Alteraciones moleculares y microorganismos asociados en el desarrollo de la estenosis aórtica por calcificación

Iván Yesid López Ardila

Trabajo de Grado para Optar al Título de Magister en Biología

Director

Sandra Guauque Olarte

Doctora en Biología Celular y Molecular

Codirectores

Fernando Rondón González

Doctor en Ciencias-Biología

Laura Cifuentes Cardona

Doctora en Ciencias-Biología

Universidad Industrial de Santander

Facultad de Ciencias

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1. RESUMEN

Título: Alteraciones moleculares y microorganismos asociados en el desarrollo de la estenosis aórtica por calcificación *

Autor: Iván Yesid López Ardila**

Palabras clave: Estenosis aórtica calcificada, microbiota, vías, genómica.

La estenosis aórtica es un estrechamiento progresivo de la válvula aórtica. Este estrechamiento restringe el flujo sanguíneo y conduce a la insuficiencia cardíaca. En la actualidad, no existe ningún tratamiento para detener la progresión de la estenosis aórtica, lo que la convierte en un importante reto sanitario. Este estudio investiga la interacción entre los factores genómicos y microbianos asociados a la estenosis aórtica, utilizando un enfoque analítico descriptivo y transversal, un enfoque descriptivo para probar la hipótesis de que ambos factores contribuyen a la enfermedad. Realizamos una revisión sistemática para identificar variaciones genéticas y analizamos la expresión de ARN (ARNm y ARNnc) junto con sus posibles genes diana asociados con la estenosis aórtica calcificada. En segundo lugar, el uso de herramientas bioinformáticas permitió identificar y caracterizar las comunidades microbianas presentes en las válvulas aórticas sanas y calcificadas. Los resultados de la revisión sistemática de las variantes genéticas asociadas al ARNm y al ARNnc asociadas a la estenosis aórtica se resumieron en un metaanálisis. La identificación de los taxones de microorganismos presentes en las válvulas fue dominante para el superreino Bacteria. Caracterización de rutas metabólicas influenciadas tanto por variantes genéticas expresadas diferencialmente en válvulas aórticas como por los microorganismos identificados de muestras con y sin estenosis aórtica por calcificación, mostraron un estrés en su mayoría producido por el metabolismo de carbohidratos y lípidos, como por la degradación de compuestos aromáticos. Este estudio proporciona un análisis exhaustivo de las variantes genéticas, los genes expresados diferencialmente y el microbioma asociado en la estenosis aórtica calcificada. Allana el camino para una comprensión más profunda de la enfermedad y el potencial de futuras estrategias terapéuticas.

* Tesis de maestría

** Facultad de ciencias. Escuela de biología. Directora: Sandra Guauque Olarte, PhD. Codirectores: Fernando Rondón González, PhD; Laura Cifuentes Cardona, PhD.

2. ABSTRACT

Tittle: Molecular alterations and associated microorganisms in the development of aortic stenosis due to calcification*

Author: Iván Yesid López Ardila**

Keywords: Calcific aortic stenosis, microbiota, pathways, genomic.

Aortic stenosis is a progressive narrowing of the aortic valve. This narrowing restricts blood flow and leads to heart failure. Currently, there is no treatment to stop the progression of aortic stenosis, making it a major healthcare challenge. This study investigates the interaction between genomic and microbial factors associated with aortic stenosis, using a descriptive and cross-sectional analytical approach, a descriptive approach to test the hypothesis that both factors contribute to the disease. We conducted a systematic review to identify genetic variations and analyzed RNA expression (mRNA and ncRNA) along with their potential target genes associated with calcified aortic stenosis. Second, the use of bioinformatics tools allowed us to identify and characterize the microbial communities present in healthy and calcified aortic valves. The results of the systematic review of mRNA-associated and cRNA-associated genetic variants associated with aortic stenosis were summarized in a meta-analysis. The identification of the taxa of microorganisms present in the valves was dominant for the superkingdom Bacteria. Characterization of metabolic pathways influenced both by genetic variants differentially expressed in aortic valves and by the microorganisms identified from samples with and without aortic stenosis by calcification, showed a stress mostly produced by the metabolism of carbohydrates and lipids, as well as by the degradation of aromatic compounds. This study provides a comprehensive analysis of genetic variants, differentially expressed genes, and associated microbiome in calcified aortic stenosis. It paves the way for a deeper understanding of the disease and the potential for future therapeutic strategies.

* Master thesis

** Faculty of Science. Department of Biology. Director: Sandra Guauque Olarte, PhD. Co-directors: Fernando Rondón González, PhD; Laura Cifuentes Cardona, PhD.

3. Prefacio

Este documento constituye el trabajo final de investigación, desarrollado en varias secciones que abordan los objetivos planteados. La introducción no solo presenta el tema, sino que también justifica la realización de este proyecto. A continuación, se detalla un objetivo general, desglosado en cuatro objetivos específicos. Estos se abordaron en los Capítulos 1 y 2, redactados en inglés y con formato de artículo científico, actualmente en proceso de preparación para su publicación en revistas especializadas. El trabajo finaliza con una conclusión general y la correspondiente bibliografía general para todo el documento. El material complementario se encuentra disponible en la carpeta compartida de la sección correspondiente.

El Capítulo 1, presenta un panorama molecular de la estenosis aórtica por calcificación (CAVS, por sus siglas en inglés), identificando genes candidatos potencialmente involucrados en la enfermedad. Se identificó a que vías moleculares pertenecen estos genes para revelar vías moleculares, roles y modulación en la CAVS, abriendo puertas para futuras terapias dirigidas. El Capítulo 2 explora el papel potencial del microbioma en la EAC. Observamos variaciones en la diversidad, composición y capacidades funcionales potenciales de las comunidades microbianas entre las válvulas sanas y las afectadas por EAC.

Nuestro análisis reveló una superposición interesante entre las vías moduladas por los genes identificados y las vías metabólicas potencialmente influenciadas por el microbioma. Esta convergencia sugiere mecanismos compartidos por los cuales tanto los factores genéticos como microbianos podrían contribuir al desarrollo de la EAC.

4. Introducción

Las válvulas son el esqueleto del corazón (mitral, pulmonar, tricúspide y aórtica), estas funcionan como compuertas que se encuentran involucradas en el flujo unidireccional de la sangre (Chen et al., 2009); las válvulas tricúspide y pulmonar se encargan de dirigir la sangre hacia el pulmón, mientras que las válvulas mitral y aórtica se encargan de dirigir esta sangre oxigenada procedente del pulmón hacia el resto del organismo, llevando oxígeno y nutrientes (Misfeld & Sievers, 2007). Las alteraciones ocurridas en cada una de ellas (inflamación, engrosamiento, rigidez y calcificación) generan diferentes tipos de problemas cardíacos (Fuster et al., 2017).

En el escenario de las enfermedades cardiovasculares, la estenosis aórtica destaca como una patología asociada al envejecimiento de la población. La estenosis aórtica es una anomalía valvular ocurrida en la válvula aórtica, es la valvulopatía más común y su prevalencia aumenta con la edad de los individuos que la padecen (2 – 4% en personas mayores de 65 años) (Ackah et al., 2023); en Colombia la expectativa de vida va en aumento (>74 años) junto con el riesgo del padecimiento de enfermedades cardiovasculares (ministerio de salud). La estenosis aórtica por calcificación conlleva un proceso degenerativo que culmina en la calcificación de la válvula aórtica, causando disminución del movimiento y pérdida de su funcionalidad (Sun et al., 2013); diferentes factores de riesgo se han asociado como sexo masculino, hipertensión, tabaquismo, hipercolestoremia, diabetes (Vieceli Dalla Sega et al. 2022).

La enfermedad puede avanzar de leve a severa con el tiempo (Schlotter et al., 2018). A pesar de la importancia y frecuencia de esta enfermedad, a la fecha la única forma de tratarla es el reemplazo valvular, pues los medicamentos que existen solo permiten tratar los

síntomas, mas no existen medicamentos que permitan evitar su progresión (Vieceli Dalla Sega et al., 2022). Estudios de asociación genética encontraron la asociación de algunos polimorfismos en genes candidatos con la estenosis aórtica o la calcificación de la válvula aórtica (Blaser et al., 2021; Thériault et al., 2018). Otros estudios han comparado la expresión de genes entre válvulas sanas y estenóticas, e identificaron genes y vías moleculares alteradas en la enfermedad (Guauque-Olarte et al., 2015; Helgadottir et al., 2018; Thériault et al., 2018); sin embargo, es necesario condensar esta información para encontrar los genes claves en el desarrollo de la enfermedad y la búsqueda de mejores métodos para diagnóstico, pronóstico y medicamentos para tratar la enfermedad. Adicionalmente recientemente se ha encontrado que la microbiota oral e intestinal se puede relacionar con desarrollo y progresión de enfermedades cardiovasculares, entre otras enfermedades (Yoshiba et al., 2023).

En este trabajo se sintetizó la información disponible en la literatura sobre las variantes genéticas asociadas con la estenosis aórtica por calcificación, la expresión de ARNm y de ARNnc en válvulas aórticas, junto con la identificación de microorganismos en tejido valvular calcificado y no calcificado mediante metagenómica.

Al combinar estos enfoques, se logró obtener una comprensión más completa de los factores moleculares y microbianos involucrados en la estenosis aórtica por calcificación. Esta aproximación permitió revelar nuevas conexiones y proporcionar una lista de blancos moleculares para identificar objetivos terapéuticos, diagnóstico y pronóstico más precisos para el manejo de la enfermedad.

5. Objetivo

General:

- Analizar la influencia de las alteraciones moleculares y de los microorganismos en el desarrollo y progresión de la estenosis aórtica por calcificación.

Específicos:

- Describir variantes genéticas, ARNm y ARNnc reportados en la literatura sobre la estenosis aórtica por calcificación.
- Establecer vías moleculares alteradas por las variantes genéticas y expresión diferencial de ARNm y mi-ARNs reportados en la literatura.
- Identificar microorganismos presentes en válvulas aórticas estenóticas y sanas mediante análisis de metagenómica.
- Establecer la contribución metabólica de la microbiota en la estenosis aórtica por calcificación.

6. Chapter 1: Integration of molecular alterations in calcific aortic valve stenosis: A systematic review and enrichment analysis.

I. Y. López-Ardila[1], F. Rondón-González[1], L. Cifuentes-Cardona[3], S. Guauque-Olarte[4]

[1]Escuela de Biología, Facultad de Ciencias, Universidad Industrial de Santander, Bucaramanga.

[2]Facultad de Odontología, Universidad Cooperativa de Colombia, Medellín-Envigado.

[3]Facultad de Medicina, Universidad Cooperativa de Colombia, Pasto.

[4]Departamento de ciencias básicas y medicina oral, Facultad de Odontología, Universidad Nacional de Colombia, Bogotá.

6.1 Abstract

Calcific aortic valve stenosis (CAVS) is the third-most common cardiac disease worldwide. In this disease, calcium accumulation in the valves limits normal function of the aortic valve. Various authors have addressed crucial aspects for understanding the development of this disease, to the analysis of genetic variants, mRNA, and ncRNA; however, this information is scattered, and the interactions between these molecules have not been explored. Our objective was to perform a gene enrichment analysis to better understand gene interactions in molecular/disease processes and pathways, the possible influenced of the ncRNA in those pathways and to uncover their possible role in CAVS etiology, diagnosis, and treatment. To compile a comprehensive list of genes that have been associated with CAVS, which mRNA differentially expressed (DEG), or non-coding RNA (ncRNAs) in calcific aortic valve stenosis studies, we used three databases (PubMed, LILACS, and ScienceDirect). Enrichment analysis based on KEGG pathways was performed in the STRING database, miRGator to identify gene targets of ncRNAs. The information from 42 articles was

extracted, resulting in the identification of 24 genetic variants, 252 ncRNAs, and 909 differentially expressed genes. The 85 significant molecular pathways belong to 5 Classes: “Cellular processes”, “Environmental information processing”, “Human diseases”, “Metabolism” and “Organismal systems” (*FDR* <0.05). In this study, we found that many predicted molecular pathways were related to some factors of disease progression. TGFB1 emerge as important candidate because have been associated with the disease, there a ncRNA differentially expressed that can affect it expression and additionally it is present in interest accord to presence between have been associated, present in four significantly enriched pathways.

Keywords: aortic stenosis, mRNA, ncRNA, disease, pathway.

