2/ZC4H2/SRC/LRFN1/SEMA4C/LIN7B/IQSEC3/ERBB2/TAMALIN/DLG4/BAIAP2/LPAR2/FOSL1/CPLX3/DBN1/NECTIN1/RGS9/PRRT2/NSG1/MAGEE1/ADAM11/DAGLA/RPH3A/SLC1A7/DNM1/GRM2/ARC/SCRIB/SHISA8/SHANK1/ADAM23/CHRM4/HTR3A/COL13A1/DNAJA3/FAIM2/HTR1B	196
CC	GO:0062023	collagen-containing extracellular matrix	1.85E-03	1.69E-03	EYS/A2M/ERBIN/ANGPTL1/ANGPT2/LAMB1/ABI3BP/NID2/ASPN/MEGF9/AHSG/PZP/LTBP1/COL6A6/IMPG2/ECM2/MMRN1/ANGPTL7/FBN2/COL4A4/OGN/CTHRC1/ACTA2/DST/FGL2/COL10A1/TNC/VCAN/PLSCR1/FN1/NTN1/LOXL4/ANGPTL2/ADAMDEC1/MMP8/F13A1/FBN1/USH2A/IL7/PCSK6/FREM2/	209

					PRG4/ANGPTL3/EMILIN2/COL24A1/COL4A2/KNG1/WNT2B/S100A9/LAMC1/COL17A1/CCDC80/ADAMTS2/HMCN2/IMPG1/SERPING1/ACAN/NPNT/COL4A5/ANGPT1/S100A8/HMCN1/COL4A1/FREM1/TGM2/TNR/LAMB4/ADAMTS20/BMP7/C1QB/COL4A6/COL19A1/COMP/COL2A1/THSD4/F2/PRG3/COL12A1/SMOC2/ADAMTS9/FGA/FRAS1/LAMA3/ADAMTS3/F3/CCN3/COL25A1/COL11A1/AMBP/COL20A1/COL6A5/GPC6/APLP1/SHH/LAMC2/FGB/CDH2/EDIL3/PTPRZ1/COL9A1/LAMA1/MUC17/C1QC/AMELX/GPC5/TGFB2/EGFLAM/SOST/FGL1/SPARCL1/HRNR/ZG16/EMILIN3/MXRA5/FLG/SULF1/VWA2/AGT/COL14A1/WNT8A/FMOD/SFRP2/PLG/SRPX2/AZGP1/COL3A1/CBLN1/VWC2/ITIH5/COL8A1/SOD3/ANGPTL5/FGG/APOC3/SPP2/SERPINA5/MFAP2/CBLN4/SERPINA3/NCAN/PRELP/COL1A2/PRSS1/LTBP4/CSTB/S100A10/LTBP3/PCOLCE/TGFB1/SERPINB6/LGALS9/S100A4/P3H1/CRELD1/TIMP1/LGALS1/MFGE8/PLOD3/ADAMTS10/COLQ/FGFBP3/A1BG/TGFB3/CTSF/EFEMP2/SERPINF1/HAPLN3/S100A6/CLEC3B/ZP3/SERPINH1/MMP23B/AEBP1/COL6A2/NPPA/MDK/COL9A2/PDGFB/RELL2/SSC5D/ANGPTL6/GPC2/ADAM11/F12/COL6A1/ANG/CILP/LAMC3/ADAMTS4/TPSAB1/FBLN5/KAZALD1/LAMA5/KRT1/COL1A1/PODN/TPSB2/DEFA1/APOE/COL5A3/DEFA1B/COL26A1/COL13A1/GDF10/ENTPD2/MMP28/LEFTY2/SERPINF2/SRPX	
CC	GO:0099572	postsynaptic specialization	2.29E-03	2.09E-03	INSYN2B/ATP7A/USP8/CDKL5/AKAP9/ERBIN/ITPR1/GRIK1/USP50/DISC1/STRN/CPEB3/LRRTM2/CPEB4/SLC8A1/VPS35/ADAM10/PJA2/CTNNB1/DNM3/PDLIM5/PTEN/SIPA1L1/TNIK/RTN4/SLC16A7/SPTBN1/LRRC4/GRIN3A/LIN7A/ZDHHC2/LRRC7/SLC30A1/EGLN1/AURKA/P2RY1/CHRNB2/HOMER1/MAP1B/DNAJC6/GRIP2/ZDHHC15/TANC1/HNRNPH2/PSD3/LHFPL4/SRGN/SHISA7/ATP2B2/SCN8A/CHRNA1/CTNND1/ADCY1/DGKI/SLC8A3/CHRND/PPP1R9A/DCC/SHISA6/DLGAP1/GRIA3/MPDZ/DCLK1/TMEM108/INSYN1/GRIA4/ERBB4/NLGN1/GABRA4/GRIN2A/ADGRA1/CAMK2A/GRIN2B/NLGN4X/CDH2/GRIA1/GABRA2/GABRB1/SHANK2/ITGA8/PTPRT/LRRTM3/CDH10/PPFIA2/GRM5/SH2D5/GRID2/ADCY8/SORCS3/PCLO/IGSF11/LRRC4C/GAP43/NOS1/ACTN2/RGS7BP/CAP2/ADGRB3/CLSTN2/GLRB/GRIA2/KCND2/GABRA5/FLRT3/GABRB2/GRIK3/SH3GL3/RPS3/RPL8/PHB2/GIT1/RPL14/KLHL17/RPS19	173

					/RPL12/RUSC1/SIGMAR1/ABHD17A/DLGAP4/PRR12/DVL1/CAPZB/RPS13/LRFN4/RGS14/NSMF/PPP1R9B/LRFN3/PICK1/RPL38/ARF1/RPL6/DNAJB1/RPS14/RPLP0/RPS25/ABI3/CAMK2N1/HOMER3/NLGN2/DLGAP3/CNIH2/RPS27/SRC/LRFN1/SEMA4C/LIN7B/IQSEC3/ADGRB1/TAMALIN/LZTS3/NEURL1/DLG4/SYNPO/SYN1/BAIAP2/DBN1/RGS9/PRRT2/PAK6/DAGLA/MAPK8IP2/MPP2/DMTN/NGFR/RPS18/NCS1/ARC/SCRIB/SHISA8/SHANK1/PALM/SYNGAP1	
CC	GO:0016442	RISC complex	2.95E-03	2.68E-03	AGO3/DICER1/MIR133A1HG/MIR21/DCP2/AGO4/AGO1/MIR1296/MIR601/MIR302B/DNM3OS/MIR186/MIR29A/MIR505/MIR553/MIR581/MIR16-1/MIR223/MIR101-1/MIR612/MIR938/MIR744/MIR17HG/MIR181A2/MIR628/NEAT1/MIR326/MIR30C1/MIR576/MIR181B2/MIR580/MIR197/MIR302C/MIRLET7F1/MIR320C1/MIR302A/MIR604/MIR29B1/MIR32/MIR573/MIR15A/MIR215/MIR148B/MIR302D/MIR624/MIRLET7G/MIR590/MIR491/MIR920/MIR454/MIR558/MIR331/MIRLET7F2/MIR30E/MIR128-1/MIR640/MIR191/MIR103A1/SPACA6-AS1/MIR98/MIR15B/MIR618/MIR1183/MIR199A1/MIR181A1/MIR761/MIR320D1/MIRLET7A1/MIR194-1/MIR1207/MIR320A/MIR144/MIR643/MIR550A3/MIR661/MIR425/MIR367/MIR423/MIR222/MIR625/MIR626/MIR361/MIR150/MIR185/MIR569/MIR611/MIR27B/MIR24-2/MIR9-2HG/MIR140/MIR195/MIR330/MIR212/MIR3065/MIR942/MIR1827/MIR130A/MIR196A1/TARBP2/MIR142/MIR25/MIR631/MIR324/MIR339/MEG3/MIR103A2/HOXA10-AS	107
CC	GO:0031332	RNAi effector complex	2.95E-03	2.68E-03	AGO3/DICER1/MIR133A1HG/MIR21/DCP2/AGO4/AGO1/MIR1296/MIR601/MIR302B/DNM3OS/MIR186/MIR29A/MIR505/MIR553/MIR581/MIR16-1/MIR223/MIR101-1/MIR612/MIR938/MIR744/MIR17HG/MIR181A2/MIR628/NEAT1/MIR326/MIR30C1/MIR576/MIR181B2/MIR580/MIR197/MIR302C/MIRLET7F1/MIR320C1/MIR302A/MIR604/MIR29B1/MIR32/MIR573/MIR15A/MIR215/MIR148B/MIR302D/MIR624/MIRLET7G/MIR590/MIR491/MIR920/MIR454/MIR558/MIR331/MIRLET7F2/MIR30E/MIR128-1/MIR640/MIR191/MIR103A1/SPACA6-AS1/MIR98/MIR15B/MIR618/MIR1183/MIR199A1/MIR181A1/MIR761/MIR320D1/MIRLET7A1/MIR194-	107

					1/MIR1207/MIR320A/MIR144/MIR643/MIR550A3/MIR661/MIR425/MIR367/MIR423/MIR222/MIR625/MIR626/MIR361/MIR150/MIR185/MIR569/MIR611/MIR27B/MIR24-2/MIR9-2HG/MIR140/MIR195/MIR330/MIR212/MIR3065/MIR942/MIR1827/MIR130A/MIR196A1/TARBP2/MIR142/MIR25/MIR631/MIR324/MIR339/MEG3/MIR103A2/HOXA10-AS	
CC	GO:0015934	large ribosomal subunit	3.24E-03	2.95E-03	NSUN3/RPL10L/RPL28/MRPL38/MRPL12/RPL29/RPL8/RPL10/RPL18A/RPL18/RPL27/MRPL4/RPL7A/RPL13/RPL14/RPL27A/RPL3/SNU13/RPL12/RPL36/MRPL9/MRPL52/MRPL41/RPL15/MRPL43/RPL37A/MRPL10/RPL13A/MRPL34/RPL19/MRPL54/MRPL2/RPL10A/RPL23A/MPV17L2/GADD45GIP1/RPLP2/MRPL11/RPL37/RPL35/NHP2/MRPL55/RPLP1/MRPL24/RPL22/RPL38/RPL6/MRPL53/RPL32/MRPL37/RPLP0/RPL35A/RPL4/RPL5/RPL24/RPL23/RPL11/MRPL48/RPL41/RPL39/RPL9/RPL26/RPL21/RPL34/MRPL23/RPL39L	66
CC	GO:0098984	neuron to neuron synapse	4.65E-03	4.23E-03	INSYN2B/ATP7A/USP8/CDKL5/AKAP9/ITPR1/GRIK1/PLXNC1/USP50/DISC1/STXBP5/STRN/ARFGEF2/CPEB3/LRRTM2/CPEB4/SLC8A1/RNF19A/VPS35/ADAM10/PJA2/CTNNB1/DNM3/PDLIM5/PTEN/SIPA1L1/TNIK/CALB1/RTN4/SLC16A7/ITGB1/SPTBN1/LRRC4/GRIN3A/LIN7A/ZDHHC2/SORT1/LRRC7/SLC30A1/EGLN1/AURKA/P2RY1/HOMER1/MAP1B/DNAJC6/GRIP2/ZDHHC15/TANC1/HNRNPH2/PSD3/SYT9/SHISA7/C1QL3/ATP2B2/RAPGEF4/PDYN/SCN8A/CTNND1/ADCY1/DGKI/SLC8A3/PPP1R9A/DCC/SHISA6/DLGAP1/GRIA3/MPDZ/DCLK1/TMEM108/INSYN1/GRIA4/ERBB4/NLGN1/GRIN2A/ADGRA1/CAMK2A/GRIN2B/NLGN4X/CDH2/SLC1A1/GRIA1/SHANK2/CALCA/ITGA8/PTPRT/LRRTM3/SYT1/GRM5/SH2D5/GRID2/ADCY8/SORCS3/PCLO/C1QL2/IGSF11/PTPRD/LRRC4C/GAP43/NOS1/ACTN2/RGS7BP/CAP2/ADGRB3/CLSTN2/GRIA2/FLRT3/GRIK3/P2RX3/SH3GL3/RPS3/RPL8/PHB2/GIT1/RPL14/KLHL17/RPS19/RPL12/RUSC1/SIGMAR1/ABHD17A/PRR12/DVL1/CAPZB/RPS13/SLC39A3/LRFN4/RGS14/NSMF/PPP1R9B/LRFN3/PICK1/RPL38/ARF1/RPL6/DNAJB1/RPS14/RPLP0/RPS25/ABI3/CAMK2N1/ROGDI/HOMER3/NLGN2/DLGAP3/CNIH2/RPS27/LRFN1/PRKAR1B/SEMA4C/LIN7B/IQSEC3/ADGRB1/TAMALIN/LZTS3/NEURL1/DLG4/SYNPO/SYN1/BAIAP2/DBN1/NECTIN1/RGS9/PRRT2/PAK6/DAGLA/MAPK8IP2/MPP2/DMTN/NGF	178

					R/RPS18/NCS1/ARC/SCRIB/SHISA8/SHANK1/PALM/SYNGAP1/PENK	
CC	GO:0045211	postsynaptic membrane	5.19E-03	4.73E-03	AKAP9/UTRN/GRIK1/STRN/SYNE1/LRRTM2/CTNNB1/KCNC1/KCNJ2/PICALM/DNM3/ITGB3/SLC16A7/GABRR2/LRRC4/GRIN3A/FARP1/LIN7A/LRRC7/SLC30A1/P2RY1/ANK3/CHRNB2/CHRM5/SLC6A4/CHRNG/GRIP2/PDLIM4/LHFPL4/HIP1/CNTN2/MUSK/SHISA7/CHRNA2/SSPN/ATP2B2/SCN8A/CHRNA1/ADCY1/DMD/CHRND/ANK2/DCC/KCTD16/SHISA6/GRIA3/CHRNA5/GLRA2/CDH9/GRIA4/ERBB4/GLRA1/NLGN1/GABRA4/GRIN2A/GABBR2/HTR2A/GRIN2B/NLGN4X/KCNMA1/CHRM3/GRIA1/KCNC2/GABRA2/IL1RAPL1/GABRB1/DGKB/GLRA3/GABRR1/SHANK2/HCN1/ITGA8/PTPRT/LRRTM4/LRRTM3/CDH10/GRM5/GRID2/SORCS3/GABRE/KCNA1/GABRG2/LRRC4C/SLC6A1/ACTN2/OPRK1/RGS7BP/TENM2/ADGRB3/CLSTN2/CBLN1/GLRB/GRIA2/GABRG3/KCND2/GPR158/GABRA5/GABRG1/FLRT3/GABRB2/CNTN1/GRIK3/CHRNA6/SLC6A11/KCTD8/TMUB1/SIGMAR1/ABHD17A/LRFN4/FXYD6/LRFN3/KCNC3/FBXO2/SNTA1/NLGN2/CNIH2/ZC4H2/LRFN1/SEMA4C/LIN7B/IQSEC3/TAMALIN/DLG4/DBN1/RGS9/PRRT2/NSG1/MAGEE1/DAGLA/RPH3A/ARC/SCRIB/SHISA8/SHANK1/CHRM4/HTR3A/COL13A1/DNAJA3/FAIM2	139
CC	GO:0034703	cation channel complex	5.19E-03	4.73E-03	AKAP9/GRIK1/KCNS1/KCNE1/SLC5A3/CACNA1E/KCNC1/KCNJ2/SCN9A/PKD1L3/KCNG2/SCN3B/KCNIP4/CACNB2/CACNA1D/CNGB3/TRPC5/RYR3/C2CD6/KCNV2/KCNS2/SCN8A/HSPA2/SCN3A/CACNB4/CNGA1/UNC80/TRPC6/TMEM262/ABCC9/CACNA2D1/RYR2/KCNG3/HCN4/KCNMB2/CNGB1/CACNG1/KCNJ3/KCNMA1/CACNA1S/KCNC2/CNTNAP2/SCN1A/KCNV1/HCN1/SCN7A/DPP10/ABCC8/KCNJ16/KCNJ6/KCNA1/CATSPERD/HTR3E/KCNJ11/CACNA1G/KCND2/CNGA3/DPP6/KCNIP1/GRIK3/CACNA1B/KCNIP3/KCNJ5/PTPA/KCNAB2/CALM3/ORAI1/ABCB8/KCNK6/CACNB1/KCNAB3/KCNC3/CACNA2D4/HCN2/CACNB3/FKBP1A/KCNMB1/KCNN4/KCNIP2/PRKACA/CACNA1H/SCNN1A/SCNN1D/STAC3/CACNA1F/CATSPER1/PKD1/LRRC26/CACNA2D2/KCNG1/TMEM249/CACNA1I/TRPM4/SCN4B/CACNG6/CACNA2D3/KCNH2/KCNA5/TRPV6/HTR3A/EFCAB9	101
CC	GO:0072562	blood microparticle	5.35E-03	4.87E-03	A2M/ZBTB38/AHSG/PZP/CP/TFRC/CFH/APOA2/FN1/ZNF559-	77