6.2 Introduction

Calcific aortic valve stenosis (CAVS) is the most common valvulopathy in adults, affecting approximately 4% in the general population over 65 years (de Oliveira Sá et al., 2020). This disease is characterized by the narrowing of the aortic valve, which impedes normal blood flow from the heart to the body (Lindman et al., 2016). This causes a degenerative process that ends in calcification of the aortic valve and death (Lerman et al., 2015). While symptoms can be managed, there's currently no medication to halt disease progression (Ackah et al., 2023). The only definitive treatment is valve replacement (Raddatz et al., 2019; Vieceli Dalla Sega et al., 2022). The lack of effective therapies to prevent or slow CAVS progression underscores the urgent need for a deeper understanding of the underlying molecular mechanisms driving this disease.

The exact cause of CAVS remains unclear, likely involving a complex interplay of genetic and environmental factors (Mourino-Alvarez et al., 2016). Genetic factors include mutations that affect the expression of genes involved in calcium metabolism, inflammation, and oxidative stress, contributing to the development and progression of CAVS (Ackah et al., 2023; Vieceli Dalla Sega et al., 2022). Additionally, Transcriptome analysis of coding and non-coding RNAs has provided valuable insights into gene expression changes associated with CAVS (Blaser et al., 2021).

Researchers have made significant strides towards identifying novel biomarkers for diagnosis, prognosis, and potential therapeutic targets (Pinto & Fragasso, 2022; Qiao et al., 2022). However, this information remains fragmented, highlighting the need for a more cohesive understanding of the disease's molecular landscape (Rysä, 2020).

Gene and transcriptome expression studies, encompassing various techniques like microarrays, RT-PCR, and RNA-seq, are commonly used to identify molecules involved in disease (Ackah et al., 2023). While each method has limitations, a comprehensive understanding of the gene pool is crucial (Rodrigues-Esteban & Xiaoyu, 2017). The identified genes are linked to CAVS because they have been reported as significantly associated with the disease, differentially expressed, or targeted by differentially expressed non-coding RNAs (ncRNAs).

To address this critical need, we conducted for the first time a systematic review to collect, from genetic association and RNA expression studies focus on CAVS, genes that have been associated with the disease and, mRNA or ncRNAs differentially expressed between calcified and non-calcified valve. Our objective was to perform a gene enrichment analysis to better understand gene interactions in pathways, the possible influence of the

ncRNA in those pathways and to uncover their possible role of the genes in CAVS etiology, diagnosis, and treatment. The research question of this systematic review was: How associated genes, mRNA and ncRNA differentially expressed interact in pathways and what is their impact in CAVS?

6.3 Methods

The study design and methodology for this systematic review were based on the guidelines of the Cochrane Handbook (Higgins et al., 2019), AMSTAR2 tool (Shea et al., 2017), and Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) (Page et al., 2021) to address the search protocol critically and objectively.

6.3.1 Inclusion criteria

A strategy was implemented to identify primary studies on aortic valves in animal model and human subjects with CAVS, specifically investigating the correlation between genetics, gene expression, and non-coding RNA.

6.3.2 Exclusion criteria

(i) Genes knockout studies

(ii) Clinical treatment studies

(iii) Therapy effects on gene expression

(iv) Review articles

6.3.3 Information sources and search

Systematic searches were conducted using electronic databases such as PubMed, LILACS, and ScienceDirect, the literature review included studies from inception to 8 February 2022, to gather a comprehensive range of available information.

6.3.4 Search strategy

The search strategy was developed based on the research question and search equation, which consisted of a combination of Medical Subject Headings (MeSH) and free terms. The search terms included aortic valve stenosis, aortic stenosis, valvular calcification, aortic valve calcification, CAVS, CAVD, gene, RNA, microRNA, miRNA, protein, miR, long non-coding, lncRNA, variant, polymorphism, SNP, and DNA.

6.3.5 Study selection

After removing duplicates, the selected articles that met the inclusion criteria were subjected to title and abstract review by IYL and JGS using the Rayyan tool (Ouzzani et al., 2016) to identify those that merited full-text examination. Any reviewer disputes during the comprehensive text revision were resolved by a third party (SGO).

6.3.6 Data collection

IYL conducted data extraction, which SGO later reviewed. All selected studies were documented using an Excel spreadsheet during the data collection. A list of excluded papers, along with their reasons for exclusion, was compiled in a table after a full-text evaluation.

6.3.7 Quality assessment

Quality assessment tools, which incorporated adjustments from the STROBE (Cuschieri, 2019) and CONSORT 2010 guidelines (Schulz et al., 2010), were used to

establish the evaluation criteria. Each paper received an assessment based on 15 items, earning a score of 1 if the criteria were satisfied and 0 otherwise. Articles were categorized by quality level as low (1-5), moderate (6-10), or high (11-15). Studies with low or moderate ratings were excluded from the analysis.

6.3.8 Synthesis methods

The information extracted from the selected articles included year, location, ancestry, sex, age, comorbidities, risk factors, BMI, disease severity, valve area index, level of valvular calcification, analysis variables (genetic variants and gene associated, mRNA, and ncRNA), and methodologies used in the studies.

For genes, mRNAs, and ncRNAs, the names were validated and unified using the NCBI Gene (Sayers et al., 2024) and UniProt.org (Bateman et al., 2023) databases. Information about polymorphisms, genotypes, frequencies, their association with CAVS, odds ratios (OR), and confidence intervals (CI) was extracted. The information extracted for mRNAs and ncRNAs studies encompassed differentially expressed genes, *p*-values, and sense of expression (upregulated/downregulated). Furthermore, the target genes of ncRNAs were extracted. If this information was unavailable in the original study, we used miRGator 3.0 (S. Cho et al., 2012) to predict them. When authors reported a different target gene for ncRNA, we wrote our predicted gene and the author's gene. Data extraction was conducted independently of the methodologies and statistical analyses used in the original studies. This approach minimizes bias from these factors in our findings.

6.3.9 Inclusion Criteria for Genes:

To include a gene in our study for performing the enrichment analysis, we applied strict inclusion criteria: i) genes associated with CAVS: Genes significantly associated with disease in GWAS or genetic association studies comparing CAVS vs non-CAVS patients. We considered significant reported p-value or adjusted p-value cut-offs depending on the study type. ii) Differentially expressed genes (DEG): An mRNA that was differentially expressed in at list one gene or transcriptome expression study comparing calcified vs non-calcified valve tissues. Genes were considered significantly if they were upregulated or downregulated based on the reported p-value or FDR cut-off. Genes with inconsistent expression direction across studies were excluded. iii) Differentially expressed ncRNA and targets: An ncRNA that was differentially expressed in at least one study comparing calcified vs non-calcified valve tissues, significantly upregulated or downregulated based on the reported p-value or FDR cut-off. When a ncRNA has an inconsistency in the direction of expression across studies were excluded. This criterion ensures that we only include genes and ncRNA with strong evidence of being altered in CAVS.

6.3.10 Risk of bias assessment

The risk of bias was assessed using RevMan 5.4 (Cochrane, 2020) software. Criteria were established and adjusted from the Risk of Bias Rating Tool for Human and Animal Studies by the Office of Health Assessment and Translation (OHAT) (OHAT, 2019), as well as from case-control studies, according to Cochrane guidelines (Higgins et al., 2019). Multiple biases, including selection, performance, detection, attrition, and reporting, were evaluated.

6.3.11 Statistical analysis

To elucidate how CAVS is impacted by the associated genes, differentially expressed mRNA and ncRNAs and their gene targets that past the inclusion criteria we performed a functional enrichment analysis using STRING (Szklarczyk et al., 2019). This analysis helps identify groups of genes that are functionally related and potentially involved in similar biological processes. We used the STRING database to analyze the protein-protein interaction network of our identified genes. This network analysis allows us to explore potential interactions among these genes and gain insights into their roles in CAVS pathogenesis. Furthermore, we extracted significant pathways from the Kyoto Encyclopedia of Genes and Genomes (KEGG) (Kanehisa, 2000). We considered pathways enriched with our genes of interest and with an FDR (False Discovery Rate) less than 5% to be statistically significant (Kanehisa et al., 2022).. The pathways are classified into KEGG processes and processes are organized in seven main clasess (1. Metabolism. 2. Genetic Information Processing. 3. Environmental Information Processing. 4. Cellular Processes. 5. Organismal Systems. 6. Human Diseases. and 7. Drug Development).

6.4 Results

6.4.1 Study selection, quality, and bias assessment

Our initial database search yielded a total of 2243 papers. Following a review process, we selected 76 studies for full-text review and categorized them based on quality: low (0), medium (35), and high (41), according to the established criteria. High-quality papers remained for data collection (Figure 1 and Supplementary Table 1). The risk of bias assessment for these 42 studies is presented in Figure 2 and Supplementy Figure 1.

6.4.2 Subjects of the study and exposure

All included studies focused on human patients across 13 countries (Australia, 1 study; Canada, 14 studies; China, 5 studies; Denmark, 1 study; England, 1 study; Finland, 8 studies; France, 1 study; Germany, 1 study; Iceland, 1 study; Poland, 2 studies; Sweden, 1 study; Turkish, 1 study; USA, 4 studies). All studies involved patients with tricuspid aortic valves (TAV). In some cases where it was not possible to distinguish between valve configurations, information about both the bicuspid aortic valve (BAV) and quadricuspid aortic valve (QAV) was included in the analysis. The age of CAVS patients ranged from 56 to 76 years, while that of non-CAVS patients ranged from 43 to 71years. Several exclusion criteria were employed across the studies, with rheumatic heart disease (RHD) being the most common (Table 1).

6.4.3 Association studies

Thirteen studies, including five genome-wide association studies (GWAS), seven genetic association studies focusing on candidate genes, and one assessing insertion/deletion polymorphisms through PCR, aimed to identify genetic variants aimed to identify genetic variants (Single Nucleotide Polymorphisms or SNPs) associated with calcific aortic valve stenosis (CAVS). These studies employed various techniques to identify SNPs, including GWAS arrays for genome-wide analysis and sequencing for targeted candidate genes. The studies comprehensively analyzed 26 genes. After excluding nonsignificant variants, we identified 24 genes associated with CAVS, encompassing 49 significant polymorphisms. The OR for these associations ranged from 0.87 to 9.32, with CI between 0.44 and 2.81 (Table 2).

Analysis of data extracted from papers included in our systematic review revealed that among the diverse genetic variants identified through various methods used by the authors, *TPRG1* (tumor protein p63 regulated 1) emerged as the gene with the most CAVS-associated polymorphisms, with seven identified variants in one study. LOC101927829 (uncharacterized LOC101927829) and IL10 (interleukin 10) were also noteworthy, with multiple polymorphisms identified in separate studies.

6.4.4 Studies of mRNAs expression

Our analysis identified 1076 genes mentioned in 24 mRNA expression studies, to ensure a high level of confidence, we focused on genes exhibiting statistically significant changes in expression (p-value or adjusted p-value < 0.05) and excluded genes with conflicting results across studies (upregulated in some studies, downregulated in others). After excluding non-differentially expressed genes and those with conflicting results across the studies, we identified a final set of 909 differentially expressed genes (p or $padj < 0.05$). Of these, 399 genes were downregulated and 510 were upregulated (Supplementary Table 2). Various methods were used across the studies, including microarray (11 studies), RT-PCR (seven studies), RNA-seq (three studies), qRT-PCR (two studies), and qPCR (one study).

PWWP3B (PWWP domain containing 3B) emerged as the gene in which altered expression in CAVS was more common as reported in six studies. The altered expression of *CA12* (carbonic anhydrase 12), *CCL5* (C-C motif chemokine ligand 5), *FPR1* (formyl peptide receptor 1), and *TMEM200A* (transmembrane protein 200A) was reported in five studies (

Table 3). The genes *IBSP* (integrin binding sialoprotein) and *SPP1* (secreted phosphoprotein 1) were the most reported with ten and 13 studies, respectively, although their expression sense showed inconsistency across studies.

6.4.5 Studies of ncRNAs expression

Our analysis identified 252 ncRNAs (246 miRNA and 6 lncRNA) that were associated with CAVS in 11 studies. These studies utilized various techniques to identify differentially expressed ncRNAs, including microarray analysis (3 studies), RNA-sequencing (1 study), and quantitative real-time PCR (qRT-PCR) (3 studies). Of these, 89 were downregulated, 32 were upregulated, and 131 did not provide information about sense. A list of ncRNAs with their identified gene targets is shown in the Supplementary Table 3.