					ZNF177/PROS1/STOM/F13A1/KNG1/HPR/HSPA2/SERPING1/HP/SLC4A1/ITGA2B/ACSM1/CFHR3/C1QB/F2/C4BPA/FGA/PON1/AMBP/FGB/CD5L/ZNF177/C1QC/HBG2/AGT/CLIC1/PLG/ACTC1/FGG/SERPINA3/C9/PRSS1/PFN1/PSMC5/INTS11/TGFB1/ENG/A1BG/HBD/TMPRSS13/HSPA7/C1R/IGHD/C8G/IGHA2/CIB2/IGLC2/IGKC/IGHA1/HBE1/IGHG2/IGLV1-47/IGHG4/IGKV2D-28/IGLC3/OAZ3/KRT1/HBB/IGHV3-13/APOE/ACTA1/HBA1/IGHM/HBA2/IGHG3/IGKV1D-12/SERPINF2/ACTG2	
CC	GO:0014069	postsynaptic density	9.09E-03	8.28E-03	INSYN2B/ATP7A/USP8/CDKL5/AKAP9/ITPR1/GRIK1/USP50/DISC1/STRN/CPEB3/LRRTM2/CPEB4/SLC8A1/VPS35/ADAM10/PJA2/CTNNB1/DNM3/PDLIM5/PTEN/SIPA1L1/TNIK/RTN4/SLC16A7/SPTBN1/LRRC4/GRIN3A/LIN7A/ZDHHC2/LRRC7/SLC30A1/EGLN1/AURKA/P2RY1/HOMER1/MAP1B/DNAJC6/GRIP2/ZDHHC15/TANC1/HNRNPH2/PSD3/SHISA7/ATP2B2/SCN8A/CTNND1/ADCY1/DGKI/SLC8A3/PPP1R9A/DCC/SHISA6/DLGAP1/GRIA3/MPDZ/DCLK1/TMEM108/INSYN1/GRIA4/ERBB4/NLGN1/GRIN2A/ADGRA1/CAMK2A/GRIN2B/NLGN4X/CDH2/GRIA1/SHANK2/ITGA8/PTPRT/LRRTM3/GRM5/SH2D5/GRID2/ADCY8/SORCS3/PCLO/IGSF11/LRRC4C/GAP43/NOS1/ACTN2/RGS7BP/CAP2/ADGRB3/CLSTN2/GRIA2/FLRT3/GRIK3/SH3GL3/RPS3/RPL8/PHB2/GIT1/RPL14/KLHL17/RPS19/RPL12/RUSC1/SIGMAR1/ABHD17A/PRR12/DVL1/CAPZB/RPS13/LRFN4/RGS14/NSMF/PPP1R9B/LRFN3/PICK1/RPL38/ARF1/RPL6/DNAJB1/RPS14/RPLP0/RPS25/ABI3/CAMK2N1/HOMER3/DLGAP3/CNIH2/RPS27/LRFN1/SEMA4C/LIN7B/IQSEC3/ADGRB1/TAMALIN/LZTS3/NEURL1/DLG4/SYNPO/SYN1/BAIAP2/DBN1/RGS9/PRRT2/PAK6/DAGLA/MAPK8IP2/MPP2/DMTN/NGFR/RPS18/NCS1/ARC/SCRIB/SHISA8/SHANK1/PALM/SYNGAP1	155
CC	GO:0032279	asymmetric synapse	1.38E-02	1.26E-02	INSYN2B/ATP7A/USP8/CDKL5/AKAP9/ITPR1/GRIK1/PLXNC1/USP50/DISC1/STRN/ARFGEF2/CPEB3/LRRTM2/CPEB4/SLC8A1/VPS35/ADAM10/PJA2/CTNNB1/DNM3/PDLIM5/PTEN/SIPA1L1/TNIK/RTN4/SLC16A7/ITGB1/SPTBN1/LRRC4/GRIN3A/LIN7A/ZDHHC2/SORT1/LRRC7/SLC30A1/EGLN1/AURKA/P2RY1/HOMER1/MAP1B/DNAJC6/GRIP2/ZDHHC15/TANC1/HNRNPH2/PSD3/SHISA7/ATP2B2/SCN8A/CTNND1/ADCY1/DGKI/SLC8A3/PPP1R9A/DCC/SHISA6/DLGAP1/GRIA3/MPDZ/DCLK	161

					1/TMEM108/INSYN1/GRIA4/ERBB4/NLGN1/GRIN2A/ADGRA1/CAMK2A/GRIN2B/NLGN4X/CDH2/SLC1A1/GRIA1/SHANK2/ITGA8/PTPRT/LRRTM3/GRM5/SH2D5/GRID2/ADCY8/SORCS3/PCLO/C1QL2/IGSF11/LRRC4C/GAP43/NOS1/ACTN2/RGS7BP/CAP2/ADGRB3/CLSTN2/GRIA2/FLRT3/GRIK3/SH3GL3/RPS3/RPL8/PHB2/GIT1/RPL14/KLHL17/RPS19/RPL12/RUSC1/SIGMAR1/ABHD17A/PRR12/DVL1/CAPZB/RPS13/LRFN4/RGS14/NSMF/PPP1R9B/LRFN3/PICK1/RPL38/ARF1/RPL6/DNAJB1/RPS14/RPLP0/RPS25/ABI3/CAMK2N1/HOMER3/DLGAP3/CNIH2/RPS27/LRFN1/SEMA4C/LIN7B/IQSEC3/ADGRB1/TAMALIN/LZTS3/NEURL1/DLG4/SYNPO/SYN1/BAIAP2/DBN1/RGS9/PRRT2/PAK6/DAGLA/MAPK8IP2/MPP2/DMTN/NGFR/RPS18/NCS1/ARC/SCRIB/SHISA8/SHANK1/PALM/SYNGAP1	
CC	GO:0044309	neuron spine	1.38E-02	1.26E-02	USP8/USP50/STRN/SYNE1/ARFGEF2/CPEB4/EEA1/SEZ6/MOB4/KCNJ2/DNM3/PTEN/OPHN1/SIPA1L1/DOCK10/CALB1/NEDD4/ITGB1/PTK2/LRRC4/FARP1/ASAP1/HOMER1/MAP1B/GRIP2/PRKAR2B/PDLIM4/SHISA7/ATP2B2/CTNND1/DGKI/SLC8A3/PPP1R9A/CTTN/SHISA6/GRIA3/IGF2BP1/GRIA4/NLGN1/KCNN2/GRIN2A/CAMK2A/SLC1A1/GRIA1/SHANK2/ITGA8/PPFIA2/GRM5/GRID2/NOS1/ACTN2/RGS7BP/MYL7/TENM2/FRMPD4/GRIA2/KCND2/PALMD/GIPC1/PPP1CA/ABHD17A/DVL1/CD3E/ARHGAP33/APBA3/RGS14/PPP1R9B/KCNC3/NR1D1/DNAJB1/RAC1/FBXO2/ABI3/STRN4/PRKACA/CNIH2/ADGRB1/LZTS3/NEURL1/DLG4/SYNPO/BAIAP2/PRRT2/DAGLA/RPH3A/MPP2/NGFR/ARC/SHISA8/APBA2/SHANK1/PALM	92
CC	GO:0031838	haptoglobin-hemoglobin complex	2.00E-02	1.83E-02	HP/HBG1/HBG2/HBD/HBM/HBE1/HBQ1/HBB/HBA1/HBA2	10
CC	GO:0071735	IgG immunoglobulin complex	2.00E-02	1.83E-02	IGLC2/IGKC/IGHA1/IGHG2/IGLL5/IGHG4/IGLC3/IGLL1/IGLC7/IGHG3	10
CC	GO:0043197	dendritic spine	2.15E-02	1.95E-02	USP8/USP50/STRN/SYNE1/ARFGEF2/CPEB4/SEZ6/MOB4/KCNJ2/DNM3/PTEN/OPHN1/SIPA1L1/DOCK10/CALB1/NEDD4/ITGB1/PTK2/LRRC4/FARP1/ASAP1/HOMER1/MAP1B/PRKAR2B/PDLIM4/SHISA7/ATP2B2/CTNND1/DGKI/SLC8A3/PPP1R9A/CTTN/SHISA6/GRIA3/IGF2BP1/GRIA4/NLGN1/KCNN2/GRIN2A/CAMK2A/SLC1A1/GRIA1/SHANK2/ITGA8/PPFIA2/GRM5/GRID2/NOS1/ACTN2/RGS7BP/MYL7/TENM2/FRMPD4/GRIA2/KCND2/PALMD/GIPC1/PPP1CA/ABHD17A/DVL1/CD3E/ARHGAP33/APBA3/RGS14/PPP1R9B/KCNC3/NR1D1/DNAJB1/RA	90

					C1/FBXO2/ABI3/STRN4/PRKACA/CNIH2/ADGRB1/LZTS3/NEURL1/DLG4/SYNPO/BAIAP2/PRRT2/DAGLA/RPH3A/MPP2/NGFR/ARC/SHISA8/APBA2/SHANK1/PALM	
CC	GO:0042788	polysomal ribosome	2.15E-02	1.95E-02	NUFIP2/RPS28/RPL8/RPL18A/RPL18/RPL7A/RPS21/RPL36/RPL19/RPL10A/RPL38/RPL6/RPS29/RPL32/RPS23/RPS26/RPL24/RPL11/BTF3/RPL41/RPL39	21
CC	GO:0098978	glutamatergic synapse	3.08E-02	2.81E-02	BTBD9/NF1/USP8/CDKL5/AKAP9/LRRK2/ERBIN/PLXNC1/DISC1/EPS15/CLCN3/ARFGEF2/JAK2/LRRTM2/CPSF2/RNF19A/EEA1/VPS35/ADAM10/CTNNB1/UBE3A/KCNJ2/GUCY1A1/DNM3/OPHN1/TNIK/DOCK10/IL1RAP/CALB1/SNX6/RTN4/ITGB3/PSEN1/SLC16A7/ITGB1/TRIO/PRKAR1A/SPTBN1/LRRC4/GRIN3A/FARP1/SORT1/EGLN1/GUCY1B1/MAPK14/AURKA/ASAP1/STK38L/P2RY1/HOMER1/STX3/GRIP2/TANC1/EPHB1/PRKAR2B/HIP1/SRGN/C1QL3/SPTB/CDH6/ATP2B2/SCN8A/SLC1A2/FILIP1/CTNND1/ADCY1/WASF3/ICAM5/FZD4/SLITRK4/CACNB4/CADPS/CPLX2/CDH11/ADGRL3/SHISA6/NOS1AP/DLGAP1/CADPS2/TNR/ERBB4/NLGN1/GRIN2A/ADGRA1/HTR2A/GPC6/NLGN4X/GRIA1/ERC2/IL1RAPL1/GHSR/FLOT1/CDH8/GABRR1/SHANK2/SPARCL1/NTNG1/HCN1/ITGA8/PTPRT/LRRTM3/SYT1/CDH10/PPFIA2/GRM5/GRID2/ADCY8/SORCS3/PCLO/C1QL2/KCNA1/PTPRD/LRRC4C/SYT4/ACTN2/RGS7BP/EPHA7/ADGRB3/CLSTN2/CBLN1/ATP2B3/SLC6A17/KCND2/ACTC1/NRG3/SH3GL2/FLRT3/GRIK3/SH3GL3/SYT10/PIN1/PFN1/PHB2/GIPC1/KLHL17/PPP1CA/ABHD17A/CORO1A/DLGAP4/DVL1/MAPK3/PORCN/SH3GL1/PPP2R1A/LRFN4/RGS14/FXYD6/LRFN3/BIN1/ARPC5L/RPL22/DNAJB1/RAC1/FBXO2/PPFIA3/HOMER3/DLGAP3/PRKACA/DGKQ/ARRB2/SRC/PRKAR1B/TAMALIN/PLXND1/NPTXR/RTN4R/DLG4/NAPA/RAC3/BAIAP2/LPAR2/DBN1/RGS9/CPLX1/PRRT2/NSG1/MAP1LC3A/DNM1/CALY/GRM2/ARC/WNT7A/LAMA5/SCRIB/SHANK1/ADAM23/APOE/HRAS/SYNGAP1/VGF/NPTX2/CPT1C	192
MF	GO:0030527	structural constituent of chromatin	5.71E-12	5.32E-12	H2BC18/H2BC4/H3C4/H2AC20/H4C4/H4C5/H4C3/H2BC15/H2BC6/H2BC8/H2AC6/H2AC17/H2AC11/H2AC8/H4C16/H2AC15/H2AC13/H2BC11/H1-2/H1-3/H2BC5/H1-4/H4C2/H3C10/H2BC9/H2BC7/H3C8/H2BC3/H2BC13/H1-6/H4C8/H2BC12/H3C12/H2AC16/H2BC26/H4C9/H2AC21/H2BC17/H2BC10/H4C6/H3C2/H4C13/H1-5/H3C13/H2BC14/H2AC4/H2AC12/H3C3/H3C6/H2BC21/H3	70

					-5/H3C7/H3C11/H2AC7/H1-1/H4C1/H3C1/H3C15/H4C12/H4C14/H4C11/H3C14/H4C15/H3-4/H1-10/HMGA1/H2AX/MACROH2A2/LMNTD2/H2AB3	
MF	GO:0003735	structural constituent of ribosome	9.98E-06	9.29E-06	LINC01004/SRBD1/RPL13AP3/RPL10L/RPS16/RPL28/RPS3/MRPL12/RPS28/MRPS2/RPS15/RPL29/RPL8/RPL10/RPL18A/NDUFA7/RPL18/RPL27/MRPL4/RPL7A/RPL13/RPS2/MRPS34/RPL14/RPL27A/RPL3/RPS21/RPS19/RPL12/RPL36/MRPL9/MRPL52/MRPL41/RPL15/MRPL43/RPL37A/MRPL10/RPL13A/MRPL34/RPL19/MRPL54/MRPL2/RPL10A/RPS13/RPL23A/RPLP2/FAU/MRPL11/IMP3/RPSA/MRPS12/RPL37/MRPS21/RPL35/MRPL55/RPS5/RPS27A/RPLP1/MRPL24/RPS4X/RPL22/MRPS15/RPL38/RPL6/RPS29/RPS8/RPL32/MRPL37/RPS14/RPLP0/RPS23/RPL35A/RPS20/RPS25/RPS6/RPL4/RPL5/RPS26/RPL24/RPL23/RPL11/RPS27/RPL41/RPS11/MRPS6/RPL39/RPL9/RPS12/RPL26/RPL21/RPL34/MRPL23/RPS3A/RPSA2/RPL39L/RPS18/RPS17/RPS4Y2/RPS9/RPS4Y1	100
MF	GO:0005216	monoatomic ion channel activity	9.29E-05	8.65E-05	ITPR2/KCNJ13/TRPM7/ITPR1/GRIK1/KCNS1/CLCN3/PKD2L2/KCNE1/ANO6/ITGAV/ATP6V1A/BEST1/CACNA1E/KCNC1/KCNJ2/KCNH7/TRPM6/KCNJ15/PSEN1/GABRR2/TRPA1/SCN9A/PKD1L3/KCNG2/GRIN3A/CYBB/SCN3B/SLC26A8/ATP5F1E/LRRC8B/CHRNB2/KCNIP4/CALHM5/CLIC4/SLC6A4/ATP5MGL/CHRNG/CACNB2/P2RX7/CACNA1D/KCNE3/ANO2/CNGB3/TRPC5/RYR3/KCNH6/TMC3/CHRNA2/KCNV2/CLCA3P/MCOLN2/KCNS2/ANO5/SCN8A/SLC24A3/CHRNA1/OPRM1/SLC9C1/KCNN3/KCNJ1/GJC1/SCN3A/CHRND/CACNB4/AQP1/KCNT2/TRPM3/SLC24A2/TMC5/TMEM150C/ANO7/CNGA1/UNC80/TRPC6/ABCC9/GRIA3/LRRC8E/KCNJ9/CACNA2D1/RYR2/BEST3/CHRNA5/GLRA2/ZACN/KCNG3/GRIA4/GLRA1/HCN4/KCNN2/GABRA4/GRIN2A/KCNMB2/CNGB1/CACNG1/GRIN2B/KCNJ3/SLC1A1/KCNMA1/CACNA1S/GRIA1/KCNC2/GABRA2/NALCN/GABRB1/GLRA3/PKD1L2/GABRR1/SLC17A8/KCNK3/NOX5/SCN1A/ANO3/KCNV1/HCN1/SCN7A/GRID2/ABCC8/PIEZO2/ANO4/KCNJ16/KCNJ6/GABRE/KCNA1/GABRG2/CLCA4/BEST2/CLIC1/KCNJ18/ANO1/GLRB/CHRFAM7A/HTR3E/KCNJ11/GRIA2/GABRG3/CACNA1G/SLC26A9/KCND2/CNGA3/CLCA2/GABRA5/KCNK16/GABRG1/CALHM4/KCNIP1/GABRB2/GRIK3/P2RX3/CHRNA6/CACNA1B/KCNIP3/KCNJ5/ATP5F1D/ATP8/ATP6/TMEM175/ATP5MF/TMC8/CLIC3/KCNAB2/A	224

					SIC3/ATP5PO/ORAI1/KCNK6/CLCN7/TMEM109/CACNB1/KCNAB3/KCNC3/TMC6/ATP6V0C/CACNA2D4/ANO9/HCN2/ATP5PF/CACNB3/TPCN1/ANO8/KCNMB1/CALHM2/TTYH2/KCNN4/KCNIP2/CACNA1H/FXYD1/SCNN1A/BNIP1/TTYH3/SCNN1D/MCOLN1/ATP5F1EP2/PIEZO1/P2RX5/CACNA1F/CATSPER1/CLCN2/SLC26A11/PKD1/LRRC26/CACNA2D2/KCNG1/ASIC1/CACNA1I/KCNH3/SLC1A7/NCS1/CLCN1/TRPM4/KCNT1/SCN4B/KCNK17/OTOP2/CACNG6/CACNA2D3/KCNH2/KCNK10/KCNA5/TRPV6/HTR3A/SLC17A3/SLC17A7/NALF2/HTR1B	
MF	GO:0022839	monoatomic ion gated channel activity	6.99E-04	6.51E-04	ITPR2/KCNJ13/ITPR1/GRIK1/KCNS1/CLCN3/KCNE1/ANO6/ITGAV/CACNA1E/KCNC1/KCNJ2/KCNH7/KCNJ15/GABRR2/TRPA1/SCN9A/KCNG2/GRIN3A/CYBB/SCN3B/CHRNB2/KCNIP4/CLIC4/CHRNG/CACNB2/P2RX7/CACNA1D/KCNE3/CNGB3/RYR3/KCNH6/TMC3/CHRNA2/KCNV2/CLCA3P/MCOLN2/KCNS2/SCN8A/CHRNA1/OPRM1/KCNN3/KCNJ1/SCN3A/CHRND/CACNB4/AQP1/KCNT2/TMC5/TMEM150C/CNGA1/ABCC9/GRIA3/KCNJ9/CACNA2D1/RYR2/CHRNA5/GLRA2/ZACN/KCNG3/GRIA4/GLRA1/HCN4/KCNN2/GABRA4/GRIN2A/KCNMB2/CNGB1/CACNG1/GRIN2B/KCNJ3/KCNMA1/CACNA1S/GRIA1/KCNC2/GABRA2/NALCN/GABRB1/GLRA3/GABRR1/KCNK3/SCN1A/KCNV1/HCN1/SCN7A/GRID2/ABCC8/PIEZO2/KCNJ16/KCNJ6/GABRE/KCNA1/GABRG2/CLIC1/KCNJ18/ANO1/GLRB/CHRFAM7A/HTR3E/KCNJ11/GRIA2/GABRG3/CACNA1G/KCND2/CNGA3/CLCA2/GABRA5/KCNK16/GABRG1/KCNIP1/GABRB2/GRIK3/P2RX3/CHRNA6/CACNA1B/KCNIP3/KCNJ5/TMC8/CLIC3/KCNAB2/ASIC3/KCNK6/CLCN7/TMEM109/CACNB1/KCNAB3/KCNC3/TMC6/CACNA2D4/HCN2/CACNB3/TPCN1/KCNMB1/KCNN4/KCNIP2/CACNA1H/SCNN1A/BNIP1/SCNN1D/MCOLN1/PIEZO1/P2RX5/CACNA1F/CATSPER1/CLCN2/LRRC26/CACNA2D2/KCNG1/ASIC1/CACNA1I/KCNH3/SLC1A7/NCS1/CLCN1/TRPM4/KCNT1/SCN4B/KCNK17/CACNG6/CACNA2D3/KCNH2/KCNK10/KCNA5/HTR3A/SLC17A3/NALF2/HTR1B	167
MF	GO:0022836	gated channel activity	6.99E-04	6.51E-04	ITPR2/KCNJ13/ITPR1/GRIK1/KCNS1/CLCN3/KCNE1/ANO6/ITGAV/CACNA1E/KCNC1/KCNJ2/KCNH7/KCNJ15/GABRR2/TRPA1/SCN9A/KCNG2/GRIN3A/CYBB/SCN3B/CHRNB2/KCNIP4/CLIC4/CHRNG/CACNB2/P2RX7/CACNA1D/KCNE3/CNGB	167

					3/RYR3/KCNH6/TMC3/CHRNA2/KCNV2/CLCA3P/MCOLN2/KCNS2/SCN8A/CHRNA1/OPRM1/KCNN3/KCNJ1/SCN3A/CHRND/CACNB4/AQP1/KCNT2/TMC5/TMEM150C/CNGA1/ABCC9/GRIA3/KCNJ9/CACNA2D1/RYR2/CHRNA5/GLRA2/ZACN/KCNG3/GRIA4/GLRA1/HCN4/KCNN2/GABRA4/GRIN2A/KCNMB2/CNGB1/CACNG1/GRIN2B/KCNJ3/KCNMA1/CACNA1S/GRIA1/KCNC2/GABRA2/NALCN/GABRB1/GLRA3/GABRR1/KCNK3/SCN1A/KCNV1/HCN1/SCN7A/GRID2/ABCC8/PIEZO2/KCNJ16/KCNJ6/GABRE/KCNA1/GABRG2/CLIC1/KCNJ18/ANO1/GLRB/CHRFAM7A/HTR3E/KCNJ11/GRIA2/GABRG3/CACNA1G/KCND2/CNGA3/CLCA2/GABRA5/KCNK16/GABRG1/KCNIP1/GABRB2/GRIK3/P2RX3/CHRNA6/CACNA1B/KCNIP3/KCNJ5/TMC8/CLIC3/KCNAB2/ASIC3/KCNK6/CLCN7/TMEM109/CACNB1/KCNAB3/KCNC3/TMC6/CACNA2D4/HCN2/CACNB3/TPCN1/KCNMB1/KCNN4/KCNIP2/CACNA1H/SCNN1A/BNIP1/SCNN1D/MCOLN1/PIEZO1/P2RX5/CACNA1F/CATSPER1/CLCN2/LRRC26/CACNA2D2/KCNG1/ASIC1/CACNA1I/KCNH3/SLC1A7/NCS1/CLCN1/TRPM4/KCNT1/SCN4B/KCNK17/CACNG6/CACNA2D3/KCNH2/KCNK10/KCNA5/HTR3A/SLC17A3/NALF2/HTR1B	
MF	GO:0015267	channel activity	6.99E-04	6.51E-04	ITPR2/KCNJ13/TRPM7/ITPR1/GRIK1/KCNS1/CLCN3/PKD2L2/KCNE1/ANO6/ITGAV/ATP6V1A/BEST1/CACNA1E/KCNC1/KCNJ2/SLC12A6/KCNH7/TRPM6/KCNJ15/PSEN1/GABRR2/TRPA1/SCN9A/PKD1L3/KCNG2/GRIN3A/CYBB/SCN3B/SLC26A8/SLC12A2/ATP5F1E/GJB7/AQP9/LRRC8B/CHRNB2/KCNIP4/CALHM5/CLIC4/SLC6A4/ATP5MGL/CHRNG/CACNB2/P2RX7/CACNA1D/KCNE3/ANO2/CNGB3/GJB3/TRPC5/RYR3/KCNH6/TMC3/CHRNA2/BCL2A1/KCNV2/CLCA3P/MCOLN2/KCNS2/ANO5/SCN8A/SLC24A3/CHRNA1/RHCE/GJA4/OPRM1/RHAG/SLC9C1/KCNN3/KCNJ1/GJC1/SCN3A/CHRND/CACNB4/AQP1/KCNT2/TRPM3/SLC24A2/TMC5/TMEM150C/ANO7/CNGA1/UNC80/TRPC6/ABCC9/GRIA3/LRRC8E/KCNJ9/CACNA2D1/RYR2/BEST3/CHRNA5/GLRA2/ZACN/KCNG3/GRIA4/GLRA1/HCN4/KCNN2/GABRA4/GRIN2A/KCNMB2/GJA8/CNGB1/CACNG1/MIP/GRIN2B/KCNJ3/SLC1A1/KCNMA1/CACNA1S/GRIA1/KCNC2/GABRA2/NALCN/GABRB1/GLRA3/PKD1L2/GABRR1/SLC17A8/KCNK3/NOX5/SCN1A/ANO3/KCNV1/HCN1/SCN7A/GRID2/ABCC8/PIEZO2/ANO4/KCNJ16/KCNJ6/GABRE/	243

					KCNA1/GABRG2/CLCA4/BEST2/CLIC1/KCNJ18/ANO1/GLRB/CHRFAM7A/HTR3E/KCNJ11/GRIA2/GABRG3/CACNA1G/SLC26A9/KCND2/CNGA3/CLCA2/GABRA5/KCNK16/GABRG1/CALHM4/KCNIP1/RHCG/GABRB2/GRIK3/P2RX3/CHRNA6/CACNA1B/KCNIP3/KCNJ5/ATP5F1D/ATP8/ATP6/BAX/TMEM175/ATP5MF/TMC8/CLIC3/KCNAB2/MPV17/ASIC3/ATP5PO/ORAI1/KCNK6/CLCN7/TMEM109/CACNB1/KCNAB3/KCNC3/TMC6/TOMM40/ATP6V0C/CACNA2D4/ANO9/HCN2/ATP5PF/CACNB3/TPCN1/ANO8/KCNMB1/CALHM2/TTYH2/KCNN4/KCNIP2/CACNA1H/FXYD1/SCNN1A/BNIP1/TTYH3/SCNN1D/MCOLN1/ATP5F1EP2/PIEZO1/AQP3/P2RX5/CACNA1F/CATSPER1/CLCN2/SLC26A11/PKD1/LRRC26/CACNA2D2/KCNG1/PANX2/ASIC1/CACNA1I/KCNH3/SLC12A7/SLC1A7/NCS1/CLCN1/TRPM4/KCNT1/SCN4B/KCNK17/OTOP2/CACNG6/CACNA2D3/KCNH2/KCNK10/KCNA5/GSDMA/TRPV6/HTR3A/SLC17A3/SLC17A7/NALF2/HTR1B	
MF	GO:0022803	passive transmembrane transporter activity	6.99E-04	6.51E-04	ITPR2/KCNJ13/TRPM7/ITPR1/GRIK1/KCNS1/CLCN3/PKD2L2/KCNE1/ANO6/ITGAV/ATP6V1A/BEST1/CACNA1E/KCNC1/KCNJ2/SLC12A6/KCNH7/TRPM6/KCNJ15/PSEN1/GABRR2/TRPA1/SCN9A/PKD1L3/KCNG2/GRIN3A/CYBB/SCN3B/SLC26A8/SLC12A2/ATP5F1E/GJB7/AQP9/LRRC8B/CHRNB2/KCNIP4/CALHM5/CLIC4/SLC6A4/ATP5MGL/CHRNG/CACNB2/P2RX7/CACNA1D/KCNE3/ANO2/CNGB3/GJB3/TRPC5/RYR3/KCNH6/TMC3/CHRNA2/BCL2A1/KCNV2/CLCA3P/MCOLN2/KCNS2/ANO5/SCN8A/SLC24A3/CHRNA1/RHCE/GJA4/OPRM1/RHAG/SLC9C1/KCNN3/KCNJ1/GJC1/SCN3A/CHRND/CACNB4/AQP1/KCNT2/TRPM3/SLC24A2/TMC5/TMEM150C/ANO7/CNGA1/UNC80/TRPC6/ABCC9/GRIA3/LRRC8E/KCNJ9/CACNA2D1/RYR2/BEST3/CHRNA5/GLRA2/ZACN/KCNG3/GRIA4/GLRA1/HCN4/KCNN2/GABRA4/GRIN2A/KCNMB2/GJA8/CNGB1/CACNG1/MIP/GRIN2B/KCNJ3/SLC1A1/KCNMA1/CACNA1S/GRIA1/KCNC2/GABRA2/NALCN/GABRB1/GLRA3/PKD1L2/GABRR1/SLC17A8/KCNK3/NOX5/SCN1A/ANO3/KCNV1/HCN1/SCN7A/GRID2/ABCC8/PIEZO2/ANO4/KCNJ16/KCNJ6/GABRE/KCNA1/GABRG2/CLCA4/BEST2/CLIC1/KCNJ18/ANO1/GLRB/CHRFAM7A/HTR3E/KCNJ11/GRIA2/GABRG3/CACNA1G/SLC26A9/KCND2/CNGA3/CLCA2/GABRA5/KCNK16/GABRG1/CALHM4/KCNIP1/RHCG/GABRB2/GRIK3/P2RX3/CHRNA6/CAC	243

					NA1B/KCNIP3/KCNJ5/ATP5F1D/ATP8/ATP6/BAX/TMEM175/ATP5MF/TMC8/CLIC3/KCNAB2/MPV17/ASIC3/ATP5PO/ORAI1/KCNK6/CLCN7/TMEM109/CACNB1/KCNAB3/KCNC3/TMC6/TOMM40/ATP6V0C/CACNA2D4/ANO9/HCN2/ATP5PF/CACNB3/TPCN1/ANO8/KCNMB1/CALHM2/TTYH2/KCNN4/KCNIP2/CACNA1H/FXYD1/SCNN1A/BNIP1/TTYH3/SCNN1D/MCOLN1/ATP5F1EP2/PIEZO1/AQP3/P2RX5/CACNA1F/CATSPER1/CLCN2/SLC26A11/PKD1/LRRC26/CACNA2D2/KCNG1/PANX2/ASIC1/CACNA1I/KCNH3/SLC12A7/SLC1A7/NCS1/CLCN1/TRPM4/KCNT1/SCN4B/KCNK17/OTOP2/CACNG6/CACNA2D3/KCNH2/KCNK10/KCNA5/GSDMA/TRPV6/HTR3A/SLC17A3/SLC17A7/NALF2/HTR1B	
MF	GO:0046982	protein heterodimerization activity	6.99E-04	6.51E-04	H2BC18/H2BC4/H3C4/RALGAPB/TAF1/H2AC20/H4C4/H4C5/H4C3/H2BC15/H2BC6/H2BC8/H2AC6/H2AC17/H2AC11/H2AC8/BARD1/H4C16/H2AC15/HIF1A/ATF6/H2AC13/H2BC11/ATF2/RALGAPA2/H2BC5/H4C2/H3C10/GTF2A1/H2BC9/MIGA1/CHUK/H2BC7/H3C8/RALGAPA1/H2BC3/SOS2/H2BC13/TLR4/H4C8/H2BC12/H3C12/IRAK3/H2AC16/ZHX1/H2BC26/TENM1/TLR6/H4C9/ITGB1/H2AC21/H2BC17/H2BC10/TOP2A/H4C6/CYBB/H3C2/DR1/H4C13/MEF2A/TCF4/H3C13/AURKA/H2BC14/MAPK6/P2RY1/H2AC4/PDSS1/H2AC12/APOA2/SLC3A1/H3C3/H3C6/H2BC21/GCA/H3-5/RRAGD/BMP6/H3C7/EXT1/H3C11/H2AC7/SLC51A/H4C1/HIP1/H3C1/ABCD2/H3C15/H4C12/BCL2A1/H4C14/CAV2/PDGFA/H4C11/FZD4/ABCG5/NPAS3/CEACAM6/H3C14/SDCBP2/AGTR1/BHLHE41/TENM3/CEACAM8/ROPN1B/GABBR2/ABCG8/MTTP/IL12B/H4C15/SIM1/SYT1/ADCY8/H3-4/NEUROD1/TENM2/TFAP2B/ADRA1A/ADRA1B/SOHLH1/SYT10/CENPT/CHRAC1/BAX/ATF4/DRAP1/PHB2/IRAK1/POLE3/USF2/HSF1/PAFAH1B3/MIGA2/TAF6L/P4HB/QTRT1/KRT10/H2AX/PPP2R1A/BUD23/KATNB1/TPM2/PIK3R2/MACROH2A2/TCF3/PHB1/MEF2D/POLE4/TAF6/TP53/CD247/BOK/NR4A1/ERBB2/ABCD1/YWHAE/BHLHE40/PDGFB/SLC7A8/KRT1/TUBB2B/NPAS1/CENPS/H2AB3	164
MF	GO:0015276	ligand-gated monoatomic ion channel activity	1.91E-03	1.78E-03	ITPR2/KCNJ13/ITPR1/GRIK1/KCNJ2/KCNH7/KCNJ15/GABRR2/TRPA1/GRIN3A/CHRNB2/CHRNG/P2RX7/CNGB3/RYR3/KCNH6/CHRNA2/MCOLN2/CHRNA1/KCNN3/KCNJ1/CHRND/AQP1/CNGA1/ABCC9/GRIA3/KCNJ9/RYR2/CHRNA5/GLRA2/Z	82

					ACN/GRIA4/GLRA1/HCN4/KCNN2/GABRA4/GRIN2A/CNGB1/GRIN2B/KCNJ3/GRIA1/GABRA2/GABRB1/GLRA3/GABRR1/HCN1/GRID2/ABCC8/KCNJ16/KCNJ6/GABRE/GABRG2/KCNJ18/GLRB/CHRFAM7A/HTR3E/KCNJ11/GRIA2/GABRG3/CNGA3/CLCA2/GABRA5/GABRG1/GABRB2/GRIK3/P2RX3/CHRNA6/KCNJ5/ASIC3/KCNK6/HCN2/TPCN1/SCNN1A/BNIP1/SCNN1D/MCOLN1/P2RX5/ASIC1/SLC1A7/TRPM4/KCNH2/HTR3A	
MF	GO:0022834	ligand-gated channel activity	2.44E-03	2.27E-03	ITPR2/KCNJ13/ITPR1/GRIK1/KCNJ2/KCNH7/KCNJ15/GABRR2/TRPA1/GRIN3A/CHRNB2/CHRNG/P2RX7/CNGB3/RYR3/KCNH6/CHRNA2/MCOLN2/CHRNA1/KCNN3/KCNJ1/CHRND/AQP1/CNGA1/ABCC9/GRIA3/KCNJ9/RYR2/CHRNA5/GLRA2/ZACN/GRIA4/GLRA1/HCN4/KCNN2/GABRA4/GRIN2A/CNGB1/GRIN2B/KCNJ3/GRIA1/GABRA2/GABRB1/GLRA3/GABRR1/HCN1/GRID2/ABCC8/KCNJ16/KCNJ6/GABRE/GABRG2/KCNJ18/GLRB/CHRFAM7A/HTR3E/KCNJ11/GRIA2/GABRG3/CNGA3/CLCA2/GABRA5/GABRG1/GABRB2/GRIK3/P2RX3/CHRNA6/KCNJ5/ASIC3/KCNK6/HCN2/TPCN1/SCNN1A/BNIP1/SCNN1D/MCOLN1/P2RX5/ASIC1/SLC1A7/TRPM4/KCNH2/HTR3A	82
MF	GO:0005096	GTPase activator activity	4.49E-03	4.18E-03	RASA1/GAPVD1/RALGAPB/NF1/HTR2B/RABGAP1/LRRK2/TBC1D5/MYO9A/TBCK/DOCK2/RANBP2/RAB3GAP2/ACAP2/SEC23A/IQGAP2/EVI5/STXBP5/FAM13B/TBC1D14/DOCK5/RASA2/ARAP2/VAV3/DOCK4/ARHGAP26/RAPGEF2/RP2/RALGAPA2/ARHGAP18/ARHGAP5/NCKAP1L/RALGAPA1/IQGAP1/ARHGEF12/SIPA1L2/OPHN1/SIPA1L1/FAM13A/AGFG1/RAB3GAP1/CHM/ECT2/RABGAP1L/ARHGAP15/ASAP2/TBC1D30/USP6NL/SRGAP1/PLEKHG6/RGS18/TBC1D19/ASAP1/BNIP2/TAGAP/ARHGAP6/RGPD8/TBC1D8B/ARHGAP24/ARHGAP29/STXBP5L/DEPDC1B/ARHGAP42/GNAQ/TBC1D8/GRTP1/RGPD2/DOCK1/DEPDC1/STARD13/RGS20/RANBP3L/DLC1/PREX2/RGPD3/RGS17/ELMOD1/ARHGAP11B/ARHGAP28/ADGRB3/ARHGAP8/ARHGAP4/ARFGAP1/RANBP3/GIT1/TBC1D10A/PREB/ARHGDIA/TBC1D10C/ARHGEF1/TBC1D17/GDI1/RASAL3/ACAP3/SH3BP1/AGAP3/NPRL2/SGSM2/SGSM3/EVI5L/TBC1D13/ARHGAP33/ARHGEF19/RANGAP1/RGS14/ARHGAP1/AGAP6/AGFG2/RASA4/RIN1/ARHGDIB/TBC1D10B/RIN3/ACAP1/TBC1D25/RANBP1/TBC1D24/RABEP2/LLGL2/ALS2CL/RASA4B/RGS12/MTSS2/RGS9/AGAP9/AGAP7P/TBC1D16/CDC42EP	139