Twenty-four ncRNA were reported in at least two papers (*MIR106a-5p, MIR125b-2-3p, MIR1287-5p, MIR133b, MIR138, MIR149-5p, MIR17-5p, MIR197-3p, MIR221-3p, MIR222-3p, MIR27b-3p, MIR31-5p, MIR320a, MIR320b, MIR320c, MIR34a-5p, MIR381-3p, MIR422a, MIR486-3p, MIR500a-5p, MIR501-3p, MIR502-3p, MIR8087, MIR939-5p*) and the rest were reported just once. Of these ncRNA, *CXCL12* (C-X-C motif chemokine ligand 12) emerged as the most common gene target (*MIR221-3p, MIR31-5p, MIR320a* and *MIR320b*).

6.4.6 KEGG Pathways

We uploaded the list of associated genes, differentially expressed genes, and targets of ncRNAs to STRING to perform an enrichment analysis. A total of 85 KEGG pathways were significantly enriched (FDR<0.05) (Supplementary Table 4); organizados en X procesos y X clases (Tabla suplementaria donde este clases, procesos, pathways, colocar p-

valor). Of these, 36 pathways were from the main class “Human Diseases”, whereas 49 pathways are members of the other classes (mencionar las otras clases en el document). The processes with more significant pathways included “Organismal systems; Immune system” (17 pathways), “Environmental information processing; signal transduction” (9 pathways), “Human disease; Infectious disease: bacterial” (9 pathways) and “Human disease; Infectious disease: viral” (8 pathways). The top three most significant pathways which also have the highest gene ratios (# input gene / total gene in pathways) were “cytokine-cytokine receptor interaction” (padj= 1.92*10-9, 43/282), “PI3K-Akt signaling pathway” (padj= 1.92*10-9, 49/349), and “ECM-receptor interaction” (padj= 2.14*10-9, 24/88) (Figure 3), all of these classified into Environmental Information Processing. Other top pathways included “osteoclast differentiation” (padj= 8.68*10-7, 23/120), “AGE-RAGE signaling pathway in diabetic complications” (padj= 1.94*10-6, 20/96), “chemokine signaling pathway” (padj= 2.09*10-6, 28/186), and “Toll-like receptor signaling pathway” (padj= 2.79*10-6, 20/100). The rest of significative pathways in the top 10 with the highest gene ratio were “viral protein interaction with cytokine and cytokine receptors” (padj= 1.83*10-7, 22/96), “tuberculosis” (padj= 3.81*10-7, 28/165), “pathways in cancer” (padj= 4.61*10-7, 54/515).

6.4.7 Integration molecules and pathways

Of the 22 genes reported with genetic variants, three were identified inside the list of DEGs and two (TGFB1 and ACE) were present in 25 of the significantly enriched pathways. Of the list of DEGs reported, 289 were associated with any pathway, with the number of genes involved in different pathways ranging from 6 to 54. According to the reported ncRNAs, 107 were predicted to affect the expression of 64 mRNA reported as DEGs in 82 significantly enriched pathways. Forty-nine of the differentially expressed genes in which

expression is predicted to be affected by ncRNA identified in this review were present in the 85 enriched pathways, but none of these genes contained a reported genetic variant (Supplementary Table 4).

Analysis of gene expression data related to CAVS revealed that, across all the enriched pathways, upregulated genes outnumbered downregulated genes twice. The extent of gene involvement varied across the pathways, ranging from 7% to 39%. TGFB1 was the most frequent gene, appearing in 22 different pathways. Also, TGFB1 contains more genetic variants associated with CAVS and shows potential interactions with two ncRNA (MIR21-5p and MIR24-2).

Among the ncRNAs, MIR155-5p emerged as the gene that can affect a major number of DEGs, with eight gene targets (PAPOLA, AGTR1, FGF7, LPL, MYO10, BCAT1, PHF17 and RUNX2). MIR124-3p and MIR16-5p followed closely, with seven interactions each, while MIR146a-5p and MIRLET7A1-5p showed six interactions (Table 4).

To understand how differentially expressed genes contribute to CAVS progression, we prioritized key KEGG pathways based on their relevance to the disease. Figures 4 to 7 visualize these important pathways, highlighting the involvement of our identified genes. Each figure illustrates the direction of gene signaling and its role within the pathway. The figures focused on four key pathways: "Calcium signaling" (Figure 4), "PI3K-AKT signaling" (Figure 5), "Osteoclast differentiation" (Figure 6), and "ECM-Receptor interaction" (Figure 7).

6.5 Discussion

We conducted for first time a systematic review to collect, from genetic association and RNA expression studies focus on CAVS, genes that have been associated, which messenger RNA (mRNA) are altered, or that are targeted by non-coding RNA (ncRNAs). Our contribution to this field was to perform a gene enrichment analysis to identify how these genes interact in different KEGG pathways. We sought to better understand how these molecules are implicated in CAVS and their potential as therapeutic targets, biomarkers, or their implication in etiology.

6.5.1 Genetic variants, mRNA and ncRNA on CAVS

According to criteria of Siedlecki et al. (2024), based on *p*-values, odds ratios (ORs) and CIs of GWAS and gene association studies, 49 SNPs in 24 genes were associated with CAVS. The genes *ACE* (Ertas et al., 2007), *APOB* (Wang et al., 2018), *CRP* (Wypasek et al., 2015), *IL10* (Gaudreault et al., 2011), *LPA* (Thanassoulis et al., 2013), *NOTCH1* (Ducharme et al., 2013), *PALMD* (Thériault et al., 2018), and *RUNX2* (Guauque-Olarte et al., 2015) were the most strongly associated with CAVS.

Kutikhin et al. (2014) identified a link between high expression of specific genetic variants to CAVS with high association to *IL10* (rs1800872), *LPA* (rs10455872) and *APOB* (rs6725189), related to CAVD in infection and inflammation (Abbood et al., 2022, Monroy-Muñoz et al., 2023) or hight level of lipids and lipoproteins in the aortic valve (Cardoso-Saldaña et al., 2019; Wang et al., 2018). The *CRP* (rs1205) concentrations suggest an effect of likely calcification by linkage disequilibrium with other inflammatory genes (Wypasek et al., 2015) and this polymorphism is related with chronic inflammation (de Santis et al., 2020). *PALMD* pressure has been linked to decreased fibrosis processes (Han et al., 2023),

rs6702619 reduce *PALMD* expression, a decreased aortic valve function is related with low levels of *PALMD* and the normal homeostasis associated with valve remodeling. These polymorphisms can constitute an early diagnostic and treatment.

CAVS genes exhibit a pleiotropic effect, with isoforms potentially promoting inflammation, osteoclast differentiation, and calcification (Kutikhin et al., 2014; Ozkan et al., 2019). There is need for further investigation of its specific isoforms and their interactions with various molecular pathways, including those driven by *RUNX2* (Engin et al., 2008; Garg et al., 2005), *IL10*, and *LPA* signaling (Thanassoulis, 2016; Thanassoulis et al., 2013). Our analysis revealed that these CAVS-associated genes are enriched in molecular pathways related to "Environmental Information Processing" via interaction with cytokine receptor and "Human diseases" via infectious agents ($p < 0.05$). This suggests a potential link between environmental factors, immune response in CAVS development.

Regarding the expression direction of the DEGs, our study revealed a 15% discordance rate among authors. These variations across studies in patient characteristics, methodologies, and sample handling likely contribute to the observed discordance in DEG expression direction. The differences include variations in statistical analysis applied to the same microarray data or the use of different methodologies altogether, such as microarray, RT-PCR, RNA-seq, and quantitative PCR (qPCR). It's important to consider that each study establishes its own inclusion/exclusion criteria, demographic patterns, and risk factor considerations. For example, most studies reported discordance in the expression direction of IBSP and SPP1, both implicated in osteoclast differentiation (J.-Y. Sun et al., 2021).

This discordances highlights the challenge of identifying reliable DEGs in CAVS research. Our analysis revealed significant variations across studies in patient

inclusion/exclusion criteria, valve configuration considered, patient demographics (age, sex), sample collection methods, and sample storage procedures. These variations, along with established CAVS risk factors such as age, sex, family history, and co-morbidities (e.g., diabetes, hypertension) that can influence gene expression patterns (H. Y. Chen et al., 2019), contribute to the observed inconsistencies in DEG identification and methodological variations (Vieceli Dalla Sega et al., 2022; Rodriguez-Esteban & Jiang, 2017). Addressing these challenges in future research design, particularly by employing more standardized approaches, will be crucial for establishing a more robust understanding of the genetic basis of CAVS.

PWWP3B, a downregulated gene, was the strongest candidate for CAVS involvement based on its consistent reporting across six independent studies of expression (Bossé et al., 2009; Cantor et al., 2021; Greene et al., 2020; Qiao et al., 2022; Teng et al., 2020; E. Zhu et al., 2019). This consistent downregulation suggests a potentially significant role for *PWWP3B* in CAVS development, further investigation is warranted to explore potential connections between *PWWP3B* function in CAVS involved stress across DNA damage response.

Among the upregulated genes, molecular pathways associated with infectious diseases and cytokine interaction emerge as particularly interesting candidates according to our analysis and are probably responsible for CAVS occurrence and development (Qiao et al., 2022). This suggests a potentially unique role for CCL5 in CAVS development, possibly linking inflammation and infectious triggers. Further investigation into CCL5 is specific function in CAVS is warranted, potentially through the lens of these identified molecular

pathways. CCL5 is a therapeutic target for different types of cancer (Svensson et al., 2015; Zeng et al., 2022).

We identified more than 200 ncRNAs differentially expressed between CAVS and non-CAVS valve tissues. We interconnect the information about the differentially expressed ncRNAs and mRNA reported in the literature (K. I. Cho et al., 2018). The ncRNAs inhibit the post-transcriptional expression of target genes and play crucial roles in the occurrence and development of various diseases (Guo et al., 2010; Rathan et al., 2016). We found *MIR124-3p* (*CDK4, NEK6, CHODL, GSN, LDLR, MYO10* and *SURF4*) and *MIR16-5p* (*KCNN4, PTGS2, CA12, IFRD1, EGFR, ARHGDIA* and *SLC16A3*) has the major number of interactions. Targeted genes are involved in multiple pathways relevant to valvular inflammation, potentially linking 42 molecular pathways found in the present study. Furthermore, the highest level of expression of these two ncRNAs have been associated with cerebral diseases (hemorrhagic and ischemic stroke) (Leung et al., 2014). We suggest as a novel diagnostic marker in CAVS.

6.5.2 KEGG Pathways related to CAVS

Our study identified 85 molecular pathways potentially influenced by genetic variations or ncRNAs and enriched by DEGs. Pathways with the highest gene ratios may provide clues to specific processes driving CAVS development. Several key pathways emerged, such as the “calcium signaling pathway”, “PI3K-AKT signaling pathway”, “osteoclast differentiation pathway”, and “ECM-Receptor interaction pathway” (Figures 4 - 7), are likely to play crucial roles and have strong potential in the inflammatory process and progression of CAVS (K. I. Cho et al., 2018).

Our analysis revealed several key pathways potentially influencing the interconnected biological processes underlying CAVS development and progression (Bossé et al., 2009). These include inflammation, cell communication within the valve tissue, endothelial dysfunction, valve cell dysfunction (altered proliferation, migration, and matrix remodeling), calcification and apoptosis, and bone resorption and extracellular matrix interaction (K. I. Cho et al., 2018). Each pathway plays a potential role: contributing to valve tissue inflammation, disruptions in cell communication and endothelial function can hinder healthy valve function, valve cell dysfunction leads to pathological changes (DiVitto2022), alterations in pathways might influence calcification and cell death (apoptosis) (Qiao et al., 2021; Matsui et al., 2022), and bone resorption and extracellular matrix interaction are involved in maintaining valve structure and might contribute to CAVS progression (Nagy et al., 2013). By investigating these pathways and their interactions, researchers can gain a deeper understanding of CAVS and develop novel therapeutic strategies targeting these pathways for improved patient outcomes.

This study investigated the role of ncRNAs in CAVS progression through their influence on KEGG pathways (Qiao et al., 2022). These pathways are involved in a variety of biological processes, including cell growth, differentiation, and death. Their dysregulation is linked to several diseases (e.g., cancer, tuberculosis, diabetes). In the present study, the most common gene targets were *CXCL12* (regulated by 17 ncRNAs) and *CCR7* (regulated by 19 ncRNAs). These genes are involved in inflammatory responses and alterations in their expression are related to viral and bacterial infections (Cambier et al., 2023).