					2/PLXNB1/TBC1D3L/AGAP11/TBC1D3F/TBC1D3I/TBC1D3C/SYNGAP1/TBC1D3H/TBC1D26/TBC1D3B/TBC1D3G	
MF	GO:0015108	chloride transmembrane transporter activity	4.49E-03	4.18E-03	CLCN3/ANO6/BEST1/SLC12A6/SLC22A1/GABRR2/SLC26A8/SLC12A2/CLIC4/SLC6A4/ANO2/SLC26A3/SLC6A12/SLC6A13/CLCA3P/ANO5/SLC26A5/SLC12A8/SLC26A4/KCNT2/ANO7/SLC4A1/SLC4A10/BEST3/GLRA2/GLRA1/GABRA4/SLC1A1/GABRA2/GABRB1/GLRA3/GABRR1/SLC17A8/ANO3/ANO4/GABRE/GABRG2/CLCA4/BEST2/CLIC1/SLC6A1/ANO1/GLRB/GABRG3/SLC26A9/CLCA2/GABRA5/GABRG1/GABRB2/SLC6A18/SLC6A11/CLIC3/CLCN7/UCP2/SLC4A2/ANO9/ANO8/TTYH2/FXYD1/TTYH3/CLCN2/SLC26A11/SLC4A3/SLC12A7/SLC1A7/CLCN1/SLC18A1/SLC17A7	68
MF	GO:0005261	monoatomic cation channel activity	6.04E-03	5.63E-03	ITPR2/KCNJ13/TRPM7/ITPR1/GRIK1/KCNS1/PKD2L2/KCNE1/ANO6/ITGAV/ATP6V1A/CACNA1E/KCNC1/KCNJ2/KCNH7/TRPM6/KCNJ15/PSEN1/TRPA1/SCN9A/PKD1L3/KCNG2/GRIN3A/SCN3B/ATP5F1E/CHRNB2/KCNIP4/CALHM5/SLC6A4/ATP5MGL/CHRNG/CACNB2/P2RX7/CACNA1D/KCNE3/CNGB3/TRPC5/RYR3/KCNH6/CHRNA2/KCNV2/CLCA3P/MCOLN2/KCNS2/SCN8A/SLC24A3/CHRNA1/OPRM1/KCNN3/KCNJ1/SCN3A/CHRND/CACNB4/AQP1/KCNT2/TRPM3/SLC24A2/CNGA1/UNC80/TRPC6/ABCC9/KCNJ9/CACNA2D1/RYR2/CHRNA5/ZACN/KCNG3/HCN4/KCNN2/GRIN2A/KCNMB2/CNGB1/CACNG1/GRIN2B/KCNJ3/KCNMA1/CACNA1S/KCNC2/NALCN/PKD1L2/KCNK3/NOX5/SCN1A/KCNV1/HCN1/SCN7A/ABCC8/PIEZO2/KCNJ16/KCNJ6/KCNA1/KCNJ18/ANO1/CHRFAM7A/HTR3E/KCNJ11/CACNA1G/KCND2/CNGA3/KCNK16/CALHM4/KCNIP1/GRIK3/P2RX3/CHRNA6/CACNA1B/KCNIP3/KCNJ5/ATP5F1D/ATP8/ATP6/TMEM175/ATP5MF/KCNAB2/ASIC3/ATP5PO/ORAI1/KCNK6/TMEM109/CACNB1/KCNAB3/KCNC3/ATP6V0C/CACNA2D4/HCN2/ATP5PF/CACNB3/TPCN1/KCNMB1/CALHM2/KCNN4/KCNIP2/CACNA1H/SCNN1A/BNIP1/SCNN1D/MCOLN1/ATP5F1EP2/PIEZO1/P2RX5/CACNA1F/CATSPER1/PKD1/LRRC26/CACNA2D2/KCNG1/ASIC1/CACNA1I/KCNH3/NCS1/TRPM4/KCNT1/SCN4B/KCNK17/OTOP2/CACNG6/CACNA2D3/KCNH2/KCNK10/KCNA5/TRPV6/HTR3A/NALF2/HTR1B	164
MF	GO:0005201	extracellular matrix structural constituent	6.81E-03	6.34E-03	LAMB1/ABI3BP/NID2/ASPN/LTBP1/COL6A6/IMPG2/MMRN1/FBN2/COL4A4/OGN/CTHRC1/FGL2/COL10A1/TNC/VCAN/F	88

					N1/FBN1/ENAM/PRG4/EMILIN2/COL24A1/COL4A2/LAMC1/COL17A1/MUC5AC/HMCN2/IMPG1/ACAN/ANOS1/NPNT/COL4A5/HMCN1/COL4A1/COL4A6/COL19A1/COMP/COL2A1/THSD4/MUC3A/PRG3/COL12A1/FGA/LAMA3/COL25A1/COL11A1/COL6A5/LAMC2/FGB/EDIL3/COL9A1/LAMA1/MUC17/AMELX/TFPI2/EMILIN3/MXRA5/COL14A1/FMOD/SRPX2/FBN3/COL3A1/COL8A1/FGG/MFAP2/PRELP/COL1A2/AMBN/LTBP4/PCOLCE/CRELD1/CD4/MFGE8/COLQ/EFEMP2/ZP3/AEBP1/COL6A2/COL9A2/COL6A1/CILP/FBLN5/LAMA5/COL1A1/PODN/COL5A3/COL13A1/SRPX	
MF	GO:0008509	monoatomic anion transmembrane transporter activity	7.40E-03	6.89E-03	CLCN3/ANO6/BEST1/SLC12A6/SLC22A1/GABRR2/SLC26A8/SLC12A2/LRRC8B/CLIC4/SLC6A4/SLC4A7/ANO2/SLC4A4/SLC26A3/SLC6A12/SLC6A13/CLCA3P/ANO5/SLC26A5/SLC1A2/SLC12A8/SLC26A4/KCNT2/ANO7/SLC4A1/LRRC8E/SLC4A10/BEST3/GLRA2/GLRA1/GABRA4/SLC1A1/GABRA2/GABRB1/GLRA3/GABRR1/SLC17A8/ANO3/ANO4/GABRE/GABRG2/CLCA4/SLC13A1/BEST2/CLIC1/SLC6A1/ANO1/GLRB/GABRG3/SLC26A9/CLCA2/GABRA5/GABRG1/GABRB2/SLC6A18/SLC6A11/CLIC3/CLCN7/UCP2/SLC4A2/ANO9/ANO8/TTYH2/FXYD1/SLC5A6/TTYH3/SLC5A5/CLCN2/SLC26A11/SLC4A3/SLC12A7/SLC1A7/CLCN1/SLC18A1/SLC17A3/SLC17A7	77
MF	GO:0030627	pre-mRNA 5'-splice site binding	1.78E-02	1.66E-02	RNU11/RNU4ATAC/RNVU1-7/RNVU1-14/RNVU1-3/RNU1-4/RNVU1-6/RNVU1-15/RNVU1-4/RNVU1-19/RNU6ATAC/RNVU1-8/SNRPC	13
MF	GO:0015103	inorganic anion transmembrane transporter activity	1.83E-02	1.71E-02	XPR1/CLCN3/ANO6/BEST1/SLC12A6/ABCC4/SLC22A1/GABRR2/SLC26A8/SLC12A2/SLC13A4/CLIC4/SLC6A4/SLC4A7/ANO2/SLC4A4/SLC26A3/SLC6A12/SLC6A13/CLCA3P/ANO5/SLC26A5/SLC12A8/SLC26A4/KCNT2/ANO7/SLC4A1/ABCC9/SLC4A10/BEST3/GLRA2/GLRA1/GABRA4/ABCC11/SLC1A1/GABRA2/GABRB1/GLRA3/GABRR1/SLC17A8/ANO3/ANO4/GABRE/GABRG2/CLCA4/SLC13A1/BEST2/CLIC1/SLC6A1/ANO1/GLRB/GABRG3/SLC26A9/CLCA2/GABRA5/GABRG1/GABRB2/SLC6A18/SLC6A11/SLC22A11/CLIC3/CLCN7/UCP2/SLC4A2/ANO9/ANO8/SLC37A4/TTYH2/FXYD1/SLC5A6/TTYH3/SLC5A5/SLC25A10/CLCN2/SLC26A11/SLC4A3/SLC12A7/SLC1A7/CLCN1/SLC18A1/SLC17A7	81
MF	GO:0031267	small GTPase binding	1.93E-02	1.80E-02	MYCBP2/GAPVD1/DOCK11/ATP7A/RABGAP1/IPO11/CDKL5/LRRK2/MYRIP/DOCK2/RANBP2/RAB3GAP2/DMXL2/RIC1/RA	138

					PGEF6/DIAPH2/IQGAP2/EVI5/ROCK2/EXOC5/USP33/CCDC186/TNPO1/DOCK5/DENND1B/AKAP13/EXOC2/DOCK4/FGD4/TRIP11/ABCA1/SORL1/GCC2/MYO5A/ROCK1/RAB11FIP2/STRN3/WDR44/PICALM/IQGAP1/MEGF9/EXOC8/PKN2/KNTC1/DOCK10/HACE1/GOLGA4/FMNL2/RAB3GAP1/RGP1/CHM/ECT2/RABGAP1L/RHOBTB3/DOCK7/TBC1D30/USP6NL/FARP1/MYO5B/GARRE1/XPO1/XPO4/NCKAP1/RAB11FIP1/DIAPH3/PLEKHG1/RGPD8/FGD6/SYTL4/RANBP17/PEX5L/DENND5B/DAAM2/DOCK1/RAPGEF4/PLCE1/BICDL2/RIMS2/ASB15/PIH1D2/GRIA1/RIMS1/MLPH/ARHGEF16/RIMS4/PFN1/GIT1/CIB1/GDI1/RABGGTA/NOXA1/DVL1/DVL3/PPP6R1/SGSM2/PKN1/SGSM3/NUTF2/GGA1/SYTL1/EVI5L/BRK1/TBC1D13/DVL2/NXT1/RANGAP1/ARHGAP1/SPHK2/TNPO2/RIN1/INF2/ARHGDIB/KCTD13/WAS/RIN3/RANBP1/PARD6A/ULK1/MAP3K11/FMNL1/MICAL1/CDC42EP1/PKN3/RAB34/TAMALIN/RAB11FIP5/RAB7A/ALS2CL/BICDL1/RPH3AL/MTSS2/RAB11FIP3/RUSC2/CDC42EP2/RPH3A/NGFR/SH3BP4/NPC1L1	
MF	GO:0005319	lipid transporter activity	1.93E-02	1.80E-02	SLC10A1/ATP11C/TMEM30A/BLTP1/APOB/ATP9B/ATG2B/ATP8B1/ATP10D/ATP8A1/BLTP3B/ANO6/ATP8B4/ABCA1/OSBPL11/VMP1/ATP11B/PLEKHA8/ABCC4/OSBPL8/SLC22A1/CERT1/ATP11A/CEACAM1/ABCA10/ATP9A/ABCA13/PLSCR1/APOA2/ABCA6/PLSCR4/GRAMD1B/SLC51A/ABCD2/PRELID2/OSBPL1A/STAR/ABCG5/ABCB11/ATP10B/ABCA12/PLSCR2/TNFAIP8L3/FABP2/SLCO4A1/MFSD2B/OSBPL6/FABP4/SLC10A6/ABCC11/ABCG8/MTTP/SLC22A9/ANO3/ANO4/SLCO2B1/SLC27A6/CIDEA/SLC22A2/ABCA8/SLCO1B3/RBP4/SLCO1B1/STRA6/TTPA/SLC22A11/CPTP/C2CD2L/STARD3/SLC10A3/PITPNM1/ABCD4/ATG9B/SLC27A1/ANO9/ATG9A/TRIAP1/OSBPL7/XKR8/PITPNM2/SLC27A5/ABCD1/ABCA3/GRAMD1A/TMEM30B/PRELID3A/APOE/PLSCR3/SLC27A3	89
MF	GO:0046873	metal ion transmembrane transporter activity	1.94E-02	1.81E-02	ITPR2/KCNJ13/ATP7A/SLC10A1/TRPM7/ITPR1/GRIK1/KCNS1/SLC30A7/PKD2L2/SLC8A1/KCNE1/ITGAV/SLC9A9/SLC5A3/CACNA1E/KCNC1/KCNJ2/SLC12A6/KCNH7/TRPM6/KCNJ15/SLC22A1/PSEN1/TRPA1/SCN9A/SLC1A3/SLC40A1/PKD1L3/KCNG2/GRIN3A/SCN3B/SLC12A2/SLC23A1/SLC30A1/TMEM165/SLC30A4/SLC38A2/KCNIP4/SLC13A4/SLC6A20/SLC6A4/SLC39A8/SLC25A37/SLC4A7/CACNB2/ATP4B/CACNA1D/KCNE3/TRPC5/RYR3/SLC38A4/KCNH6/SLC4A4/KCNV2/SLC6	206

					A12/ATP7B/SLC6A13/ATP2B2/CLCA3P/SLC9A2/MCOLN2/KCNS2/SCN8A/SLC24A3/SLC1A2/SLC12A8/SLC8A3/OPRM1/SLC9C1/KCNN3/KCNJ1/SCN3A/CACNB4/AQP1/KCNT2/TRPM3/SLC24A2/SLC9C2/TRPC6/ABCC9/KCNJ9/CACNA2D1/RYR2/SLC4A10/SLC6A15/KCNG3/SLC30A10/SLC5A1/HCN4/KCNN2/GRIN2A/KCNMB2/SLC5A4/CACNG1/SLC10A6/NIPAL1/SLC9A4/GRIN2B/KCNJ3/SLC1A1/KCNMA1/CACNA1S/ATP12A/KCNC2/NALCN/SLC28A3/PKD1L2/SLC17A8/KCNK3/SCN1A/KCNV1/HCN1/SCN7A/ABCC8/SLC28A1/KCNJ16/KCNJ6/KCNA1/CLDN16/SLC13A1/SLC17A4/SLC13A2/SLC39A12/SLC6A1/SLC38A3/KCNJ18/SLC6A7/ATP2B3/KCNJ11/CACNA1G/KCND2/KCNK16/KCNIP1/SLC17A2/GRIK3/SLC6A18/SLC5A12/CACNA1B/SLC6A11/KCNIP3/KCNJ5/TMEM175/SLC39A13/KCNAB2/SLC39A4/ASIC3/SLC10A3/ORAI1/KCNK6/ATP13A1/SLC39A3/CACNB1/KCNAB3/KCNC3/CACNA2D4/HCN2/CACNB3/TPCN1/ATP2A3/KCNMB1/SLC38A7/SLC41A1/KCNN4/KCNIP2/CACNA1H/SCNN1A/BNIP1/SLC5A6/SLC5A5/SLC41A3/SCNN1D/MCOLN1/CACNA1F/CATSPER1/PKD1/SLC9A1/SLC9A3/LRRC26/CACNA2D2/KCNG1/ASIC1/CACNA1I/KCNH3/SLC29A1/SLC12A7/SLC1A7/SLC5A10/NCS1/TRPM4/KCNT1/SCN4B/SLC5A2/KCNK17/CACNG6/CACNA2D3/KCNH2/KCNK10/SLC18A1/KCNA5/TRPV6/SLC17A3/SLC17A7/NALF2/TUSC3/HTR1B	
MF	GO:0005254	chloride channel activity	2.03E-02	1.89E-02	CLCN3/ANO6/BEST1/GABRR2/SLC26A8/CLIC4/ANO2/CLCA3P/ANO5/KCNT2/ANO7/BEST3/GLRA2/GLRA1/GABRA4/GABRA2/GABRB1/GLRA3/GABRR1/SLC17A8/ANO3/ANO4/GABRE/GABRG2/CLCA4/BEST2/CLIC1/ANO1/GLRB/GABRG3/SLC26A9/CLCA2/GABRA5/GABRG1/GABRB2/CLIC3/CLCN7/ANO9/ANO8/TTYH2/FXYD1/TTYH3/CLCN2/SLC26A11/SLC1A7/CLCN1/SLC17A7	47
MF	GO:0005229	intracellular calcium activated chloride channel activity	2.07E-02	1.93E-02	ANO6/BEST1/ANO2/ANO5/ANO7/ANO3/ANO4/CLCA4/ANO1/CLCA2/ANO9/ANO8/TTYH2/TTYH3	14
MF	GO:0003779	actin binding	2.07E-02	1.93E-02	TTN/ACTR3C/MACF1/LRRK2/UTRN/TRPM7/MYRIP/MYO9A/DIAPH2/TMOD3/IQGAP2/SYNE1/PHACTR2/SYNE3/NEXN/RDX/FGD4/MYO5A/SNTB2/MYH10/IQGAP1/GBP1/ANLN/PDLIM5/ABL2/OPHN1/NEB/SYNE2/ACTR3/FMNL2/DNASE1/MEFV/FMN1/ITGB1/ITPRID2/IPP/SVIL/SPTBN1/PTK2/PRKCE/MYO5B/B	205