6.5.3 Integration of results

Integrating the results of genetic association, mRNAs and ncRNAs studies on CVAS through a gene enrichment analysis sheds light on the genetic underpinnings of CAVS susceptibility. The identified genes are found to contribute at different stages of CAVS development by participating in critical processes (inflammation, thickening and narrowing). Groups of genes like interleukins, chemokines and cytokines hold promise as potential therapeutic targets across these stages. Their involvement in CAVS progression through inflammation, immune system dysregulation, and cell differentiation highlights their crucial roles in driving valve thickening, calcification, and other hallmark features of the disease (Akdis et al., 2016; McGovern & Wilson, 2014).

Our analysis identified a potential link between inflammation and CAVS progression through the *TGFB1* signaling pathway and the ncRNA *miR-21-5p*. *TGFB1*, a cytokine involved in cell communication and implicated in CAVS, interacts with all four prioritized pathways identified in our study. Interestingly, it's the only gene within these pathways that interacts with a reported ncRNA, *miR-21-5p*. This suggests that *miR-21-5p* might act as a regulator of these pathways, potentially impacting CAVS development and progression. Studies have shown that *TGFB1* can induce *miR-21* upregulation, which in turn has been linked to the promotion of fibrosis and cardiac stress, both contributing factors in CAVS (Rong-Han et al., 2016).

Furthermore, the TNF protein family, of which FasL is a member, also plays a role in this potential regulatory network (P.-Y. Chen et al., 2023). Our findings suggest that miR-21 might interact with the chemotherapeutic drug gemcitabine, potentially leading to chemoresistance through the Fas/FasL pathway, which is partially responsible for druabine-

induced cell death (Li et al., 2017; Wang et al., 2013). This finding, although related to gemcitabine resistance, highlights a potential connection between the TNF signaling pathway (known to be involved in inflammation) and CAVS. Further investigation into the specific role of *miR-21-5p* in regulating *TGFB1* signaling and its impact on CAVS progression is warranted.

6.5.4 Compound interactions

Our study finds the direction of potential treatments by prioritizing enriched pathways based on both their statistical significance and their biological relevance to the disease. By focusing on these high-priority pathways, we can identify promising targets for drug development and develop effective therapeutic strategies for patients with CAVS. Traditional therapies aimed at reducing LDL levels, calcification, and vascular inflammation have not yielded the expected results (Vieceli Dalla Sega et al., 2022), and the work to find effective medications for treating CAVS is still being undergone (Moncla et al., 2023).

According to our findings, several targets for the treatment of CAVS includes *IL10* and *LPA* with polymorphisms highly associated (rs1800872 and rs10455872, respectively) with the disease, although both gene were not part of any of the significantly enriched pathways. Other genes are interesting, *PWWP3B* and *CCL5* belongs to several enriched pathways. Our integrated analysis highlights *TGFB1* and miR-21-5p as potentially impactful targets for CAVS treatment. These findings require further investigation, but they pave the way for the development of more targeted therapeutic strategies.

6.6 Limitations

The studies included in this review employed various methodologies for gene and ncRNA expression analysis, such as microarray, RT-PCR, RNA-seq, and qPCR. This heterogeneity in methodologies could introduce limitations in data comparability and interpretation. Standardized approaches would be beneficial for future studies to ensure more robust and generalizable findings. Functional studies are crucial to validate the identified associations and elucidate the mechanisms by which genes, mRNAs, and ncRNAs contribute to CAVS pathogenesis. Large-scale studies with well-defined patient cohorts are needed to confirm our findings and identify additional genetic and molecular factors involved in CAVS. Investigating the interactions between genetic variants, differentially expressed genes, and ncRNAs could provide valuable insights into the complex interplay of factors contributing to CAVS.

6.7 Conclusion

This study identified genes potentially involved in CAVS development, aligned with previous research. We analyzed these molecules within molecular pathways, revealing their modulation and potential roles in the disease. This knowledge can guide future targeted therapies. Integrating the analysis of genes with genetic variants, mRNA, and ncRNA data allowed us to identify pathways potentially contributing to CAVS. The analysis highlighted *TGFB1* within these pathways, particularly its interaction with ncRNAs. Furthermore, observed mRNA dysregulation suggests abnormal protein production, potentially impacting cellular processes crucial for valve function. Understanding these molecular alterations and their downstream effects is essential for deciphering CAVS development and improving diagnosis.

Figure 1. *Prisma diagram flow.*

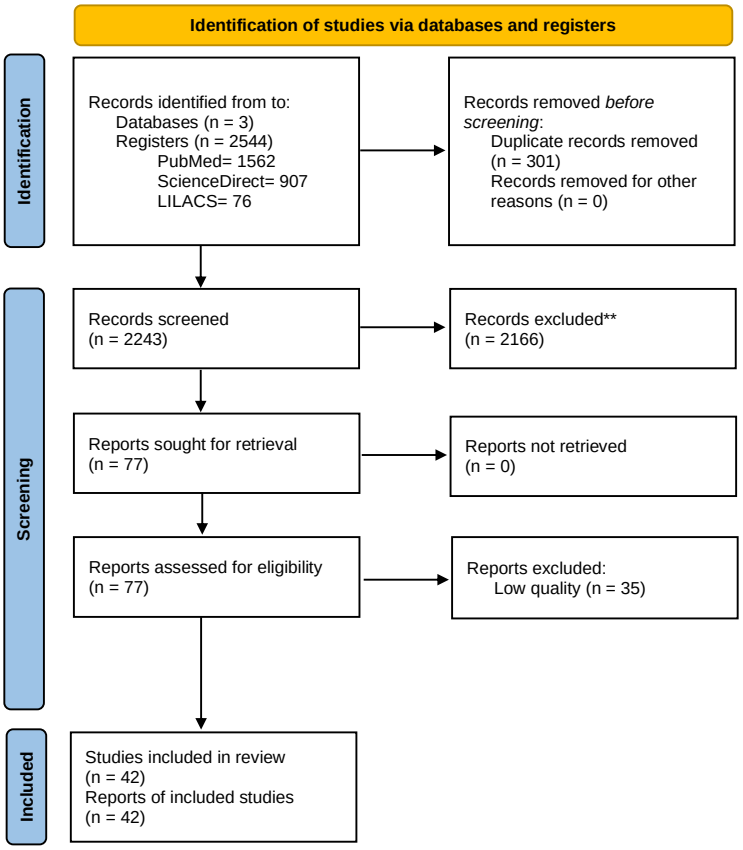


Figure 2. *Risk to bias assessment*.

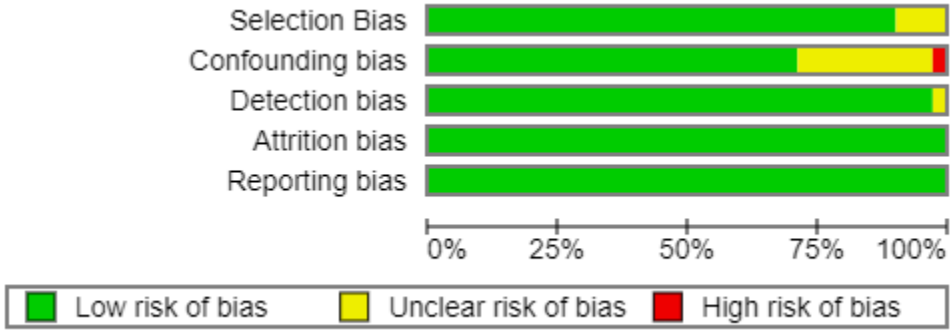


Figure 3. *The top ten most significant enriched pathways based on the differentially expressed genes. The blue bars illustrate the number of downregulated genes, while the red bars represent the number of upregulated genes. Ratios are presented as percentages, with genes involved in the present study compared with overall genes in each pathway.*

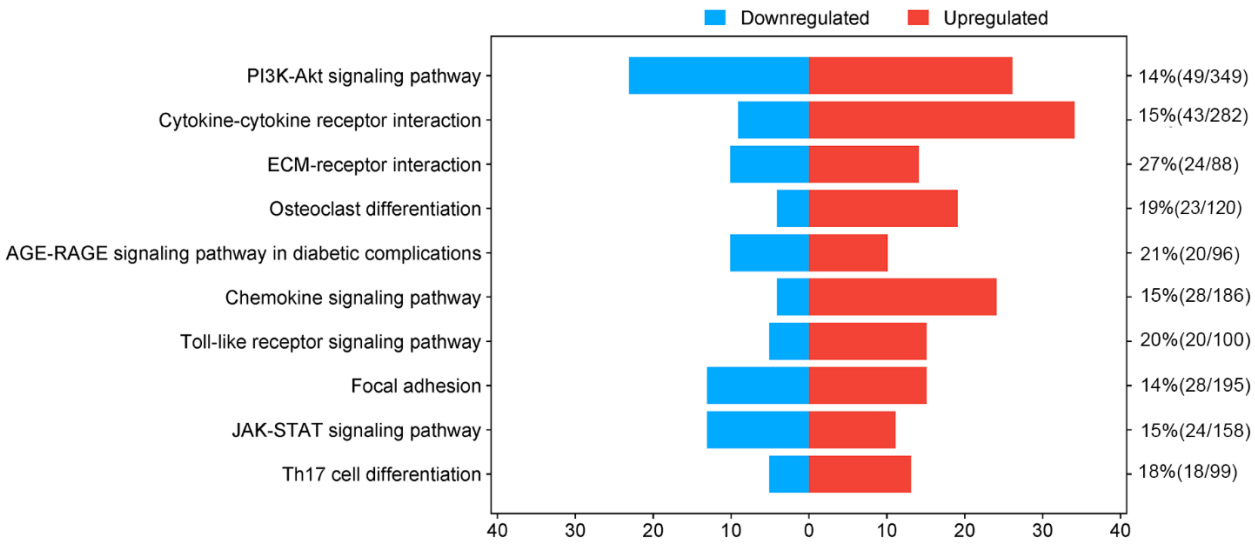


Figure 4. *KEGG Calcium signaling pathway (hsa04020) representation. Differentially expressed genes are shown in blue (downregulated) and red (upregulated). Genes regulated by at least one ncRNA are shown in bold.*

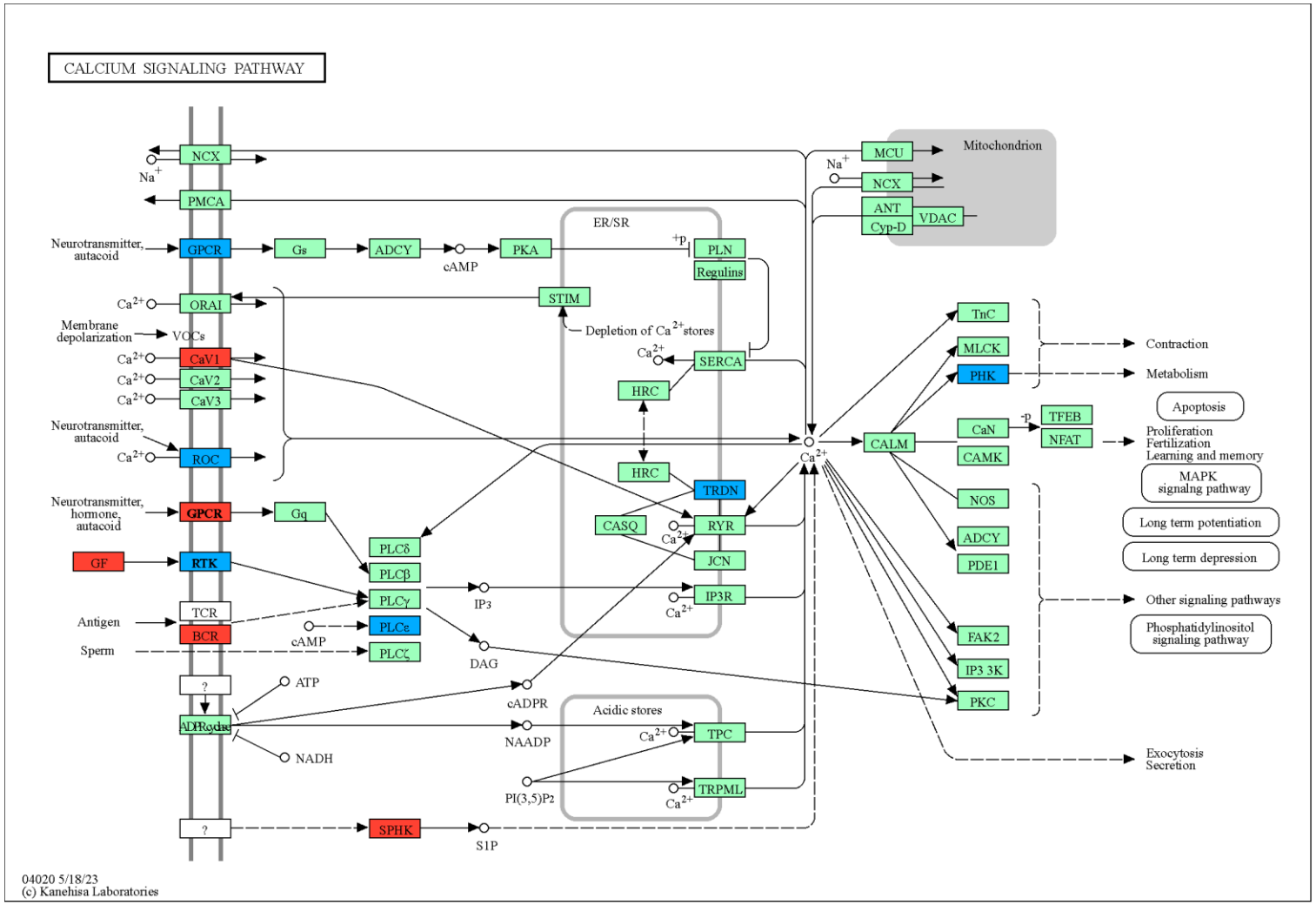


Figure 5. *KEGG PI3K-AKT signaling pathway (hsa04151) representation. Differentially expressed genes are shown in blue (downregulated) and red (upregulated). Genes regulated by at least one ncRNA are shown in bold.*