					AIAP2L1/VCL/SSH2/CCDC88A/MYLK/PFN4/CEACAM1/SPTA1/ACTR2/KLHL2/MYO10/TLN1/DST/DIAPH3/STK38L/PSTPIP2/MYOT/TMOD2/EPB41/FLNB/MAP1B/SLC6A4/ABRA/VIL1/AVIL/KIF18A/XIRP2/CALD1/CTNNAL1/TLN2/CACNB2/PDLIM4/CAPZA2/HIP1/MYO1H/TRPC5/SYNPO2/GAS7/SHROOM4/MICAL2/MYO3B/DAAM2/SPTB/GAS2L3/PLS1/TMOD1/CSRP3/COBLL1/TNS1/MYO1B/DIXDC1/WASF3/DMD/SORBS1/MYOZ3/PPP1R9A/LMOD2/SNCA/PHACTR3/SHROOM3/PLS3/FERMT2/WIPF3/MYOZ2/FMN2/ANTXR1/EGFR/PIP/MYH2/KLHL4/KCNMA1/FERMT1/MYBPC1/MYH15/CTNNA3/TNNI1/POF1B/MYH13/MYO3A/MYH4/LRRC10/ADCY8/KBTBD13/SNTG1/ACTN2/CAP2/MYH1/MLPH/MYOZ1/NRAP/TAGLN3/MYH8/MYH7/MYPN/BCL7B/FXYD5/PFN1/LIMD2/EMD/TLNRD1/GIPC1/MARCKSL1/KLHL17/MIB2/RUSC1/CORO1A/PDLIM2/P4HB/EPS8L2/CAPZB/PARVG/TMEM201/PHPT1/PPP1R9B/BIN1/TPM2/ARPC4/EVL/ARPC5L/PICK1/S100A4/CFL1/LSP1/MAP1S/VILL/INF2/CORO1B/TAGLN/WAS/SNTA1/ABI3/WASHC1/COTL1/FSCN1/FMNL1/CROCC/TNNI2/MICAL1/PDLIM7/GAS2L1/ALDOA/WASH3P/FHL3/SYNPO/VASH1/SYN1/MTSS2/DBN1/EPS8L1/SHROOM1/TNNC1/ANKRD24/DMTN/ANG/ANKRD35/CORO2B/PPP1R18/MYBPC2/CORO7/ESPNL/TMSB15B/AIF1L/LMOD1/LDB3	
MF	GO:0015370	solute:sodium symporter activity	2.69E-02	2.51E-02	SLC10A1/SLC5A3/SLC22A1/SLC1A3/SLC12A2/SLC23A1/SLC38A2/SLC13A4/SLC6A20/SLC6A4/SLC4A7/SLC38A4/SLC4A4/SLC6A12/SLC6A13/SLC1A2/SLC4A10/SLC6A15/SLC5A1/SLC5A4/SLC10A6/SLC1A1/SLC28A3/SLC17A8/SLC28A1/SLC13A1/SLC17A4/SLC13A2/SLC6A1/SLC38A3/SLC6A7/SLC17A2/SLC6A18/SLC5A12/SLC6A11/SLC10A3/SLC38A7/SLC5A6/SLC5A5/SLC29A1/SLC1A7/SLC5A10/SLC5A2/SLC18A1/SLC17A3/SLC17A7	46
MF	GO:1903231	mRNA base-pairing translational repressor activity	3.32E-02	3.09E-02	MIR21/MIR644A/MIR186/MIR29A/MIR505/MIR16-1/MIR223/MIR101-1/MIR181A2/MIR326/MIR30C1/MIR613/MIR2355/MIR302C/MIRLET7F1/MIR3173/MIR302A/MIR29B1/MIR548P/MIR32/MIR573/MIR15A/MIR215/MIR148B/MIR302D/MIR28/MIRLET7G/MIR590/MIR491/MIR920/MIR372/MIR374A/MIR30E/MIR128-1/MIR640/MIR191/MIR103A1/MIR562/MIR301A/MIR98/MIR15B/MIR199A1/MIRLET7A1/MIR194-	72

					1/MIR3909/MIR4632/MIR1207/MIR320A/MIR3619/MIR1277/MIR144/MIR661/MIR425/MIR638/MIR423/MIR222/MIR625/MIR181B1/MIR361/MIR150/MIR185/MIR27B/MIR140/MIR195/MIR330/MIR212/MIR130A/MIR196A1/MIR142/MIR25/MIR769/MIR339	
MF	GO:0005244	voltage-gated monoatomic ion channel activity	3.32E-02	3.09E-02	KCNJ13/KCNS1/CLCN3/KCNE1/ANO6/ITGAV/CACNA1E/KCNC1/KCNJ2/KCNH7/KCNJ15/SCN9A/KCNG2/GRIN3A/CYBB/SCN3B/KCNIP4/CLIC4/CACNB2/CACNA1D/KCNE3/KCNH6/KCNV2/CLCA3P/KCNS2/SCN8A/OPRM1/KCNN3/KCNJ1/SCN3A/CACNB4/KCNT2/ABCC9/KCNJ9/CACNA2D1/KCNG3/HCN4/KCNN2/GRIN2A/CACNG1/GRIN2B/KCNJ3/KCNMA1/CACNA1S/KCNC2/NALCN/KCNK3/SCN1A/KCNV1/HCN1/SCN7A/ABCC8/KCNJ16/KCNJ6/KCNA1/CLIC1/KCNJ18/ANO1/KCNJ11/CACNA1G/KCND2/KCNK16/KCNIP1/CACNA1B/KCNIP3/KCNJ5/CLIC3/KCNAB2/KCNK6/CLCN7/TMEM109/CACNB1/KCNAB3/KCNC3/CACNA2D4/HCN2/CACNB3/TPCN1/KCNIP2/CACNA1H/CACNA1F/CATSPER1/CLCN2/LRRC26/CACNA2D2/KCNG1/CACNA1I/KCNH3/NCS1/CLCN1/KCNT1/SCN4B/KCNK17/CACNG6/CACNA2D3/KCNH2/KCNK10/KCNA5/SLC17A3/HTR1B	100
MF	GO:0022832	voltage-gated channel activity	3.32E-02	3.09E-02	KCNJ13/KCNS1/CLCN3/KCNE1/ANO6/ITGAV/CACNA1E/KCNC1/KCNJ2/KCNH7/KCNJ15/SCN9A/KCNG2/GRIN3A/CYBB/SCN3B/KCNIP4/CLIC4/CACNB2/CACNA1D/KCNE3/KCNH6/KCNV2/CLCA3P/KCNS2/SCN8A/OPRM1/KCNN3/KCNJ1/SCN3A/CACNB4/KCNT2/ABCC9/KCNJ9/CACNA2D1/KCNG3/HCN4/KCNN2/GRIN2A/CACNG1/GRIN2B/KCNJ3/KCNMA1/CACNA1S/KCNC2/NALCN/KCNK3/SCN1A/KCNV1/HCN1/SCN7A/ABCC8/KCNJ16/KCNJ6/KCNA1/CLIC1/KCNJ18/ANO1/KCNJ11/CACNA1G/KCND2/KCNK16/KCNIP1/CACNA1B/KCNIP3/KCNJ5/CLIC3/KCNAB2/KCNK6/CLCN7/TMEM109/CACNB1/KCNAB3/KCNC3/CACNA2D4/HCN2/CACNB3/TPCN1/KCNIP2/CACNA1H/CACNA1F/CATSPER1/CLCN2/LRRC26/CACNA2D2/KCNG1/CACNA1I/KCNH3/NCS1/CLCN1/KCNT1/SCN4B/KCNK17/CACNG6/CACNA2D3/KCNH2/KCNK10/KCNA5/SLC17A3/HTR1B	100
MF	GO:0042805	actinin binding	3.70E-02	3.44E-02	TTN/PDLIM5/CSRP2/MYOT/XIRP2/CACNA1D/PDLIM4/TRPC5/SYNPO2/PPARG/CSRP3/MAGI1/KCNN2/PROM1/PTPRT/LRR	24

					C10/NRAP/MYPN/CSRP1/PDLIM2/RARA/PDLIM7/KCNA5/LDB3	
MF	GO:0099094	ligand-gated monoatomic cation channel activity	3.88E-02	3.62E-02	ITPR2/KCNJ13/ITPR1/GRIK1/KCNJ2/KCNH7/KCNJ15/TRPA1/CHRNB2/CHRNG/P2RX7/CNGB3/RYR3/KCNH6/CHRNA2/MCOLN2/CHRNA1/KCNN3/KCNJ1/CHRND/AQP1/CNGA1/ABCC9/KCNJ9/RYR2/CHRNA5/ZACN/HCN4/KCNN2/GRIN2A/CNGB1/GRIN2B/KCNJ3/HCN1/ABCC8/KCNJ16/KCNJ6/KCNJ18/CHRFAM7A/HTR3E/KCNJ11/CNGA3/GRIK3/P2RX3/CHRNA6/KCNJ5/ASIC3/KCNK6/HCN2/TPCN1/SCNN1A/BNIP1/SCNN1D/MCOLN1/P2RX5/ASIC1/TRPM4/KCNH2/HTR3A	59
MF	GO:0140303	intramembrane lipid transporter activity	3.89E-02	3.62E-02	ATP11C/TMEM30A/ATP9B/ATP8B1/ATP10D/ATP8A1/ANO6/ATP8B4/ABCA1/VMP1/ATP11B/ATP11A/ATP9A/PLSCR1/PLSCR4/ATP10B/ABCA12/PLSCR2/ANO3/ANO4/ATG9B/ANO9/ATG9A/XKR8/ABCA3/TMEM30B/PLSCR3	27
MF	GO:0051020	GTPase binding	4.00E-02	3.73E-02	MYCBP2/RASA1/GAPVD1/DOCK11/ATP7A/RABGAP1/IPO11/CDKL5/LRRK2/MYRIP/DOCK2/RANBP2/RAB3GAP2/DMXL2/RIC1/RAPGEF6/DIAPH2/IQGAP2/EVI5/ROCK2/EXOC5/USP33/CCDC186/TNPO1/DOCK5/DENND1B/AKAP13/EXOC2/DOCK4/FGD4/TRIP11/ABCA1/SORL1/GCC2/MYO5A/ROCK1/RAB11FIP2/STRN3/WDR44/PICALM/IQGAP1/MEGF9/EXOC8/PKN2/KNTC1/DOCK10/HACE1/GOLGA4/FMNL2/RAB3GAP1/RGP1/CHM/ECT2/FNBP1L/RABGAP1L/RHOBTB3/DOCK7/SPTBN1/TBC1D30/USP6NL/FARP1/MYO5B/GARRE1/XPO1/XPO4/NCKAP1/RAB3IP/RAB11FIP1/DIAPH3/PLEKHG1/RGPD8/FGD6/SYTL4/RANBP17/RRAGD/PEX5L/DENND5B/DAAM2/DOCK1/RAPGEF4/PLCE1/BICDL2/RIMS2/ASB15/PIH1D2/GRIA1/RADIL/RIMS1/MLPH/ARHGEF16/RIMS4/PFN1/GIT1/PREB/CIB1/GDI1/RABGGTA/NOXA1/DVL1/DVL3/PPP6R1/SGSM2/PKN1/SGSM3/NUTF2/GGA1/SYTL1/EVI5L/BRK1/TBC1D13/DVL2/NXT1/RANGAP1/ARHGAP1/BIN1/SPHK2/TNPO2/RIN1/INF2/ARHGDIB/KCTD13/WAS/RIN3/RANBP1/PARD6A/ULK1/MAP3K11/FMNL1/RABAC1/MICAL1/CDC42EP1/PKN3/RAB34/TAMALIN/RAB11FIP5/RAB7A/ALS2CL/BICDL1/RPH3AL/MTSS2/RAB11FIP3/RASIP1/RUSC2/CDC42EP2/RPH3A/NGFR/GNB3/SH3BP4/NPC1L1	149
MF	GO:0061778	intracellular chloride channel activity	4.00E-02	3.73E-02	ANO6/BEST1/ANO2/ANO5/ANO7/ANO3/ANO4/CLCA4/ANO1/CLCA2/ANO9/ANO8/TTYH2/TTYH3	14

MF	GO:0005242	inward rectifier potassium channel activity	4.00E-02	3.73E-02	KCNJ13/KCNJ2/KCNH7/KCNJ15/KCNH6/KCNN3/KCNJ1/ABCC9/KCNJ9/KCNN2/KCNJ3/ABCC8/KCNJ16/KCNJ6/KCNJ18/KCNJ11/KCNJ5/KCNK6/KCNH2	19
MF	GO:0022843	voltage-gated monoatomic cation channel activity	4.00E-02	3.73E-02	KCNJ13/KCNS1/KCNE1/ITGAV/CACNA1E/KCNC1/KCNJ2/KCNH7/KCNJ15/SCN9A/KCNG2/CACNB2/CACNA1D/KCNE3/KCNH6/KCNV2/KCNS2/SCN8A/OPRM1/KCNN3/KCNJ1/SCN3A/CACNB4/KCNT2/ABCC9/KCNJ9/CACNA2D1/KCNG3/HCN4/KCNN2/CACNG1/KCNJ3/KCNMA1/CACNA1S/KCNC2/KCNK3/SCN1A/KCNV1/HCN1/SCN7A/ABCC8/KCNJ16/KCNJ6/KCNA1/KCNJ18/KCNJ11/CACNA1G/KCND2/KCNK16/CACNA1B/KCNJ5/KCNAB2/KCNK6/TMEM109/CACNB1/KCNAB3/KCNC3/CACNA2D4/HCN2/CACNB3/KCNIP2/CACNA1H/CACNA1F/CATSPER1/LRRC26/CACNA2D2/KCNG1/CACNA1I/KCNH3/NCS1/KCNT1/KCNK17/CACNG6/CACNA2D3/KCNH2/KCNK10/KCNA5/HTR1B	78
MF	GO:0030695	GTPase regulator activity	4.68E-02	4.36E-02	MYCBP2/HERC1/RASA1/GAPVD1/DOCK11/ARFGEF1/DENND4A/RALGAPB/NF1/HTR2B/RABGAP1/LRRK2/TBC1D5/MYO9A/TBCK/DOCK2/RANBP2/RAB3GAP2/RIC1/ACAP2/DOCK8/DENND4C/SEC23A/RAPGEF6/ITSN2/IQGAP2/EVI5/STXBP5/FAM13B/TBC1D14/ARFGEF2/SBF2/DOCK5/RASA2/GPSM2/ARAP2/DENND1B/AKAP13/VAV3/DOCK4/ARHGAP26/KRIT1/RAPGEF2/RP2/FGD4/RALGAPA2/ARHGAP18/ARHGAP5/NCKAP1L/RALGAPA1/DIS3/IQGAP1/SOS2/ARHGEF12/SIPA1L2/CPEB2/OPHN1/DENND2C/SIPA1L1/SH3BP5/FAM13A/AGFG1/DOCK10/RAB3GAP1/RGP1/CHM/ECT2/RABGAP1L/DOCK7/ARHGAP15/TRIO/P2RY12/ASAP2/TBC1D30/USP6NL/FARP1/SRGAP1/GNA13/EGF/CCDC88A/PLEKHG6/RGS18/TBC1D19/ECT2L/RAB3IP/ASAP1/BNIP2/PLEKHG1/TAGAP/ARHGAP6/RGPD8/HERC2/TBC1D8B/FGD6/ARHGAP24/ARHGAP29/STXBP5L/DEPDC1B/ARHGAP42/GNAQ/TBC1D8/PSD3/ARHGEF38/MCF2L2/GRTP1/DENND5B/RGPD2/FRMD7/DOCK1/DEPDC1/RAPGEF4/STARD13/ARHGEF37/RGS20/ARHGEF33/PLCE1/RAPGEF5/NGEF/RANBP3L/ARHGEF28/DLC1/PLEKHG7/PREX2/KIAA1755/ARFGEF3/RGPD3/DENND2A/RGS17/ELMOD1/ARHGAP11B/ARHGAP28/RIMS1/ADGRB3/GCGR/ARHGEF16/ARHGAP8/RASGRP2/ARHGAP4/ARFGAP1/DENND1C/RANBP3/GIT1/TBC1D10A/PREB/ARHGDIA/TBC1D10C/ARHGEF1/TBC1D17/GDI1/GPS1/RASAL3/TNK2/ACAP3/SH3BP1/AGAP3/NPRL2/	223

					SGSM2/EPS8L2/DENND6B/SH2D3A/SGSM3/GPS2/EVI5L/TBC1D13/ARHGAP33/ARHGEF19/RANGAP1/PLCD4/RGS14/ARHGAP1/AGAP6/LAMTOR4/AGFG2/RASA4/RIN1/ARHGDIB/TBC1D10B/WAS/RIN3/ACAP1/GPSM1/TBC1D25/RANBP1/TBC1D24/RABEP2/PTGIR/GPSM3/RALGDS/IQSEC3/NUCB1/LLGL2/PCP2/PLEKHG4/EEF1B2/ALS2CL/RASA4B/RGS12/MTSS2/EPS8L1/RGS9/PLEKHG5/IQSEC2/AGAP9/AGAP7P/ARHGEF25/TBC1D16/CDC42EP2/KNDC1/PLXNB1/RGL3/TBC1D3L/SH3BP4/AGAP11/RHOD/TBC1D3F/TBC1D3I/TBC1D3C/SYNGAP1/DNAJA3/TBC1D3H/TBC1D26/TBC1D3B/TBC1D3G	
MF	GO:0060589	nucleoside-triphosphatase regulator activity	4.68E-02	4.36E-02	MYCBP2/HERC1/RASA1/GAPVD1/DOCK11/ARFGEF1/DENND4A/RALGAPB/NF1/HTR2B/RABGAP1/LRRK2/TBC1D5/MYO9A/TBCK/DOCK2/RANBP2/RAB3GAP2/RIC1/ACAP2/DOCK8/DENND4C/SEC23A/RAPGEF6/ITSN2/IQGAP2/EVI5/STXBP5/FAM13B/TBC1D14/ARFGEF2/SBF2/DOCK5/RASA2/GPSM2/ARAP2/DENND1B/AKAP13/VAV3/DOCK4/ARHGAP26/KRIT1/RAPGEF2/RP2/FGD4/RALGAPA2/ARHGAP18/ARHGAP5/NCKAP1L/RALGAPA1/DIS3/IQGAP1/SOS2/ARHGEF12/SIPA1L2/CPEB2/OPHN1/DENND2C/SIPA1L1/SH3BP5/FAM13A/AGFG1/DOCK10/RAB3GAP1/RGP1/CHM/ECT2/RABGAP1L/DOCK7/ARHGAP15/TRIO/P2RY12/ASAP2/TBC1D30/USP6NL/FARP1/SRGAP1/GNA13/EGF/CCDC88A/PLEKHG6/RGS18/TBC1D19/ECT2L/RAB3IP/ASAP1/BNIP2/PLEKHG1/TAGAP/ARHGAP6/RGPD8/HERC2/TBC1D8B/FGD6/ARHGAP24/ARHGAP29/STXBP5L/DEPDC1B/ARHGAP42/GNAQ/TBC1D8/PSD3/ARHGEF38/MCF2L2/GRTP1/DENND5B/RGPD2/FRMD7/DOCK1/DEPDC1/RAPGEF4/STARD13/ARHGEF37/RGS20/ARHGEF33/PLCE1/RAPGEF5/NGEF/RANBP3L/ARHGEF28/DLC1/PLEKHG7/PREX2/KIAA1755/ARFGEF3/RGPD3/DENND2A/RGS17/ELMOD1/ARHGAP11B/ARHGAP28/RIMS1/ADGRB3/GCGR/ARHGEF16/ARHGAP8/RASGRP2/ARHGAP4/ARFGAP1/DENND1C/RANBP3/GIT1/TBC1D10A/PREB/ARHGDIA/TBC1D10C/ARHGEF1/TBC1D17/GDI1/GPS1/RASAL3/TNK2/ACAP3/SH3BP1/AGAP3/NPRL2/SGSM2/EPS8L2/DENND6B/SH2D3A/SGSM3/GPS2/EVI5L/TBC1D13/ARHGAP33/ARHGEF19/RANGAP1/PLCD4/RGS14/ARHGAP1/AGAP6/LAMTOR4/AGFG2/RASA4/RIN1/ARHGDIB/TBC1D10B/WAS/RIN3/ACAP1/GPSM1/TBC1D25/RANBP1/TBC1D24/RABEP2/PTGIR/GPSM3/RALGDS/IQSEC3/NUCB1/LLGL	223

					2/PCP2/PLEKHG4/EEF1B2/ALS2CL/RASA4B/RGS12/MTSS2/EPS8L1/RGS9/PLEKHG5/IQSEC2/AGAP9/AGAP7P/ARHGEF25/TBC1D16/CDC42EP2/KNDC1/PLXNB1/RGL3/TBC1D3L/SH3BP4/AGAP11/RHOD/TBC1D3F/TBC1D3I/TBC1D3C/SYNGAP1/DNAJA3/TBC1D3H/TBC1D26/TBC1D3B/TBC1D3G	
MF	GO:0098631	cell adhesion mediator activity	4.68E-02	4.36E-02	TMOD3/NEXN/ITGA1/PDLIM5/ITGB1/BAIAP2L1/DSC2/ITGA2/GLDN/CNTN2/ITGA11/CXADR/PKP2/VCAM1/IGSF9/CNTN4/NFASC/DSCAM/DSG2/NTNG1/LRRC4C/EPCAM/CNTN5/CNTN1/MYPN/PPP1CA/ROBO3/PAK4/RPSA/S100A11/NINJ1/CDC42EP1/BAIAP2/RPSA2/KRT18/MADCAM1/JUP/AGER	38
MF	GO:0031720	haptoglobin binding	4.78E-02	4.45E-02	HBG1/HBG2/HBD/HBM/HBE1/HBQ1/HBB/HBA1/HBA2	9
MF	GO:1904315	transmitter-gated monoatomic ion channel activity involved in regulation of postsynaptic membrane potential	4.92E-02	4.58E-02	GRIK1/GABRR2/GRIN3A/CHRNB2/CHRNG/CHRNA2/CHRNA1/CHRND/GRIA3/CHRNA5/GLRA2/ZACN/GRIA4/GLRA1/GABRA4/GRIN2A/GRIN2B/GRIA1/GABRA2/GABRB1/GLRA3/GRID2/GABRG2/GLRB/CHRFAM7A/HTR3E/GRIA2/GABRG3/GABRA5/GABRB2/GRIK3/CHRNA6/HTR3A	33

Appendix 6. Enrichment analysis of tuberculosis in PLHIV vs HIV via clusterProfiler

Ontology	ID	Description	p.adjust	qvalue	geneID	Count
BP	GO:0050727	regulation of inflammatory response	6.68E-06	6.17E-06	S100A12/S100A8/HLA-E/AIM2/HGF/FCGR1A/SLAMF8/NLRC4/MMP8/S100A9/NAIP/IL1R1/FABP4/CYP19A1/WFDC1/ACOD1/NLRP13/ELANE/ACE2/IL22RA2/TSLP/DNASE1L3/MIR146A/CDH5/AGER/MIR15B/IL22	27
BP	GO:0042742	defense response to bacterium	6.83E-04	6.31E-04	S100A12/S100A8/GBP6/HP/HLA-E/FCGR1A/SLAMF8/NLRC4/GBP5/S100A9/NAIP/ANXA3/LCN2/DEFA1B/ELANE/CXCL13/TRAV27/SFTPD/WFDC12	19
BP	GO:0002544	chronic inflammatory response	1.13E-02	1.05E-02	VNN1/S100A8/S100A9/CYP19A1/CXCL13	5
BP	GO:0050900	leukocyte migration	2.34E-02	2.16E-02	ITGA7/HSD3B7/S100A12/S100A8/SLAMF8/S100A9/CD300H/IL1R1/ITGB3/CYP19A1/ITGA2B/CD177/DEFA1B/ELANE/CXCL13/SFTPD/MIR146A/DBH/AGER	19
BP	GO:0032612	interleukin-1 production	2.34E-02	2.16E-02	IL1R2/CEACAM1/AIM2/CARD17P/NLRC4/GBP5/NAIP/IGHD/AGER/MIR98	10
BP	GO:0032652	regulation of interleukin-1 production	2.34E-02	2.16E-02	IL1R2/CEACAM1/AIM2/CARD17P/NLRC4/GBP5/NAIP/IGHD/AGER/MIR98	10
BP	GO:0050729	positive regulation of inflammatory response	2.34E-02	2.16E-02	S100A12/S100A8/HLA-E/AIM2/FCGR1A/NLRC4/MMP8/S100A9/NAIP/FABP4/TSLP	11
BP	GO:0031348	negative regulation of defense response	2.98E-02	2.75E-02	IRAK3/CEACAM1/HLA-E/HGF/SLAMF8/ARG1/CYP19A1/WFDC1/ACOD1/ELANE/IL22RA2/MIR146A/RAB7B/CDH5/MIR15B/IL22	16
BP	GO:0001819	positive regulation of cytokine production	4.85E-02	4.48E-02	IL18R1/IRAK3/CYP1B1/CLEC5A/CD274/HLA-E/AIM2/HGF/NLRC4/MMP8/GBP5/FLOT1/NAIP/IL1R1/PRG3/ELANE/TSLP/IGHD/RAB7B/AGER/SCRIB	21
BP	GO:0050832	defense response to fungus	4.85E-02	4.48E-02	S100A12/S100A8/ARG1/S100A9/DEFA1B/ELANE	6
BP	GO:0006959	humoral immune response	4.96E-02	4.58E-02	CFH/S100A12/CD59/HLA-E/S100A9/CFHR3/DEFA1B/ACOD1/CFD/ELANE/TSLP/CXCL13/WFDC12	13
BP	GO:0019730	antimicrobial humoral response	4.96E-02	4.58E-02	S100A12/HLA-E/S100A9/DEFA1B/ACOD1/ELANE/TSLP/CXCL13/WFDC12	9

BP	GO:0051092	positive regulation of NF-kappaB transcription factor activity	4.96E-02	4.58E-02	IL18R1/IRAK3/S100A12/S100A8/AIM2/NLRC4/S100A9/FLOT1/RAB7B/AGER	10
BP	GO:0002523	leukocyte migration involved in inflammatory response	4.96E-02	4.58E-02	S100A8/SLAMF8/S100A9/ELANE	4
CC	GO:0042101	T cell receptor complex	2.59E-11	2.33E-11	TRAV12-1/TRAV8-1/TRGV9/TRAV13-2/TRBC2/TRAV25/TRAV38-2DV8/TRAV27/TRBV5-1/TRBV28/TRDV3/TRBV12-4/TRAV24/TRBV30/TRBV20-1/TRBV7-9/TRBV6-1/TRBV6-8/TRBV7-2/TRBV18	20
CC	GO:0098802	plasma membrane signaling receptor complex	3.73E-09	3.35E-09	IL18R1/ITGA7/CHRNA1/ITGB3/ITGA2B/GABBR1/TRAV12-1/TRAV8-1/TRGV9/TRAV13-2/TRBC2/TRAV25/TRAV38-2DV8/TRAV27/TRBV5-1/TRBV28/TRDV3/TRBV12-4/TRAV24/TRBV30/TRBV20-1/TRBV7-9/TRBV6-1/TRBV6-8/TRBV7-2/TRBV18	26
CC	GO:0042581	specific granule	8.41E-05	7.56E-05	CD59/MCEMP1/CEACAM1/HP/CLEC5A/ARG1/MMP8/GPR84/TCN1/ANXA3/LCN2/PRG3/CD177/ELANE	14
CC	GO:0035580	specific granule lumen	7.34E-03	6.60E-03	HP/ARG1/MMP8/TCN1/LCN2/PRG3/ELANE	7
CC	GO:0070820	tertiary granule	9.37E-03	8.43E-03	CD59/MCEMP1/CEACAM1/HP/CLEC5A/CYSTM1/MMP8/GPR84/TCN1/PRG3/CD177	11
CC	GO:0061702	canonical inflammasome complex	9.65E-03	8.68E-03	AIM2/NLRC4/CASP5/NAIP	4
CC	GO:0070821	tertiary granule membrane	1.20E-02	1.08E-02	CD59/MCEMP1/CEACAM1/CLEC5A/CYSTM1/GPR84/CD177	7
CC	GO:0034774	secretory granule lumen	1.64E-02	1.47E-02	S100A12/S100A8/HP/GYG1/HGF/ARG1/MMP8/S100A9/TCN1/LCN2/PRG3/DEFA1B/CFD/ELANE/DBH	15
CC	GO:0060205	cytoplasmic vesicle lumen	1.64E-02	1.47E-02	S100A12/S100A8/HP/GYG1/HGF/ARG1/MMP8/S100A9/TCN1/LCN2/PRG3/DEFA1B/CFD/ELANE/DBH	15
CC	GO:0031983	vesicle lumen	1.64E-02	1.47E-02	S100A12/S100A8/HP/GYG1/HGF/ARG1/MMP8/S100A9/TCN1/LCN2/PRG3/DEFA1B/CFD/ELANE/DBH	15
CC	GO:0030667	secretory granule membrane	3.65E-02	3.28E-02	VNN1/CD59/MCEMP1/CEACAM1/LHFPL2/CLEC5A/CYSTM1/GPR84/ITGB3/ITGA2B/LILRB3/CD177/PLA1A/DBH	14

MF	GO:0042605	peptide antigen binding	2.53E-03	2.22E-03	HLA-E/HLA-DMA/TRAV12-1/TRGV9/TRBV28/TRBV7-9/HLA-DQA2	7
MF	GO:0003823	antigen binding	6.35E-03	5.58E-03	HLA-E/HLA-DMA/TRAV12-1/TRGV9/IGHV2-70/TRBV28/IGHD/IGKV2D-28/TRBV7-9/HLA-DQA2/IGHV3-66	11
MF	GO:0036041	long-chain fatty acid binding	1.35E-02	1.19E-02	S100A8/S100A9/FABP4/FABP2	4
MF	GO:0061135	endopeptidase regulator activity	2.59E-02	2.28E-02	HMSD/AIM2/CARD17P/NLRC4/GBP5/NAIP/WFDC1/CST6/NGF/WFDC12	10
MF	GO:0061134	peptidase regulator activity	3.09E-02	2.72E-02	HMSD/AIM2/CARD17P/NLRC4/GBP5/NAIP/WFDC1/PCOLCE2/CST6/NGF/WFDC12	11
MF	GO:0050786	RAGE receptor binding	3.09E-02	2.72E-02	S100A12/S100A8/S100A9	3
MF	GO:0008395	steroid hydroxylase activity	4.21E-02	3.70E-02	CYP1B1/CYP19A1/CYP7A1/CYP46A1	4
MF	GO:0005504	fatty acid binding	4.45E-02	3.91E-02	S100A8/S100A9/FABP4/FABP2/UGT1A8	5
MF	GO:0045028	G protein-coupled purinergic nucleotide receptor activity	4.66E-02	4.10E-02	P2RY14/GPR87/P2RY4	3
MF	GO:0033293	monocarboxylic acid binding	4.66E-02	4.10E-02	S100A8/S100A9/FABP4/FABP2/UGT1A8/CYP27C1	6
MF	GO:0004497	monooxygenase activity	4.66E-02	4.10E-02	CYP1B1/CYP19A1/CYP27C1/CYP7A1/DBH/CYP46A1/CYP2D6	7
MF	GO:0002020	protease binding	4.94E-02	4.34E-02	ATP9A/CARD17P/NLRC4/FLOT1/IL1R1/ITGB3/CD177/ELANE	8

Appendix 7. Enrichment analysis of tuberculosis in PLHIV vs non-infected via clusterProfiler

Ontology	ID	Description	p.adjust	qvalue	geneID	Count
BP	GO:0002181	cytoplasmic translation	2.28E-07	2.23E-07	DHX36/CPEB3/CPEB4/MCTS2/NCBP1/DHX29/NEMF/CPEB2/LIN28A/IGF2BP1/RBM24/RPS16/RPL28/RPS3/RPS28/EIF3K/RPS15/RPL29/RPL18A/MIF4GD/RPL8/RPL10/RPL18/RPL27/RPL13/RPL7A/RPL27A/RPL14/RPS2/RPL36/RPL3/RPS21/EIF3G/EIF3F/RPS19/RPL15/RPL12/RPL37A/RPL13A/RPL19/DRG2/RPS13/RPL10A/RPL23A/RPSA/RPS27A/RACK1/FAU/RPLP2/RPL37/RPL35/RPL22/RPS4X/RPS5/RPS29/RPLP1/RPS8/FTSJ1/RPL6/RPL38/RPS20/RPS14/RPL32/RPS23/RPL35A/RPS6/RPS25/RPS26/RPLP0/RPL24/RPL11/RPL5/RPL4/RPL23/RPL30/ZNF385A/RPS27/PARP16/RPL39/RPL41/RPS11/RPL26/RPL34/RPS12/RPL9/RPL21/RPS10/RPS3A/RPS18/EIF3C/RPS17	91
BP	GO:0006334	nucleosome assembly	4.02E-04	3.93E-04	H2BC4/H3C4/SHPRH/H4C4/H4C5/ATRX/H2BC6/H4C3/H2BC8/H2BC15/RSF1/KAT6A/H4C16/H1-3/H1-2/H2BC11/H4C2/H2BC13/H1-4/H3C8/H2BC7/BAZ1A/H2BC3/H3C10/H4C9/SMARCA5/H3C12/H4C8/H2BC9/H1-6/H3C2/H4C6/H3C6/H2BC17/H2BC10/H3C13/H1-5/H2BC14/H3C7/H4C13/TSPYL6/H3C15/H3C3/H4C12/H3C11/H4C1/H3C1/H1-1/TSPY26P/H4C11/H3-4/H3C14/CHRAC1/H1-10/POLE3/ANP32B/NAA60/MACROH2A2/H2AX/TSPYL2/DAXX/H2AB3/BRD2/NAP1L3	64
BP	GO:0034728	nucleosome organization	4.45E-03	4.35E-03	H2BC4/H3C4/SHPRH/ARID2/H4C4/H4C5/ATRX/H2BC6/H4C3/H2BC8/H2BC15/RSF1/KAT6A/SETD2/H4C16/LIN54/H1-3/H1-2/H2BC11/H4C2/CHD1/H2BC13/H1-4/H3C8/H2BC7/BAZ1A/H2BC3/H3C10/H4C9/SMARCA5/H3C12/H4C8/H2BC9/H1-6/H3C2/H4C6/H3C6/H2BC17/H2BC10/H3C13/H1-5/H2BC14/H3C7/H4C13/TSPYL6/H3C15/H3C3/H4C12/H3C11/H4C1/H3C1/H1-1/TSPY26P/H4C11/H3-4/H3C14/CHRAC1/H1-10/POLE3/HMGA1/ANP32B/NAA60/MACROH2A2/H2AX/TSPYL2/DAXX/H2AB3/BRD2/NAP1L3	69
BP	GO:0071168	protein localization to chromatin	1.50E-02	1.47E-02	MCM9/NIPBL/VCPIP1/H4C4/H4C5/WAPL/H4C3/TASOR/SETD2/H2AC8/H4C16/MMS22L/H2BC11/H4C2/H4C9/H4C8/H4	36