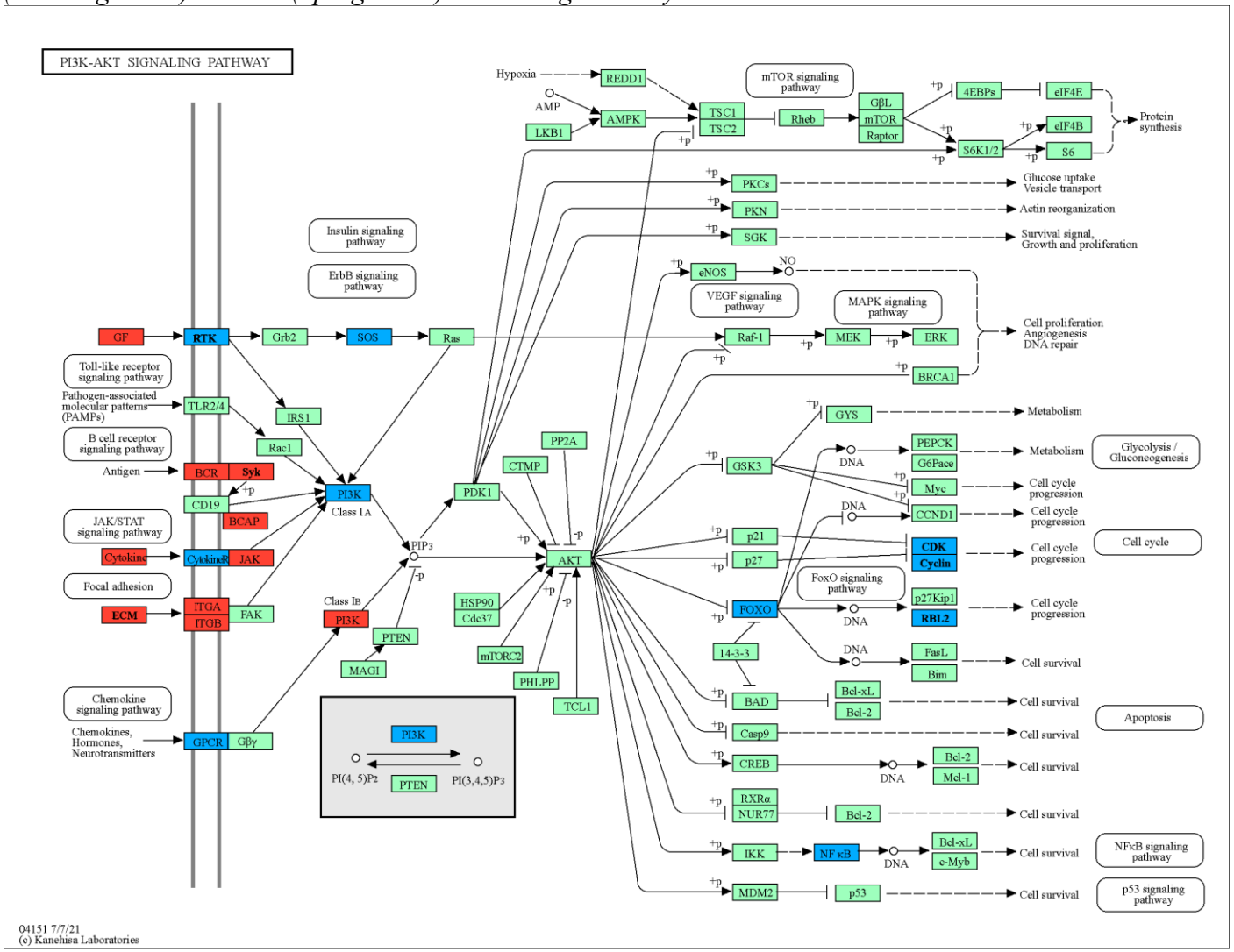


Figure 6. *KEGG Osteoclast differentiation pathway (hsa04380) representation. Differentially expressed genes are shown in blue (downregulated) and red (upregulated). Genes regulated by at least one ncRNA are shown in bold. The SNP rs6957 located in TGFβ was significantly associated with CAVS (Gaudreault et al., 2011) and is marked with an asterisk.*

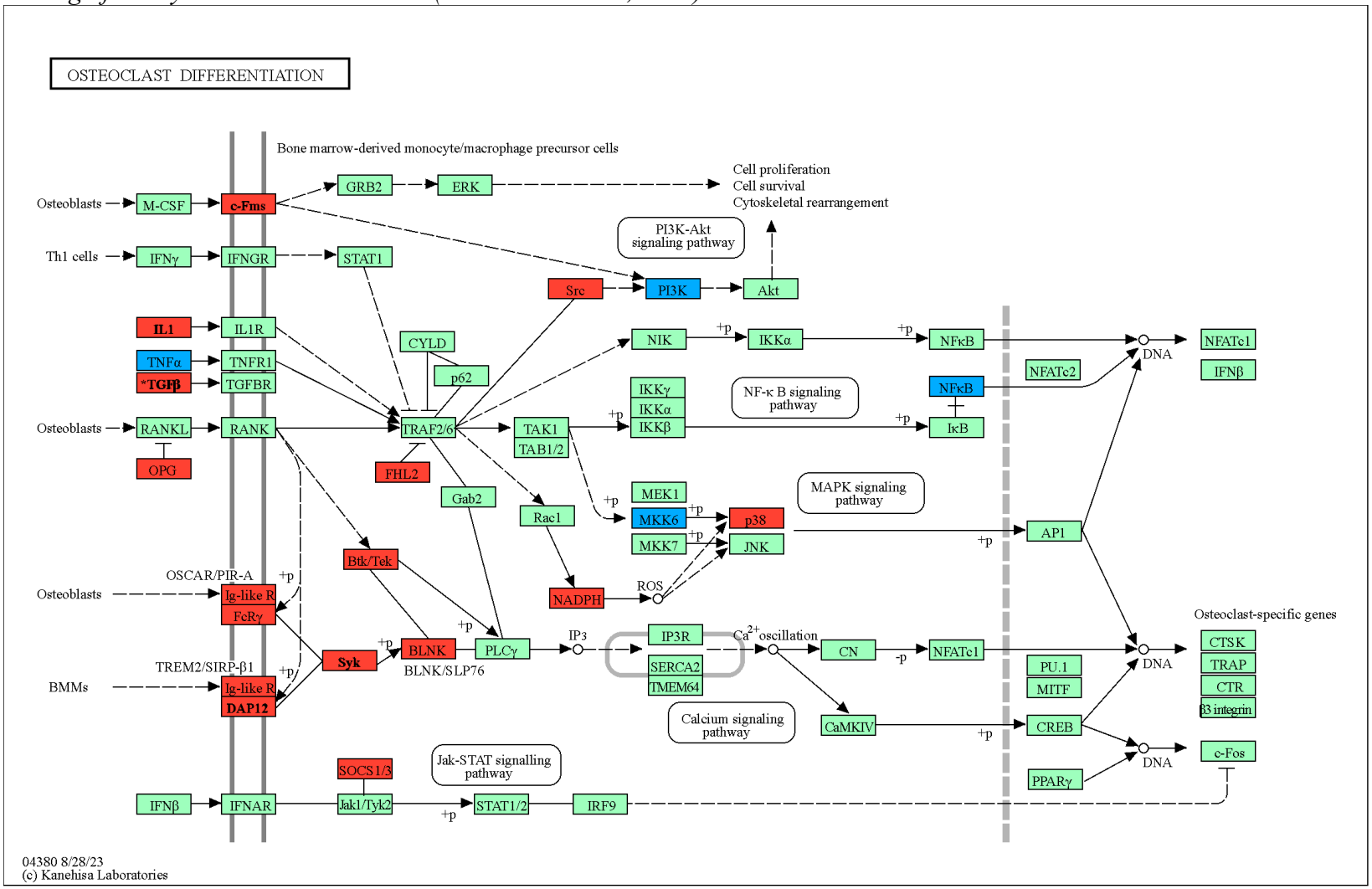


Figure 7. *KEGG ECM-Receptor interaction pathway (hsa04512) representation. Differentially expressed genes are shown in blue (downregulated) and red (upregulated). Genes regulated by at least one ncRNA are shown in bold.*

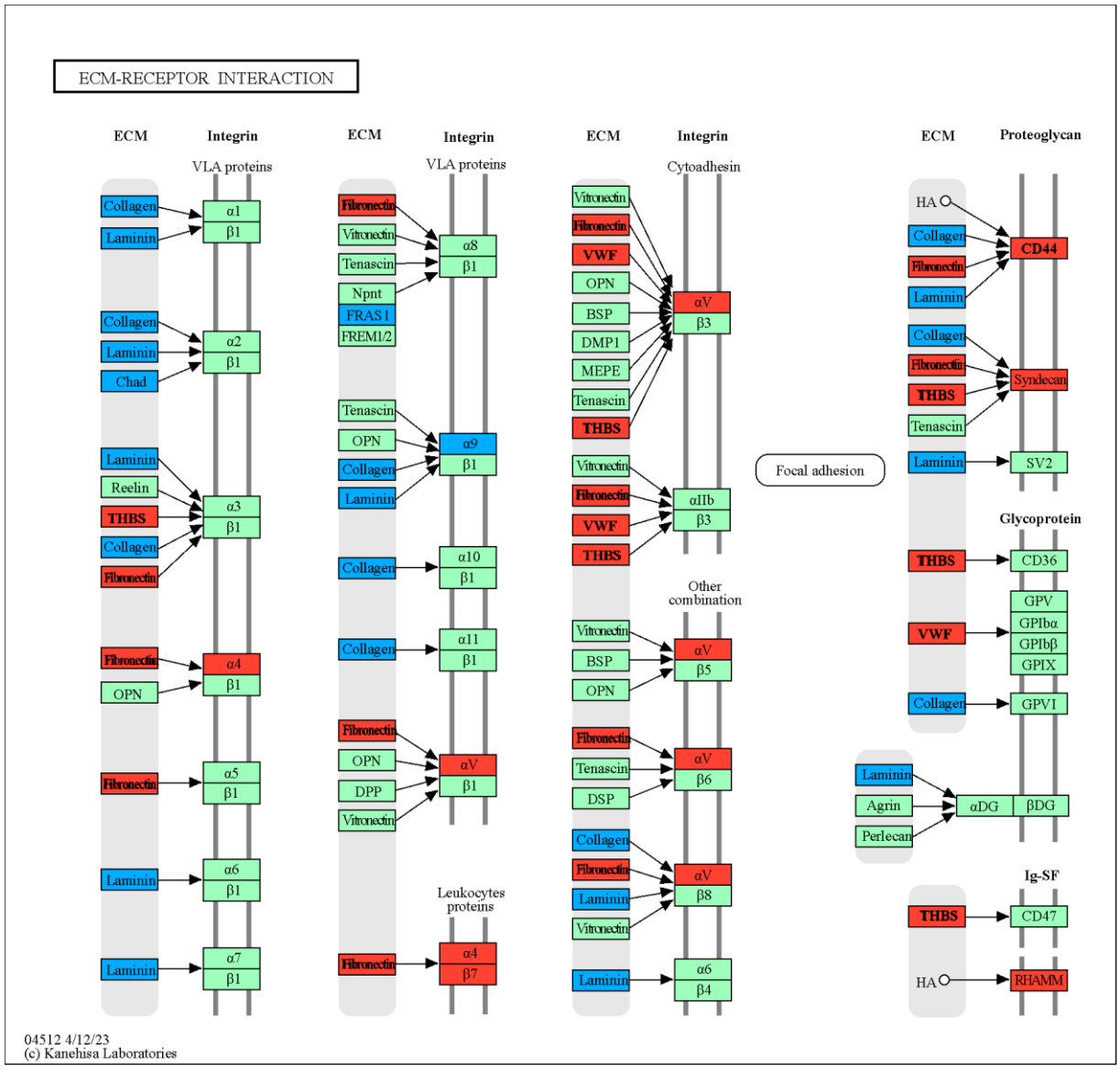


Table 1. *Overview of the studies included. A total of 42 papers including patients with CAVS were used for extracting data on molecules of interest and the methods of analysis*