					C6/ESCO2/VRK1/H1-5/MCM8/APLF/H2AC4/H4C13/ESR1/H4C12/H4C1/CTCFL/H4C11/SIRT6/WBP2/MACROH2A2/SGF29/SPI1/TONSL/LEF1	
BP	GO:0061644	protein localization to CENP-A containing chromatin	2.77E-02	2.70E-02	H4C4/H4C5/H4C3/H2AC8/H4C16/H2BC11/H4C2/H4C9/H4C8/H4C6/H2AC4/H4C13/H4C12/H4C1/H4C11	15
CC	GO:0022626	cytosolic ribosome	8.25E-18	7.70E-18	LTN1/HBS1L/ASCC3/DHX29/NEMF/GSPT1/RPS16/RPL28/RPS3/RPS28/RPS15/RPL29/RPL18A/RPL8/RPL10/RPL18/RPL27/ZNF598/RPL13/RPL7A/RPL27A/RPL14/RPS2/RPL36/RPL3/RPS21/SNU13/RPS19/RPL15/RPL12/RPL37A/RPL13A/RPL19/RNF25/RPS13/RPL10A/RPL23A/RPSA/RPS27A/RACK1/FAU/RPLP2/RPL37/RPL35/NHP2/RPL22/RPS4X/RPS5/RPS29/RPLP1/RPS8/RPL6/RPL38/RPS20/RPS14/RPL32/RPS23/RPL35A/RPS6/RPS25/RPS26/RSL1D1/RPLP0/RPL24/RPL11/RPL5/RPL4/RPL23/RPL30/RPS27/RPL36AL/RPL39/RPL41/RPS11/RPL26/RPL34/RPS12/RPL9/RPL21/RPSA2/RPS10/RPS3A/RPS18/RPL39L/RPS17/RPS4Y2/RPS4Y1	87
CC	GO:0022625	cytosolic large ribosomal subunit	1.62E-11	1.51E-11	RPL28/RPL29/RPL18A/RPL8/RPL10/RPL18/RPL27/RPL13/RPL7A/RPL27A/RPL14/RPL36/RPL3/SNU13/RPL15/RPL12/RPL37A/RPL13A/RPL19/RPL10A/RPL23A/RPLP2/RPL37/RPL35/NHP2/RPL22/RPLP1/RPL6/RPL38/RPL32/RPL35A/RSL1D1/RPLP0/RPL24/RPL11/RPL5/RPL4/RPL23/RPL30/RPL36AL/RPL39/RPL41/RPL26/RPL34/RPL9/RPL21/RPL39L	47
CC	GO:0044391	ribosomal subunit	6.42E-10	5.99E-10	NSUN3/DHX29/RPS16/RPL28/MRPL38/RPS3/MRPL12/MRPS2/RPS28/RPS15/RPL29/RPL18A/RPL8/RPL10/RPL18/RPL27/RPL13/RPL7A/RPL27A/MRPS34/RPL14/RPS2/RPL36/RPL3/MRPL4/RPS21/SNU13/MRPL41/RPS19/MRPL9/MRPL52/RPL15/RPL12/MRPL54/RPL37A/RPL13A/MRPL43/RPL19/MRPL10/RPS13/RPL10A/MRPL34/MRPL2/RPL23A/MRPS21/RPSA/MRPL55/RPS27A/RACK1/FAU/RPLP2/RPL37/GADD45GIP1/RPL35/MRPL11/MRPS12/MPV17L2/NHP2/MRPS26/RPL22/RPS4X/IMP3/MRPL24/RPS5/RPS29/RPLP1/AURKAIP1/RPS8/RPL6/MRPS15/RPL38/MRPL37/RPS20/RPS14/RPL32/RPS23/RPL35A/RPS6/RPS25/RPS26/RSL1D1/RPLP0/RPL24/RPL11/RPL5/RPL4/RPL23/RPL30/RPS27/RPL36AL/RPL39/RPL41/RPS11/MRPS33/RPL26/RPL34/RPS12/RPL9/MRPL23/RPL21/RPSA2/RPS10/RPS3A/RPS18/RPL39L/RPS17/RPS4Y2/RPS4Y1	108

CC	GO:0022627	cytosolic small ribosomal subunit	5.23E-08	4.88E-08	DHX29/RPS16/RPS3/RPS28/RPS15/RPS2/RPS21/RPS19/RPS13/RPSA/RPS27A/RACK1/FAU/RPS4X/RPS5/RPS29/RPS8/RPS20/RPS14/RPS23/RPS6/RPS25/RPS26/RPS27/RPS11/RPS12/RPSA2/RPS10/RPS3A/RPS18/RPS17/RPS4Y2/RPS4Y1	33
CC	GO:0005840	ribosome	7.95E-08	7.41E-08	LTN1/LINC01004/NUFIP2/HBS1L/NSUN3/ASCC3/DHX29/NEMF/EIF2AK2/GSPT1/RPL13AP3/RPS16/RPL28/MRPL38/RPS3/MRPL12/MRPS2/RPS28/RPS15/RPL29/RPL18A/RPL8/RPL10/RPL18/RPL27/ZNF598/RPL13/RPL7A/RPL27A/MRPS34/RPL14/NDUFA7/RPS2/RPL36/RPL3/MRPL4/RPS21/SNU13/MRPL41/RPS19/MRPL9/MRPL52/RPL15/RPL12/APEX1/MRPL54/RPL37A/RPL13A/MRPL43/SF1/RPL19/RNF25/MRPL10/RPS13/RPL10A/MRPL34/MRPL2/RPL23A/MRPS21/RPSA/MRPL55/RPS27A/RACK1/FAU/RPLP2/RPL37/GADD45GIP1/RPL35/MRPL11/MRPS12/MPV17L2/NHP2/MRPS26/RPL22/RPS4X/IMP3/MRPL24/RPS5/RPS29/RPLP1/AURKAIP1/RPS8/RPL6/MRPS15/RPL38/MRPL37/RPS20/RPS14/RPL32/RPS23/RPL35A/RPS6/RPS25/RPS26/RSL1D1/RPLP0/RPL24/RPL11/RPL5/RPL4/MTG1/RPL23/RPL30/RPS27/RPL36AL/BTF3/RPL39/RPL41/RPS11/MRPS33/RPL26/RPL34/RPS12/RPL9/MRPL23/RPL21/RPSA2/RPS10/RPS3A/RPS18/RPL39L/RPS17/RPS4Y2/RPS4Y1	124
CC	GO:0000786	nucleosome	1.10E-07	1.02E-07	H2BC18/H2BC4/H3C4/SHPRH/H2AC20/H4C4/H4C5/H2BC6/H2AC17/H4C3/H2BC8/H2BC15/EPC2/H2AC11/KDM1B/H2AC6/KAT6A/SLF1/TRRAP/H2AC8/H4C16/H2AC15/H2BC5/H1-3/H1-2/H2BC11/H4C2/H2AC13/H2BC13/H1-4/H3C8/H2BC7/H2BC3/H3C10/H2BC12/H4C9/H3C12/H4C8/H2BC26/H2AC21/H2BC9/H1-6/H3C2/H4C6/H3C6/H2AC16/H2BC17/H2BC10/H2AC7/H3C13/H1-5/H2AC4/H2BC14/H3C7/H4C13/H2AC12/H3-5/H3C15/H3C3/H4C12/H3C11/H4C1/H3C1/H1-1/TGM2/H4C11/H3-4/H3C14/DMAP1/H1-10/MACROH2A2/H2AX/SPHK2/H2AB3	74
CC	GO:0015934	large ribosomal subunit	9.83E-06	9.17E-06	NSUN3/RPL28/MRPL38/MRPL12/RPL29/RPL18A/RPL8/RPL10/RPL18/RPL27/RPL13/RPL7A/RPL27A/RPL14/RPL36/RPL3/MRPL4/SNU13/MRPL41/MRPL9/MRPL52/RPL15/RPL12/MRPL54/RPL37A/RPL13A/MRPL43/RPL19/MRPL10/RPL10A/MRPL34/MRPL2/RPL23A/MRPL55/RPLP2/RPL37/GADD45GIP1/RPL35/MRPL11/MPV17L2/NHP2/RPL22/MRPL24/RPLP1/RPL6/RPL38/MRPL37/RPL32/RPL35A/RSL1D1/RPLP0/RPL24/RPL1	66

					1/RPL5/RPL4/RPL23/RPL30/RPL36AL/RPL39/RPL41/RPL26/RPL34/RPL9/MRPL23/RPL21/RPL39L	
CC	GO:0042788	polysomal ribosome	9.64E-04	8.99E-04	NUFIP2/RPS28/RPL18A/RPL8/RPL18/RPL7A/RPL36/RPS21/RPL19/RPL10A/RPS29/RPL6/RPL38/RPL32/RPS23/RPS26/RPL24/RPL11/RPL30/BTF3/RPL39/RPL41	22
CC	GO:0043505	CENP-A containing nucleosome	1.57E-03	1.47E-03	H4C4/H4C5/H4C3/H2AC8/H4C16/H2BC11/H4C2/H4C9/H4C8/H4C6/H2AC4/H4C13/H4C12/H4C1/H4C11	15
CC	GO:0061638	CENP-A containing chromatin	1.57E-03	1.47E-03	H4C4/H4C5/H4C3/H2AC8/H4C16/H2BC11/H4C2/H4C9/H4C8/H4C6/H2AC4/H4C13/H4C12/H4C1/H4C11	15
CC	GO:0015935	small ribosomal subunit	2.54E-03	2.37E-03	DHX29/RPS16/RPS3/MRPS2/RPS28/RPS15/MRPS34/RPS2/RPS21/RPS19/RPS13/MRPS21/RPSA/RPS27A/RACK1/FAU/MRPS12/MRPS26/RPS4X/IMP3/RPS5/RPS29/AURKAIP1/RPS8/MRPS15/RPS20/RPS14/RPS23/RPS6/RPS25/RPS26/RPS27/RPS11/MRPS33/RPS12/RPSA2/RPS10/RPS3A/RPS18/RPS17/RPS4Y2/RPS4Y1	42
CC	GO:0034506	chromosome, centromeric core domain	4.27E-03	3.98E-03	H4C4/H4C5/H4C3/H2AC8/H4C16/H2BC11/H4C2/H4C9/H4C8/H4C6/H2AC4/H4C13/H4C12/H4C1/H4C11	15
CC	GO:1990351	transporter complex	1.17E-02	1.09E-02	TMEM30A/AKAP9/ATP11C/NDUFS1/STXBP5/KCNS1/ATP10D/GRIK1/ATP8B1/ATP8A1/ATP8B4/ATP6V1A/ANO6/SLC5A3/PEX13/ERGIC2/ATP11B/PLN/CACNA1E/KCNE1/KCNC1/BEST1/KCNJ2/ATP11A/SCN9A/GRIN3A/GABRR2/KCNG2/PKD1L3/SCN3B/ATP6V1D/CLIC4/LRRC8B/ATP6V1C1/KCNIP4/CHRNB2/CACNA1D/RYR3/CACNB2/C2CD6/CHRNA2/CNGB3/SCN8A/ATP4B/TRPC5/TMEM262/CHRNA1/HSPA2/CLIC1/KCNV2/CLCA3P/ANO2/SHISA7/CLIC2/KCNB1/KCNMA1/ABCG5/TRPC6/KCNS2/SCN7A/UNC80/SCN3A/CACNG1/CACNA2D1/KCNG3/CHRNA5/GRIA3/CNGA1/ABCG8/VWC2L/SHISA6/GRIN2B/KCNMB2/DPP10/GABRB1/CHRND/CATSPERD/ATP1B4/ABCC9/CACNA1G/GABRA4/CACNA1S/GLRA2/CHRNA6/GLRA1/GABRA2/ABCC8/GLRA3/ND3/ND6/ND2/ND4L/ATP6V1F/ND5/CYTB/NDUFA11/COX1/NDUFB11/NDUFB7/NDUFA7/NDUFS7/NDUFS8/PTPA/CYC1/CLIC3/NDUFS3/NDUFS6/NDUFB10/KCNAB2/PORCN/NDUFA13/NDUFC1/KCNAB3/TIMM13/NDUFB9/ND1/NDUFV1/ORAI1/ABCD4/CACNB1/ABCB8/CALM3/CLCN7/KCNC3/NDUFB4/ERGIC3/HCN2/ND4/PEX14/NDUFAB1/CACNB3/ATP6V0C/KCNK6/NDUFB2/TIMM9/CACNA2D4/BCS1L/CNIH2/KCNMB1/KCNN4/ABHD12/FXYD1/KC	174

					NIP2/CACNA1F/FKBP1A/CACNA1H/SCNN1D/TTYH2/STAC3/TTYH3/PRKACA/SCNN1A/TMEM249/LRRC26/CATSPER1/KCNG1/TMEM30B/CACNA2D2/CATSPER2/LRRC38/OLFM2/CACNA1I/CLCN1/SCN4B/SHISA8/TRPV6/CACNA2D3/CACNG6/NDUFA3/EFCAB9/GRIN1/SCN4A/HTR3A/GRIK4	
CC	GO:0005891	voltage-gated calcium channel complex	2.39E-02	2.23E-02	CACNA1E/SCN9A/CACNA1D/CACNB2/C2CD6/SCN8A/TMEM262/HSPA2/SCN7A/SCN3A/CACNG1/CACNA2D1/CATSPERD/CACNA1G/CACNA1S/CACNB1/CACNB3/CACNA2D4/CACNA1F/FKBP1A/CACNA1H/STAC3/TMEM249/CATSPER1/CACNA2D2/CATSPER2/CACNA1I/CACNA2D3/CACNG6/EFCAB9/SCN4A	31
CC	GO:0016442	RISC complex	4.13E-02	3.85E-02	DICER1/AGO3/MIR133A1HG/AGO1/AGO4/DCP2/MIR21/MIR601/MIR1296/DNM3OS/MIR302B/MIR223/MIR505/MIR938/MIR29A/MIR16-1/MIR181A2/MIR302A/MIR30C1/MIR553/MIR326/MIR612/MIR628/MIR576/MIR181B2/MIR744/MIR302C/MIR186/MIR17HG/MIR101-1/MIR29B1/MIR302D/MIR624/MIR197/MIR640/MIR32/MIR320C1/MIRLET7G/MIR581/MIR590/MIR491/MIR320D1/MIR604/MIR558/MIR580/MIRLET7F2/MIR15A/MIR618/MIR454/MIR98/MIRLET7F1/MIR128-1/MIR30E/MIR573/MIR1183/MIR15B/MIR920/MIR215/MIR199A1/MIR331/MIR367/MIR103A1/MIR24-2/MIR194-1/MIR661/MIR569/MIR593/MIR761/MIR425/MIR181A1/MIR550A3/MIR643/MIR222/MIR150/MIR27B/MIR626/MIR148B/MIR191/MIR185/MIRLET7A1/TARBP2/MIR142/MIR25/MIR23AHG/MIR631/MEG3/MIR324/MIR342/MIR339	89
CC	GO:0031332	RNAi effector complex	4.13E-02	3.85E-02	DICER1/AGO3/MIR133A1HG/AGO1/AGO4/DCP2/MIR21/MIR601/MIR1296/DNM3OS/MIR302B/MIR223/MIR505/MIR938/MIR29A/MIR16-1/MIR181A2/MIR302A/MIR30C1/MIR553/MIR326/MIR612/MIR628/MIR576/MIR181B2/MIR744/MIR302C/MIR186/MIR17HG/MIR101-1/MIR29B1/MIR302D/MIR624/MIR197/MIR640/MIR32/MIR320C1/MIRLET7G/MIR581/MIR590/MIR491/MIR320D1/MIR604/MIR558/MIR580/MIRLET7F2/MIR15A/MIR618/MIR454/MIR98/MIRLET7F1/MIR128-1/MIR30E/MIR573/MIR1183/MIR15B/MIR920/MIR215/MIR19	89

					9A1/MIR331/MIR367/MIR103A1/MIR24-2/MIR194-1/MIR661/MIR569/MIR593/MIR761/MIR425/MIR181A1/MIR550A3/MIR643/MIR222/MIR150/MIR27B/MIR626/MIR148B/MIR191/MIR185/MIRLET7A1/TARBP2/MIR142/MIR25/MIR23AHG/MIR631/MEG3/MIR324/MIR342/MIR339	
MF	GO:0030527	structural constituent of chromatin	7.82E-14	7.55E-14	H2BC18/H2BC4/H3C4/H2AC20/H4C4/H4C5/H2BC6/H2AC17/H4C3/H2BC8/H2BC15/H2AC11/H2AC6/H2AC8/H4C16/H2AC15/H2BC5/H1-3/H1-2/H2BC11/H4C2/H2AC13/H2BC13/H1-4/H3C8/H2BC7/H2BC3/H3C10/H2BC12/H4C9/H3C12/H4C8/H2BC26/H2AC21/H2BC9/H1-6/H3C2/H4C6/H3C6/H2AC16/H2BC17/H2BC10/H2AC7/H3C13/H1-5/H2AC4/H2BC14/H3C7/H4C13/H2AC12/H3-5/H3C15/H3C3/H4C12/H3C11/H4C1/H3C1/H1-1/H4C11/H3-4/H3C14/H1-10/HMGA1/MACROH2A2/H2AX/H2AB3/LMNTD2	67
MF	GO:0003735	structural constituent of ribosome	5.00E-11	4.83E-11	LINC01004/SRBD1/RPL13AP3/RPS16/RPL28/RPS3/MRPL12/MRPS2/RPS28/RPS15/RPL29/RPL18A/RPL8/RPL10/RPL18/RPL27/RPL13/RPL7A/RPL27A/MRPS34/RPL14/NDUFA7/RPS2/RPL36/RPL3/MRPL4/RPS21/MRPL41/RPS19/MRPL9/MRPL52/RPL15/RPL12/MRPL54/RPL37A/RPL13A/MRPL43/RPL19/MRPL10/RPS13/RPL10A/MRPL34/MRPL2/RPL23A/MRPS21/RPSA/MRPL55/RPS27A/FAU/RPLP2/RPL37/RPL35/MRPL11/MRPS12/RPL22/RPS4X/IMP3/MRPL24/RPS5/RPS29/RPLP1/RPS8/RPL6/MRPS15/RPL38/MRPL37/RPS20/RPS14/RPL32/RPS23/RPL35A/RPS6/RPS25/RPS26/RPLP0/RPL24/RPL11/RPL5/RPL4/RPL23/RPL30/RPS27/RPL36AL/RPL39/RPL41/RPS11/MRPS33/RPL26/RPL34/RPS12/RPL9/MRPL23/RPL21/RPSA2/RPS10/RPS3A/RPS18/RPL39L/RPS17/RPS4Y2/RPS4Y1	101
MF	GO:0046982	protein heterodimerization activity	2.44E-05	2.36E-05	H2BC18/H2BC4/H3C4/RALGAPB/TAF1/H2AC20/H4C4/H4C5/H2BC6/H2AC17/H4C3/H2BC8/H2BC15/H2AC11/H2AC6/BARD1/ATF6/TCF12/HIF1A/H2AC8/ATF2/H4C16/RALGAPA2/GTF2A1/H2AC15/SOS2/H2BC5/TLR4/H2BC11/H4C2/H2AC13/CHUK/RALGAPA1/H2BC13/MIGA1/IRAK3/H3C8/H2BC7/TOP2A/CYBB/H2BC3/ZHX1/H3C10/H2BC12/H4C9/DR1/H3C12/TLR6/H4C8/TENM1/H2BC26/H2AC21/H2BC9/ITGB1/MEF2A/H3C2/H4C6/H3C6/H2AC16/AURKA/TCF4/H2BC17/H2BC10/H2AC7/H3C13/PDSS1/EXT1/P2RY1/GCA/APOA2/H2AC4/	151