Author, Yerar	Country	CVP	Diagnostic	Criteria exclusion	Study type	Methods
Anger et al. 2009	Germany	TAV	AS	CAD, RI, RHD	mRNA	Microarray
Bossé et al. 2009	Canada	TAV	AS	D, RI	mRNA	Microarray
Breyne et al. 2010	France	BAV/TAV	AS	RHD	mRNA	RT-PCR
Cantor et al. 2021	Canada	TAV	AS	D, RI	mRNA	RNA-Seq
Chen et al. 2020	Europe	TAV	AS	CVD	GWAs	Microarray
Coffey et al. 2016	Australia	TAV	AS	BAV, VR, RHD, CKD	miRNA	Microarray
Ducharme et al. 2013	Canada	TAV	AS	RHD, E, ID	Genetic association	Array
Ertas et al. 2007	Turkish	TAV	AS	RHD, CAD, CHF, MDc	Genetic association	PCR
Gaudreault et al. 2011	Canada	TAV	severe AS	RHD, E, ID	Genetic association	Array
Greene et al. 2020	USA	BAV/TAV	AS	CHD	mRNA	qPCR
Guauque-Olarte et al. 2015	Canada	TAV	Mild/Severe AS	CHD	GWAs; mRNA	Microarray; RNA-Seq
Hadji et al. 2016	Canada	TAV	AS	RHD, E, ID	lncRNAs	RNA-seq
Helske et al. 2004	Finland	BAV/TAV/CAV	AS	RI, D, MR	mRNA	RT-PCR
Jiao et al. 2019	China	TAV	AS	CHD, RHD, C	miRNA	Microarray
Kamstrup et al. 2014	Denmark	TAV	AS	CHD, GD	Genetic association	SNP
Kossar et al. 2020	USA	TAV	AS	BAV, GD, MI, E, C	mRNA	RNA-seq
Li et al. 2020	England	TAV	AS	RHD	GWAs	Microarray
Lu et al. 2019	China	TAV	AS	CHD, GD, RHD	miRNA	qRT-PCR
Mahmut et al. 2014	Canada	BAV/TAV	AS	RHD, E, ID	mRNA	Microarray - RT-PCR
Mkannez et al. 2018	Canada	TAV	AS	D	mRNA	Microarray
Nagy et al. 2012	Sweden	TAV	AS	RHD	mRNA	RT-PCR
Peltonen et al. 2007	Finland	BAV/TAV	AS	RHD	mRNA	RT-PCR
Peltonen et al. 2009	Finland	BAV/TAV	severe AS	RHD	mRNA	RT-PCR
Peltonen et al. 2009	Finland	BAV/TAV	AS	RHD	mRNA	qRT-PCR
Peltonen et al. 2011	Finland	BAV/TAV	AS	RHD	mRNA	RT-PCR
Pohjolainen et al. 2012	Finland	BAV/TAV	AS	RHD	mRNA	RT-PCR
Qiao et al. 2022	Canada; Finland	TAV	AS	S, D, RI	mRNA	Microarray
Schlotter et al. 2018	USA	TAV	severe AS	-	mRNA	RNA-seq
Song et al. 2019	USA	TAV	AS	-	miRNA	qRT-PCR
Sun et al. 2021	Canada; Finland	BAV/TAV	AS	S, D, RI	mRNA	Microarray
Teng et al. 2020	Canada; Finland	BAV/TAV	AS	S, D, RI	mRNA	Microarray
Thanassoulis et al. 2013	Iceland	ND	AS	CHD	GWAs	Microarray
Thériault et al. 2018	Canada	TAV	AS	RHD	GWAs	Microarray
Wang et al. 2018	China	TAV	AS	RHD, CHD, CKD	Genetic association	PCR-RFLP
Wang et al. 2021	Canada; Finland	BAV - TAV	AS	RHD, S, D, RI	mRNA	Microarray
Wypasek et al. 2015	Poland	ND	AS	RHD, C, E, MI	Genetic association	RT-PCR
Wypasek et al. 2014	Poland	ND	AS	RHD, C, CHD, E, MI	Genetic association	RT-PCR
Yang et al. 2020	China	TAV	AS	CHD, RHD, PHD, E, CRD, MDc	miRNA	RT-PCR
Yang et al. 2020	Canada; Finland	BAV/TAV	AS	S, D, RI	mRNA	Microarray
Zhang y Ma. 2019	Finland	BAV/TAV	AS	S, D, RI	mRNA	Microarray
Zhu et al. 2019	Finland	BAV/TAV	AS	S, D, RI	mRNA	Microarray

*BAV: Bicuspid aortic valve; VR: valvular regurgutation; RHD: Rheumatic heart disease; CKD:chronic kidney disease; E:endocarditis; ID:inflammatory disease; CAD:coronary artery disease; CHF:congestive heart failure; MDc:metabolic disease that may cause calcification; CHD:congenital heart disease; PHD:pulmonary heart disease; CRD:chronic renal dysfunction; C:cancer; MI:myocardial infarction; RI:renal insufficiency; D:diabetes; MR:mitral regurgitation; GD:genetic diseases; CVP:configuration valve patiens; S:smoker

Table 2. *Genes significantly associated with CAVS. Eight genetic association papers were analyzed covering association of 46 significant variants in 22 genes*

Gene	Variant	OR	CI	Author	Diagnosis
ACE	insertion/deletion intron16	3.2	1.5-7.2	Ertas et al. 2007	CAVS
APOB	rs1042031	ND	ND	Gaudreault et al. 2011	Severe CAVS
	rs6725189	1.59	1.04-2.43	Wang et al. 2018	CAVS
		ND	ND	Gaudreault et al. 2011	Severe CAVS
	rs693	1.89	1.27-2.81	Wang et al. 2018	CAVS
CACNA1C	rs2239118 rs1034936	0.52	0.23-0.89	Guauque-Olarte et al. 2015	Mild/Severe CAVS
CREB5	rs118040196	7.32	0.44-1.05	Guauque-Olarte et al. 2015	Mild/Severe CAVS
	rs76323786	7.53			
	rs78850423	7.53			
	rs79158915	7.83			
CRP	rs1205	4.47	1.73-11.57	Wypasek et al. 2015	CAVS
CYP27B1	rs2254210	ND	ND	Gaudreault et al. 2011	Severe CAVS
	rs4328262	ND	ND	Gaudreault et al. 2011	Severe CAVS
EVA1C	rs10483012	9.32	0.44-1.05	Guauque-Olarte et al. 2015	Mild/Severe CAVS
FADS1	rs174547	0.87	0.83-0.93	Chen et al. 2020	CAVS
GOLGA8A	rs3894644	8.54	0.44-1.05	Guauque-Olarte et al. 2015	Mild/Severe CAVS
IL10	rs1554286 rs1800872 rs1800896 rs3021094 rs3024491 rs3024498	ND	ND	Gaudreault et al. 2011	Severe CAVS
LINC01205	rs139795084	7.48	0.44-1.05	Guauque-Olarte et al. 2015	Mild/Severe CAVS
LINC01619	rs117740534	7.51	0.44-1.05	Guauque-Olarte et al. 2015	Mild/Severe CAVS
LOC101927829	rs112995365	3.23	0.44-1.05	Guauque-Olarte et al. 2015	Mild/Severe CAVS
	rs113299180	3.21			
	rs11715795	3.33			
	rs11718740	3.24			
	rs12491632	3.14			
	rs79874757	3.24			
LOC339166	rs75561073	8.66	0.44-1.05	Guauque-Olarte et al. 2015	Mild/Severe CAVS
LPA	rs10455872	2.05	1.32-2.05	Thanassoulis et al. 2013	CAVS
MTMR2	rs117752934	6.89	0.44–1.05	Guauque-Olarte et al. 2015	Mild/Severe CAVS
NOTCH1	rs13290979	1.25	1.08-1.45	Ducharme et al. 2013	CAVS
PALMD	rs6702619	1.29	1.14-1.46	Thériault et al. 2018	CAVS
	rs7543130	1.06	0.83-0.93	Chen et al. 2020	CAVS
PSG7	rs17345014	2.77	0.44–1.05	Guauque-Olarte et al. 2015	Mild/Severe CAVS
PTH	rs6254	ND	ND	Gaudreault et al. 2011	Severe CAVS
RUNX2	rs114193529 rs144071310	3.49	2.15-8.62	Guauque-Olarte et al. 2015	Mild/Severe CAVS
TGFB1	rs6957	ND	ND	Gaudreault et al. 2011	Severe CAVS
TPRG1	rs138995217	4.12	0.44–1.05	Guauque-Olarte et al. 2015	Mild/Severe CAVS
	rs16864172	4.03			
	rs73055977	4.03			
	rs7614851	4.03			
	rs7638684	4.03			
	rs9815491	4.03			
	rs9857444	4.03			
UQCRC2	rs141826387	6.94	0.44–1.05	Guauque-Olarte et al. 2015	Mild/Severe CAVS

CI: Confidence Interval. ND: No data. OR: Odds ratio. All studies included tricuspid valves (TAV). Thassanoulis et al. 2013 and Wypasek et al. 2015 did not indicated the valve configuration.

Table 3. *List of top differentially expressed genes between CAVS and non-CAVS. The number of studies for each gene are listed in author column*

Gene	Sense	Author	Configuration
PWWP3B	downregulated	Bossé et al. 2009	TAV
		Cantor et al. 2021	TAV
		Greene et al. 2020	BAV/TAV
		Qiao et al. 2022	TAV
		Teng et al. 2020	BAV/TAV
		Zhu et al. 2019	BAV/TAV
AGTR1	downregulated	Bossé et al. 2009	TAV
		Guauque-Olarte et al. 2015	TAV
		Zhu et al. 2019	BAV/TAV
		Peltonen et al. 2011	BAV/TAV
ANGPTL7	downregulated	Qiao et al. 2022	TAV
		Teng et al. 2020	BAV/TAV
		Zhang y Ma. 2019	BAV/TAV
		Zhu et al. 2019	BAV/TAV
ARL4C	upregulated	Bossé et al. 2009	TAV
		Guauque-Olarte et al. 2015	TAV
		Qiao et al. 2022	TAV
		Zhang y Ma. 2019	BAV/TAV
C6	downregulated	Qiao et al. 2022	TAV
		Sun et al. 2021	BAV/TAV
		Teng et al. 2020	BAV/TAV
		Zhu et al. 2019	BAV/TAV
CA12	upregulated	Bossé et al. 2009	TAV
		Qiao et al. 2022	TAV
		Sun et al. 2021	BAV/TAV
		Zhang y Ma. 2019	BAV/TAV
		Zhu et al. 2019	BAV/TAV
CCL5	upregulated	Bossé et al. 2009	TAV
		Qiao et al. 2022	TAV
		Teng et al. 2020	BAV/TAV
		Yang et al. 2020	BAV/TAV
		Zhu et al. 2019	BAV/TAV
FPR1	upregulated	Bossé et al. 2009	TAV
		Qiao et al. 2022	TAV
		Teng et al. 2020	BAV/TAV
		Yang et al. 2020	BAV/TAV
		Zhu et al. 2019	BAV/TAV
TMEM200A	upregulated	Bossé et al. 2009	TAV
		Greene et al. 2020	BAV/TAV
		Qiao et al. 2022	TAV
		Sun et al. 2021	BAV/TAV
		Zhu et al. 2019	BAV/TAV
CXCL12	upregulated	Bossé et al. 2009	TAV
		Kossar et al. 2020	TAV
		Qiao et al. 2022	TAV
		Zhu et al. 2019	BAV/TAV