					H2BC14/H3C7/RRAGD/H4C13/SLC51A/ABCD2/H2AC12/H3-5/CEACAM6/SDCBP/SLC3A1/H3C15/H3C3/HIP1/H4C12/H3C11/EPAS1/H4C1/H3C1/BMP6/BHLHE41/CEACAM8/PDGFA/FZD4/CAV2/KCNB1/BCL2A1/H4C11/ABCG5/AGTR1/CAV1/NPAS3/H3-4/ABCG8/ADRA1A/SDCBP2/H3C14/MTTP/GABBR2/CENPT/BAX/CHRAC1/ATF4/PAFAH1B3/DRAP1/PHB2/POLE3/IRAK1/USF2/HSF1/MIGA2/TAF6L/QTRT1/TPM2/BUD23/KRT10/MACROH2A2/PPP2R1A/PIK3R2/H2AX/MEF2D/PHB1/TCF3/KATNB1/POLE4/CD247/TAF6/NR4A1/PDGFB/BHLHE40/YWHAE/BOK/SLC7A8/H2AB3/SLC7A9/TUBB2B/CENPS/NPAS1/ADORA1/KRT1	
MF	GO:0005096	GTPase activator activity	5.88E-04	5.68E-04	RASA1/GAPVD1/NF1/RALGAPB/RABGAP1/TBC1D5/LRRK2/HTR2B/DOCK2/RAB3GAP2/MYO9A/RANBP2/ACAP2/TBCK/SEC23A/EVI5/IQGAP2/FAM13B/STXBP5/TBC1D14/RASA2/RP2/ARAP2/DOCK4/VAV3/NCKAP1L/ARHGAP5/RAPGEF2/ARHGAP26/ARHGAP18/DOCK5/IQGAP1/RALGAPA2/SEC23B/FAM13A/SIPA1L1/ECT2/RALGAPA1/SIPA1L2/ARHGEF12/CHM/AGFG1/OPHN1/SRGAP1/RABGAP1L/USP6NL/ASAP2/ARHGAP15/ASAP1/PLEKHG6/TBC1D30/BNIP2/TBC1D19/DOCK1/DEPDC1B/ARHGAP24/GNAQ/ARHGAP6/ARHGAP29/ARHGAP42/TBC1D8B/RGS18/TBC1D8/RGPD8/GRTP1/STARD13/DEPDC1/RGPD2/RASAL2/IQGAP3/STXBP5L/DLC1/PREX2/RGS20/RANBP3L/TIAM2/RGS17/RAP1GAP/ADGRB3/ARHGAP4/ARFGAP1/TBC1D10C/RANBP3/TBC1D10A/GIT1/ARHGDIA/ARHGEF1/TBC1D17/GDI1/PREB/NPRL2/ACAP3/RASAL3/SH3BP1/SGSM2/SGSM3/AGAP3/ARHGEF19/ARHGAP33/EVI5L/RASA4/RANGAP1/TBC1D13/RGS14/AGAP6/AGFG2/ARHGAP1/RIN1/RANBP1/ACAP1/ARHGDIB/RABEP2/RIN3/TBC1D10B/ALS2CL/LLGL2/RGS12/MTSS2/AGAP7P/RASA4B/AGAP9/TBC1D3L/PLXNB1/TBC1D3D/TBC1D3C/AGAP11/RGS7	127
MF	GO:0031267	small GTPase binding	1.32E-03	1.27E-03	MYCBP2/GAPVD1/DOCK11/ATP7A/RABGAP1/CDKL5/LRRK2/DOCK2/IPO11/DMXL2/RAB3GAP2/RIC1/RANBP2/EVI5/MYRIP/RAPGEF6/EXOC5/IQGAP2/DIAPH2/ROCK2/USP33/TNPO1/AKAP13/CCDC186/DOCK4/DENND1B/FGD4/ABCA1/MYO5A/SORL1/ERC1/DOCK5/TRIP11/IQGAP1/ROCK1/MEGF9/FMNL2/PICALM/ECT2/WDR44/STRN3/RGP1/DOCK10/EXOC8/GO	128

					LGA4/GARRE1/CHM/GCC2/RHOBTB3/PKN2/HACE1/KNTC1/RABGAP1L/USP6NL/DOCK7/MYO5B/XPO1/TBC1D30/FARP1/NCKAP1/DIAPH3/FGD6/DOCK1/PLEKHG1/SYTL4/NCF2/RANBP17/RGPD8/DAAM2/DENND5B/RAPGEF4/PEX5L/IQGAP3/PIH1D2/CAV1/RIMS2/ADCYAP1R1/RNF152/ASB15/RAP1GAP/PFN1/CIB1/GIT1/NOXA1/GDI1/DVL1/SGSM2/SGSM3/GGA1/NXT1/RABGGTA/DVL3/PKN1/SYTL1/PPP6R1/NUTF2/BRK1/EVI5L/DVL2/RANGAP1/TBC1D13/SPHK2/ARHGAP1/RIN1/RANBP1/ARHGDIB/ULK1/PARD6A/INF2/WAS/KCTD13/RIN3/TAMALIN/ALS2CL/RAB34/MAP3K11/FMNL1/PKN3/RPH3AL/CDC42EP1/BICDL1/MTSS2/RAB11FIP3/RAB11FIP5/RANGRF/NPC1L1/NGFR/RPH3A	
MF	GO:0051020	GTPase binding	6.79E-03	6.56E-03	MYCBP2/RASA1/GAPVD1/DOCK11/ATP7A/RABGAP1/CDKL5/LRRK2/DOCK2/IPO11/DMXL2/RAB3GAP2/RIC1/RANBP2/EVI5/MYRIP/RAPGEF6/EXOC5/IQGAP2/DIAPH2/ROCK2/USP33/TNPO1/AKAP13/CCDC186/DOCK4/DENND1B/FGD4/ABCA1/MYO5A/SORL1/ERC1/DOCK5/TRIP11/IQGAP1/ROCK1/MEGF9/FMNL2/PICALM/ECT2/WDR44/STRN3/RGP1/DOCK10/EXOC8/GOLGA4/GARRE1/CHM/GCC2/RHOBTB3/PKN2/HACE1/FNBP1L/SPTBN1/KNTC1/RABGAP1L/USP6NL/DOCK7/MYO5B/XPO1/TBC1D30/FARP1/NCKAP1/DIAPH3/FGD6/DOCK1/PLEKHG1/SYTL4/RRAGD/NCF2/RANBP17/RGPD8/DAAM2/DENND5B/RAPGEF4/PEX5L/IQGAP3/PIH1D2/CAV1/RIMS2/ADCYAP1R1/RNF152/ASB15/RAP1GAP/PFN1/CIB1/GIT1/NOXA1/GDI1/PREB/DVL1/SGSM2/SGSM3/GGA1/NXT1/RABGGTA/DVL3/PKN1/SYTL1/PPP6R1/NUTF2/BRK1/EVI5L/DVL2/RANGAP1/BIN1/TBC1D13/SPHK2/ARHGAP1/RIN1/RANBP1/ARHGDIB/ULK1/PARD6A/INF2/WAS/KCTD13/RABAC1/RIN3/TAMALIN/ALS2CL/RAB34/MAP3K11/FMNL1/PKN3/RPH3AL/CDC42EP1/BICDL1/RASIP1/MTSS2/RAB11FIP3/RAB11FIP5/RANGRF/GNB3/NPC1L1/NGFR/RPH3A	137
MF	GO:0030695	GTPase regulator activity	7.03E-03	6.79E-03	HERC1/MYCBP2/RASA1/GAPVD1/DOCK11/ARFGEF1/NF1/RALGAPB/DENND4A/RABGAP1/TBC1D5/LRRK2/HTR2B/DOCK2/RAB3GAP2/MYO9A/RIC1/RANBP2/ACAP2/TBCK/DOCK8/SEC23A/EVI5/DENND4C/RAPGEF6/IQGAP2/FAM13B/STXBP5/TBC1D14/ITSN2/ARFGEF2/SBF2/AKAP13/RASA2/RP2/ARAP2/DOCK4/GPSM2/DENND1B/FGD4/VAV3/SH3BP5/NCKAP1L/ARHGAP5/RAPGEF2/ARHGAP26/ARHGAP18/DOCK5/IQGAP	202

					1/RALGAPA2/SEC23B/SOS2/FAM13A/SIPA1L1/ECT2/RALGAPA1/RGP1/DOCK10/SIPA1L2/DENND2C/ARHGEF12/CHM/TRIO/AGFG1/CPEB2/OPHN1/CCDC88A/SRGAP1/RABGAP1L/USP6NL/DOCK7/ASAP2/GNA13/ARHGAP15/ASAP1/ECT2L/PLEKHG6/TBC1D30/BNIP2/FARP1/EGF/FGD6/HERC2/TBC1D19/DOCK1/PLEKHG1/DEPDC1B/PSD3/ARHGAP24/GNAQ/ARHGAP6/ARHGAP29/ARHGEF38/P2RY12/ARHGAP42/TBC1D8B/RGS18/MCF2L2/TBC1D8/RGPD8/GRTP1/STARD13/DEPDC1/DENND5B/RGPD2/RAPGEF4/RASAL2/IQGAP3/STXBP5L/DLC1/PREX2/RGS20/RANBP3L/TIAM2/ARHGEF33/ARHGEF37/RAPGEF5/ARFGEF3/FRMD7/ARHGEF28/NGEF/RGS17/RAP1GAP/ADGRB3/RASGRP2/ARHGAP4/ARFGAP1/DENND1C/TBC1D10C/RANBP3/TBC1D10A/GIT1/ARHGDIA/TNK2/ARHGEF1/TBC1D17/GPS1/GDI1/PREB/NPRL2/ACAP3/EPS8L2/RASAL3/SH3BP1/SGSM2/SGSM3/SH2D3A/EIF2B4/AGAP3/ARHGEF19/DENND6B/ARHGAP33/EVI5L/PLCD4/GPS2/RASA4/RANGAP1/TBC1D13/RGS14/AGAP6/LAMTOR4/AGFG2/ARHGAP1/RIN1/PCP2/RANBP1/IQSEC3/ACAP1/ARHGDIB/RABEP2/WAS/GPSM1/PLEKHG4/RIN3/TBC1D10B/EEF1B2/ALS2CL/LLGL2/PTGIR/RALGDS/RGS12/VAV2/NUCB1/MTSS2/RGL3/AGAP7P/PLEKHG5/RASA4B/KNDC1/ARHGEF25/EPS8L1/RANGRF/AGAP9/GPSM3/TBC1D3L/PLXNB1/TBC1D3D/RHOD/TBC1D3C/AGAP11/DNAJA3/RGS7	
MF	GO:0060589	nucleoside-triphosphatase regulator activity	7.03E-03	6.79E-03	HERC1/MYCBP2/RASA1/GAPVD1/DOCK11/ARFGEF1/NF1/RALGAPB/DENND4A/RABGAP1/TBC1D5/LRRK2/HTR2B/DOCK2/RAB3GAP2/MYO9A/RIC1/RANBP2/ACAP2/TBCK/DOCK8/SEC23A/EVI5/DENND4C/RAPGEF6/IQGAP2/FAM13B/STXBP5/TBC1D14/ITSN2/ARFGEF2/SBF2/AKAP13/RASA2/RP2/ARAP2/DOCK4/GPSM2/DENND1B/FGD4/VAV3/SH3BP5/NCKAP1L/ARHGAP5/RAPGEF2/ARHGAP26/ARHGAP18/DOCK5/IQGAP1/RALGAPA2/SEC23B/SOS2/FAM13A/SIPA1L1/ECT2/RALGAPA1/RGP1/DOCK10/SIPA1L2/DENND2C/ARHGEF12/CHM/TRIO/AGFG1/CPEB2/OPHN1/CCDC88A/SRGAP1/RABGAP1L/USP6NL/DOCK7/ASAP2/GNA13/ARHGAP15/ASAP1/ECT2L/PLEKHG6/TBC1D30/BNIP2/FARP1/EGF/FGD6/HERC2/TBC1D19/DOCK1/PLEKHG1/DEPDC1B/PSD3/ARHGAP24/GNAQ/ARHGAP6/ARHGAP29/ARHGEF38/P2RY12/ARHGAP42/TBC1D8B/RGS18/MCF2L2/TBC1D8/RGPD8/GRTP1/STARD13/DEPD	202

					C1/DENND5B/RGPD2/RAPGEF4/RASAL2/IQGAP3/STXBP5L/DLC1/PREX2/RGS20/RANBP3L/TIAM2/ARHGEF33/ARHGEF37/RAPGEF5/ARFGEF3/FRMD7/ARHGEF28/NGEF/RGS17/RAP1GAP/ADGRB3/RASGRP2/ARHGAP4/ARFGAP1/DENND1C/TBC1D10C/RANBP3/TBC1D10A/GIT1/ARHGDIA/TNK2/ARHGEF1/TBC1D17/GPS1/GDI1/PREB/NPRL2/ACAP3/EPS8L2/RASAL3/SH3BP1/SGSM2/SGSM3/SH2D3A/EIF2B4/AGAP3/ARHGEF19/DENND6B/ARHGAP33/EVI5L/PLCD4/GPS2/RASA4/RANGAP1/TBC1D13/RGS14/AGAP6/LAMTOR4/AGFG2/ARHGAP1/RIN1/PCP2/RANBP1/IQSEC3/ACAP1/ARHGDIB/RABEP2/WAS/GPSM1/PLEKHG4/RIN3/TBC1D10B/EEF1B2/ALS2CL/LLGL2/PTGIR/RALGDS/RGS12/VAV2/NUCB1/MTSS2/RGL3/AGAP7P/PLEKHG5/RASA4B/KNDC1/ARHGEF25/EPS8L1/RANGRF/AGAP9/GPSM3/TBC1D3L/PLXNB1/TBC1D3D/RHOD/TBC1D3C/AGAP11/DNAJA3/RGS7	
MF	GO:0003779	actin binding	2.97E-02	2.87E-02	TTN/ACTR3C/MACF1/LRRK2/UTRN/TRPM7/MYO9A/TMOD3/MYRIP/IQGAP2/SYNE1/DIAPH2/PHACTR2/FGD4/MYO5A/SYNE3/IQGAP1/NEXN/RDX/FMNL2/SNTB2/GBP1/SYNE2/MYH10/PDLIM5/ABL2/ANLN/ACTR3/DNASE1/OPHN1/ITPRID2/MEFV/CCDC88A/FMN1/ACTR2/TLN1/SVIL/SPTBN1/SPTA1/BAIAP2L1/CEACAM1/VCL/PRKCE/MYO5B/NEB/SSH2/ITGB1/DST/PTK2/KLHL2/IPP/MYO10/MYOT/PSTPIP2/TMOD2/STK38L/DIAPH3/CTNNA1/KIF18A/FLNB/MICAL2/EPB41/PXK/MYLK/TLN2/PFN4/ABRA/GAS7/CAPZA2/MAP1B/AVIL/MYO3B/CACNB2/EPB41L3/CALD1/CTNNAL1/DAAM2/MYO1H/HIP1/TRPC5/SYNPO2/PLS1/VIL1/TMOD1/MYOZ3/GAS2L3/SPTB/SHROOM4/COBLL1/SORBS1/TNS1/PHACTR3/XIRP2/IQGAP3/CSRP3/PDLIM4/DMD/LMOD2/SNCA/KCNMA1/MAP1A/WASF3/MYO1B/ANTXR1/PLS3/WIPF3/FAM107A/KLHL4/NEBL/SHROOM3/MYOZ2/FMN2/LRRC10/MYH4/BCL7B/FXYD5/PFN1/EMD/LIMD2/GIPC1/KLHL17/MARCKSL1/MIB2/TLNRD1/RUSC1/EPS8L2/CORO1A/PDLIM2/TPM2/ARPC5L/TMEM201/PARVG/CAPZB/PHPT1/BIN1/PICK1/EVL/PPP1R9B/VILL/ARPC4/S100A4/TAGLN/LSP1/SNTA1/CFL1/MAP1S/TNNI2/CROCC/CORO1B/WASHC1/INF2/WAS/COTL1/PDLIM7/ABI3/CXCR4/FMNL1/FSCN1/GAS2L1/WASH3P/DBN1/SYNPO/MTSS2/VASH1/FHL3/EPS8L1/TNNC1/ANKRD24/CORO2B/ANKRD35/SYN1/SHROOM1/DMTN/SPTBN5/MYBPC2/CORO7/ESPNL/ACTN3/LDB3	179