Table 4. *List of ncRNAs with most interactions according to differentially expressed gene target predicted by miRGator 3.0 among the reviewed articles. Upregulated genes are shown in bold. *Gene targets indicated by the authors. The studies included only tricuspid valves.*

miRNA	sense of expression	Gene target	Author
MIR124-3p	Downregulated	CDK4,**NEK6**,CHODL,GSN,**LDLR**,**MYO10**,SURF4	Coffey et al, 2016
MIR146a-5p	N.D.	**CDKN3**,EGFR,NFKB1,**CXCR4**,ATOH8,**CCL5***	Qiao et al, 2022
MIR155	Upregulated	PAPOLA,AGTR1,FGF7,LPL,MYO10,BCAT1,PHF17,RUNX2,CSF1R*	Bossé et al, 2009
MIR155-5p	N.D.	PAPOLA,AGTR1,**FGF7**,LPL,**MYO10**,**BCAT1**,PHF17,**RUNX2**,**CSF1R***	Qiao et al, 2022
MIR16-5p	Downregulated	**KCNN4**,PTGS2,**CA12**,**IFRD1**,EGFR,**ARHGDIA**,**SLC16A3**	Coffey et al, 2016
MIRLET7A1 5p	N.D.	CCND2,**PRDM1**,NFKB1,**SLC20A1**,CASP8,**IL6**,**CCR7***	Qiao et al, 2022

7. Chapter 2: Functional prediction, richness and diversity of microbiota from calcified and healthy aortic valves

I. Y. López-Ardila[1], F. Rondón-González[1], L. Cifuentes-Cardona[3], S. Guauque-Olarte[4]

[1]Escuela de Biología, Facultad de Ciencias, Universidad Industrial de Santander, Bucaramanga.

[2]Facultad de Odontología, Universidad Cooperativa de Colombia, Medellín-Envigado

[3]Facultad de Odontología, Universidad Cooperativa de Colombia, Pasto

[4]Departamento de ciencias básicas y medicina oral, Facultad de Odontología, Universidad Nacional de Colombia, Bogotá

7.1 Abstract:

The influence of microorganisms inside the human body have been associated with the development of different diseases, including some cardiovascular diseases. With the objective of analyzing the microorganisms role in CAVS, we used publicly available RNA sequencing data from aortic valves of individuals with and without CAVS, available in the Gene Expression Omnibus (GEO), to describe the taxonomic composition of the microorganisms identified. We worked with four datasets (GSE138531, GSE76718, GSE148219, and GSE153555). The read files of 23 CAVS and 21 non-CAVS individuals were analyzed. A total of 5970 species of microorganisms were found, with 48% of shared species between groups. The Super-kingdom more represented was Bacteria, followed by Archaea, Eukaryote, and Viruses. The bacterial metabolic contribution predicted with Picrust2 for the CAVS group indicates a possible relation to the diseases by the metabolism of carbohydrates and lipids. The greatest diversity was found in the CAVS group, with the

taxa SDRs indicative of food and soil handling; The metabolic contribution is related to processes of apoptosis and degradation of aromatic compounds, which may be related to inflammatory processes of the valves.

Keywords: Aortic stenosis, aortic valve, metagenomics, microorganisms.

7.2 Introduction:

The most common valvular disease worldwide is calcific aortic valve stenosis (CAVS). The disease affects approximately 2-4% of people over 65 years (Ackah et al., 2023). CAVS is a chronic, degenerative, and continuous process (O'Brien, 2007). This chronic, degenerative disease leads to progressive valve calcification and stenosis, ultimately hindering blood flow and increasing the risk of heart failure (Dweck et al., 2012). While traditional risk factors like hypertension, dyslipidemia, and diabetes contribute to CAVS, the complex interplay of underlying mechanisms remains elusive (Vieceli Dalla Sega et al., 2022). Currently there is no pharmaceutical treatment for the CAVS; although surgery is an option, up to 50% of patients cannot undergo surgery due to comorbidities (Bosmans et al., 2015)

Despite advancements in understanding genetic and molecular aspects of CAVS, such as *LPA (rs10455872)* and *NOTCH1 (rs13290979)* (Thassanoulis et al 2013; Thériault et al., 2019), effective medical treatments remain limited. Current therapeutic options are primarily surgical interventions, with limited suitability for a significant portion of patients due to comorbidities (Bosmans et al., 2015). Consequently, identifying novel therapeutic targets necessitates a comprehensive understanding of CAVS pathogenesis.

Emerging evidence suggests a potential role for the microbiome in the development and progression of CAVS (Li et al., 2020; Tang et al., 2019). While the gut microbiome has been extensively studied in relation to cardiovascular diseases. Studies recent have also implicated the oral microbiome in aortic valve stenosis (Pierri et al., 2006; Oliveira et al., 2019). detection of microorganisms within calcified aortic valves supports the hypothesis of a local microbial contribution to the disease process (Moreno et al., 2017).

Understanding the composition and function of the aortic valve microbiome, along with its interactions with the host, is crucial for developing novel diagnostic and therapeutic strategies for CAVS (Alushi et al., 2020; F. A. F. Oliveira et al., 2019). The aim of this study was to identify microorganisms (Bacteria, Archaea, Virus, and Eukaryotes) in human aortic valves from individuals with and without CAVS. A metagenomic approach was employed to identify the microbial communities present in the aortic valves and to clarify their metabolic contribution by inference.

7.3 Methods:

7.3.1 Search

Publicly available RNA sequencing data relevant to our research were retrieved from the NCBI Gene Expression Omnibus (GEO) database (Barrett et al., 2013) on March 24, 2022. The search keywords were: 'aortic valve', 'homo sapiens', and 'high throughput sequencing'. To ensure data homogeneity, the study included aortic valves tissue from adult patients with CAVS and tricuspid aortic valves, was excluded dataset with RNA sequencing of microRNAs.

The data was obtained through publicly links provided by the European Nucleotide Accession (ENA) (Yuan et al., 2024). Quality control and preprocessing steps were employed to ensure data integrity and prepare the data for analysis, including the removal of low-quality reads (<20) and adapter sequences using fastqc v.0.11.5 (Wingett & Andrews, 2018) and trimmomatic v.0.39 (Bolger et al., 2014). The data processing was carried out on the Universidad Cooperativa de Colombia (UCC) server.

7.3.2 Identification of microorganisms

Microorganism communities were characterized using bioinformatics pipelines for taxonomic identification (Odom et al., 2023). We targeted bacteria, archaea, viruses, and eukaryotes. Kraken2-Bracken (Lu et al., 2017; Wood et al., 2019) was employed with a minimum confidence threshold of 0.1 for taxonomic assignment. The Greengenes database (DeSantis et al., 2006) was used for bacterial identification based on 16S rRNA gene sequences. For eukaryotic pathogens, we utilized EuPath (Aurrecoechea et al., 2017), combining BLAST and HMM profile methods. The Standard database (Wood et al., 2019) was used for general taxonomic assignments of archaea, bacteria, and viruses. It is constructed using Kraken2-build and provides reference sequences for taxonomic assignment; constructed with kraken2-build. The taxonomic levels for the report were determined using Braken at the levels of Phylum, Class, Order, Family, Genus, and Species for each database utilized. The results were then uploaded to the R-package (R Core Team, 2019) Pavian (Breitwieser & Salzberg, 2020) to generate a classification report.

7.3.3 Richness and Diversity indices

Alpha and beta indices were calculated using the package Vegan (Oksanen et al., 2015). The Alpha diversity was measured by calculating the richness or quantity of species

of microorganisms and their relative abundance with the Shannon, Simpson and eveness indices (Moreno, 2001). The beta diversity is the grade of variation in the composition of microorganisms between groups (García-Q. et al., 2021) was measured calculating the coefficient of similarity by Jaccard index (Moreno, 2001) and Bray-Curtis index (Park et al., 2022).

7.3.4 Differential Abundance Analysis

To identify significant differences in the abundance of microorganisms between the two groups (CAVS and non-CAVS), the DESeq2 R package (Love et al., 2014) was used. The DESeq2 package is designed to normalise, visualise and test for differential analysis between groups from counts obtained by high-throughput sequencing techniques such as metagenomics. A significance level (FDR) of 5% was used. The analysis was performed at different taxonomic levels (species, genus, and phylum) for each database used. A minimum of 10 reads per individual was used for the comparison of microorganism counts.

7.3.5 Functional Analysis

A functional analysis was performed to infer potential functional capabilities of the identified microbial communities. The analysis considered taxonomic information at the specie level based on the sequence of the 16s rRNA coding gene sequencing. Thus, only the counts obtained from the analysis with the Greengenes database were used. Functional annotations were assigned using picrust2-2.4.1 (Douglas et al., 2020) and visualized using the R package ggpicrust2 (Yang et al., 2023).

7.4 Results

7.4.1 Datasets and participant characteristics

Four GEO datasets GSE76718 (Guauque-Olarte et al., 2016), GSE138531 (Kossar et al., 2020), GSE148219 (MacGrogan et al., 2020), and GSE153555 (Greene et al., 2020) were selected. After applying the individual's selection criteria, the data from 44 individuals were kept. These individuals were divided into two groups. The CAVS group consisted of 23 samples with calcific aortic valves, while the non-CAVS group consisted of 21 samples with non-calcific aortic valves. The mean age of CAVS group was 68.4 ± 7.4, with 18 males, two females, and three individuals whose gender was not disclosed. In the non-CAVS group, the mean age was 47.5 ± 18.0, with 16 males and 5 females (Table 5).

7.4.2 Identification of microorganisms

Based on the RNA sequences, the organisms present in each individual were identified and classified by taxa. The number of classified reads ranged from 2,182,850 to 120,177,109 per individual in the CAVS group and from 7,305,258 to 50,037,531 per individual in the non-CAVS group. The CAVS group had a mean mapped read of microorganisms of 554,562 ± 954,182, while the non-CAVS group had a mean mapped read to microorganisms of 81,494 ± 131,830 (Table 6).

The microorganisms were categorized into super kingdoms bacteria, archaea, viruses, eukaryote. A total of 5970 species were identified between the groups for all domains for a total of 14,466,300 reads of microorganisms between all databases used (Greengenes – 143 species, Standard – 5760 species, Eupath – 257 species). In both groups, the top 10 of microorganisms in terms of read number belong to Bacteria. The top 10 species in the CAVS

group (>273.000 reads) were *Stutzerimonas stutzeri, Acinetobacter sp. FDAARGOS_560, Cupriavidus basilensis, Burkholderia cepacian, Burkholderia pseudomallei, Salmonella enterica, Sphingobacterium multivorum, Yersinia pestis, Acinetobacter baumannii,* and *Cupriavidus necator*. In the non-CAVS groups (>24.000 reads), the top 10 species species were *Escherichia coli, Salmonella enterica, Bacillus cereus, Klebsiella pneumoniae, Salmonella sp. SJTUF14178, Salmonella bongori, Burkholderia dolosa, Staphylococcus aureus, Yersinia pestis,* and *Enterobacter hormaechei*.

The phyla Proteobacteria and Firmicutes were present in all samples with the higher number of reads, followed by Bacteroidota, Actinobacteria, Cyanobacteria, Artververicota, Euryarchaeota, Planctomycetota, Ascomycota and Deinococcus. The specie *Bacillus cereus* was present in all samples with the highest number of reads (Supplementary Figure 2). The unique species with most reads were *Halovivax sp. CGA30* in CAVS group in 14 samples; and *Mycolicibacterium aichiense* in non-CAVS groups in six samples.

7.4.3 Microbial Community Diversity

In terms of species the CAVS group showed 4257 Bacteria, 102 Eukaryotes, 88 Archaea and 56 Viruses. Richness in the non-CAVS group showed 4040 Bacteria, 130 Eukaryotes, 126 Archaea, 68 Virus. Was observed higher values of evenness in CAVS group with 0.11 than non-CAVS group with 0.09 groups. Indicative that in non-CAVS group, few species dominate the community in comparison with CAVS group. The Shannon index in the non-CAVS (1.98±0.83) group shows less dispersion than in the CAVS group (2.09±0.76) (Figure 9). The Bray-Curtis similarity index shows that the CAVS group has a similarity minimum of 0% and maximum of 92%; with respect to the non-CAVS group, the maximum similarity was 98%, minimum similarity was of 6% (Figure 10).

According to the three databases (Greengenes, Standard and Eupath) used for taxonomic assignment, we identified 4503 species of microorganisms in CAVS patients and 4335 species in non-CAVS individuals. Among the common species of microorganisms, 49.4% are common in Bacteria, 28.1% in Archaea, 26.5%, 64.0% in Viruses, and 45.3% in Eukaryote (Figure 11).

We are interested specially in the bacterial community present in the samples. According to the Standard database we identified 4212 bacterial species affiliated to 1377 genera, 402 families, 191 orders, 85 classes, and 39 phyla in the CAVS group and 4011 bacterial species affiliated to 1324 genera, 464 families, 212 orders, 98 classes, and 36 phyla in the non-CAVS group.

7.4.4 Differential taxa abundance between groups

The comparison of the frequency of microorganisms between groups at the genus and species levels indicates that 17 genera and 49 species were significantly different between the groups (Table 7). The genera *Sphingobacterium, Brevundimonas, Cupriavidus, Delftia*, and *Sphingobium* are common between databases. The species *Salmonella enterica*, *Sphingobacterium multivorum* and *Brevundimonas diminuta* are common between databases. In all cases, the sense of fold change was common between databases. At the genera and species level, we found that none was reported with differential expression between groups were established as periodontal pathogenic.

7.4.5 Metabolic inference

Between groups we found 24 pathways ($p<0.05$) related to bacterial 16s DNA sequence in Greengenes database. In the CAVS group, the major process involved pathways

activated by active stress conducing to apoptosis (1 pathway), and metabolism of aromatic compounds (6 pathways). Respect to non-CAVS groups, the presence of bacteria is related to metabolism of carbohydrates and lipids (17 pathways) (Figure 11).

7.5 Discussion

In the present study, we explored the presence of microorganisms, determined from RNA sequences extracted from a public database for 44 human adults with tricuspid aortic valves (TAV) with endocarditis and heart infection risk as exclusion criteria. The individuals were from the USA (Greene et al., 2020; Kossar et al., 2020), Canada (Guauque-Olarte et al., 2016), and Spain (MacGrogan et al., 2020), and were divided into two groups: CAVS and non-CAVS.

Of all the species present in aortic valves, 26.9% species were unique to the CAVS group and 24.6% were exclusive to the non-CAVS group, with a quantity of reads approximately 10 times higher in the CAVS group. The differences encountered in the composition of reported microorganisms and number of reads may be associated with habitat difference because calcific areas are more related to the major density of microorganisms than non-calcific areas (F. A. F. Oliveira et al., 2019; Pierri et al., 2006).

Previous studies detected bacteria and virus species in aortic valves from patients with CAVS with diverse methodologies (chemical and morphology). Shared taxa with our study are *Listeria* spp., *Staphylococcus warneri*, *Propionibacterium acnes* and *Pantoea* spp.,but in few samples and low frequency (Bayram et al., 2011; Higuchi et al., 2002; F. A. F. Oliveira et al., 2019; Pierri et al., 2006; Radke et al., 2002). In relation with other metagenomics analysis, we found in CAVS and non-CAVS samples common species such as *Clostridioides difficile* and *Nocardia cyriacigeorgica* (Yoshiba et al., 2023), and

Sphingomonas, Bifidobacterium, *Bradyrhizobium* genera (Curini et al., 2023) with higher frequency in the CAVS group.

The most abundant phyla in the CAVS group were Proteobacteria, Thaumarchaeota, Uroviricota, and Discosea, while for the non-CAVS group were Proteobacteria, Euryarchaeota, Artververiricota, and Apicomplexa. Many reads were attributed to Bacteria, principally to the phyla Proteobacteria and Firmicutes, as well as the species Bacillus cereus, which was present in all samples. The most abundant species was the pathogenic bacteria *Stutzerimonas stutzeri* for the CAVS group (3 samples), and *Escherichia coli* for the non-CAVS group (2 samples), identified in few samples but in high abundances. *Stutzerimonas stutzeri* is commonly found in soil, and *Escherichia coli* is associated with fecal contamination. Proteobacterias and the genera *Bacillus* have been described as dominant in oral cavity (A. M. Oliveira et al., 2012).

Among the taxa with significantly different abundance in the CAVS group vs the non-CAVS group, are Bacteria. Among the differential abundant genera, bacterias such as *Sphingobacterium* and *Brevundimonas* were found, these arecommonly found in soil and are not documented inside the human body (Gomila et al., 2022; Jang et al., 2024). The most significant bacteria with the highest fold-change found is related to food spoiling, causing infections, and included species as *Yersinia pestis* and *Salmonella enterica* (Godínez-Oviedo et al., 2024; Zhang et al., 2020).

Our research indicates that oral pathologies have a close association with heart diseases. For example, gingival ulceration in periodontitis can lead to bacteremia and may induce the formation of atherosclerotic plaques (Bartova et al., 2014; DeStefano et al., 1993). Oral diseases such as periodontitis caused by bacteria may predispose for cardiovascular

disease (Bayram et al., 2011; Kolltveit et al., 2002; Pierri et al., 2006). Many of the microorganisms found in patients with CAVS have been associated with oral health (F. A. F. Oliveira et al., 2019); the transmission may have occured through the bloodstream (Bayram et al., 2011; Yoshiba et al., 2023). Although in few densities, analysis of the samples revealed that the presence of bacterial species from the red and orange complexes described by Socransky & Haffajee (2005). The following bacteria were found in both groups: *Prevotella nigrescens* (12 CAVS samples and 10 non-CAVS samples), *Prevotella intermedia* (4 CAVS samples and 2 non-CAVS samples), *Parvimonas micra* (1 CAVS sample and 3 non-CAVS samples), *Fusobacterium nucleatum* (3 CAVS samples and 5 non-CAVS samples) and *Campylobacter gracilis* (1 CAVS sample and 1 non-CAVS sample). *Streptococcus constellatus* was unique to the CAVS group (1 sample).

The presence of contaminants in metagenomic studies, including our own, is a significant challenge. We identified potential contaminants such as Cupriavidus basilensis, Burkholderia cepacia, Yersinia pestis, Escherichia coli, Pseudomonas stutzeri, Klebsiella pneumoniae, Enterobacter hormaechei, and Enterobacter cloacae in both CAVS and non-CAVS groups (Dewhirst et al., 2010; Salter et al., 2014; Strong et al., 2014). These contaminants can originate from various sources like laboratory environments, reagents, or sample handling (Jurasz et al., 2021). Their presence can lead to false positive findings, biased abundance estimates, and incorrect taxonomic assignments (Davis et al., 2018). Future studies should prioritize strategies to minimize contamination and validate findings through independent methods.

Furthermore, we conducted an evaluation of the microbiota function via PICRUSt2 software. This metagenome predictor compares the significance of differential abundance of

predicted functional gene profiles from bacterial 16S rRNA DNA sequences. (Douglas et al., 2020 ;Yang et al., 2023). The potential event signaling predicted by KEGG pathways showed a potential link between microbiota and metabolic profile, which is positively related to stress and degradation of different aromatic compounds. The pathways of apoptosis include the subpathways calcium signaling pathway (hsa04020), the TNF signaling pathway (hsa04668), and the PI3K-Akt signaling pathway (hsa04151). The K-Akt signaling pathway (hsa04151), NF-kappa B signaling pathway (hsa04064) and MAPK signaling pathway (hsa04010) were also found in our review as significant. Although there is no evidence that the breakdown of aromatic compounds is linked to CAVS, there is a clear association between cardiovascular disease and aromatic compounds that cause inflammation (Mallah et al., 2021).

Our analysis revealed a negative correlation between the abundance of predicted functional bacteria and metabolites of carbohydrates and lipids. This suggests that the presence of these bacteria is potentially linked to stress-induced pathway alterations previously associated with CAVS. The increase in fold-change in CAVS relates processes that indicate an increase in cell death processes and those related to the degradation of aromatic compounds, potentially indicate an increase in inflammation processes. In the non-CAVS group, an increase in lipid and carbohydrate metabolization was observed, this may be related to low lipid accumulation in valves that do not represent the condition. This process is related to different processes that lead to calcification of the valves in calcification aortic stenosis.

This study analyzed the human aortic valve microbiome, revealing a strong link between the types of microbes present and the geographic origin of the samples (Supplementary Figure 3). This indicates that location plays a significant role in determining

the composition of microbial communities. It is notable that the study design may have excluded samples that could have been influenced by other infectious agents. In addition to geography, factors such as diet, hygiene habits, and even transmission through objects may also contribute to the diversity of these communities (Gupta et al., 2017). These findings highlight the complex interplay between environmental factors and the human microbiome.

Our study revealed distinct microbial communities associated with aortic valve samples from different geographic regions, aligning with previous research demonstrating geographic variability in the human microbiome (Gupta et al., 2017; Zaura et al., 2013; Blaser et al., 2013; Yatsunenko et al., 2012). These findings suggest that geographic location may influence the composition of the aortic valve microbiome, potentially through factors such as diet, hygiene, and environmental exposures (Lafaurie et al., 2022).

However, our study has several limitations. The relatively small sample size from each geographic region restricts the generalizability of our findings. Additionally, the absence of detailed individual-level lifestyle data prevents a comprehensive analysis of the factors shaping the aortic valve microbiome. Furthermore, the identification of contaminant species in our samples, including some with relatively high abundance, highlights the challenges of metagenomic studies. While these contaminants pose limitations, they also represent an opportunity to explore the presence of novel or unexpected microorganisms. Future studies with larger, more diverse cohorts and comprehensive data collection are needed to fully elucidate the factors influencing the aortic valve microbiome across geographic regions.

7.6 Conclusion

Our study provides novel insights into the complex interplay between the aortic valve microbiome and CAVS. We observed significant differences in the microbial composition between CAVS and non-CAVS groups, suggesting a potential association between specific microbial profiles and disease development. The presence of oral bacteria, such as those from the red and orange complexes, in both groups highlights the potential role of oral-systemic connections in CAVS. However, the exact mechanisms by which these microorganisms contribute to CAVS pathogenesis remain to be elucidated.

While our findings suggest a potential link between the microbiome and CAVS, it is essential to acknowledge the limitations of our study, including the cross-sectional design and relatively small sample size. Further longitudinal studies with larger cohorts are needed to establish causality and to explore the temporal dynamics of the aortic valve microbiome in relation to disease progression. Additionally, functional studies are warranted to investigate the specific roles of identified microorganisms in CAVS pathogenesis.

Figure 8. *Illustrates the general workflow of data analysis. It begins with the search of databases and ends with the diversity index and metabolic prediction. The workflow followed was designed to minimise the possibility of misidentification of microorganisms*.

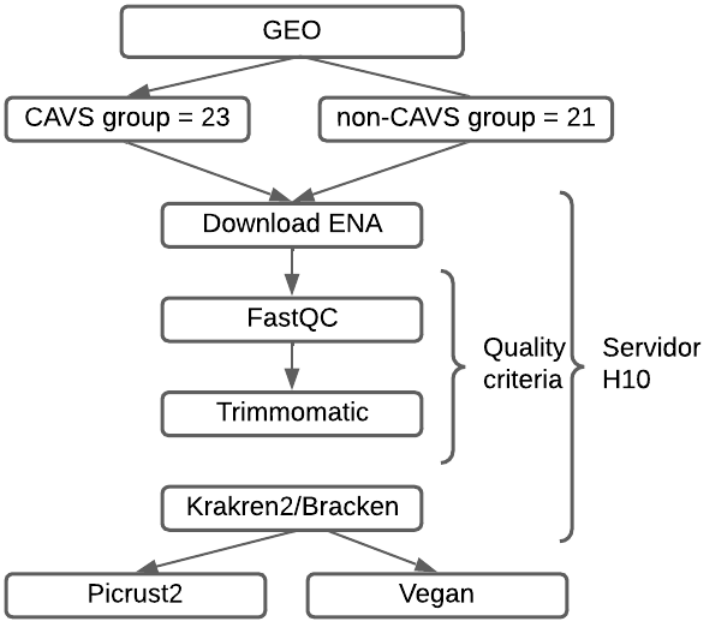


Figure 9. *Number and percentage of (a) phyla, (b) genera, and (c) species common to both CAVS and non-CAVS groups. The number of species in the CAVS group is greater than that in the non-CAVS group*.

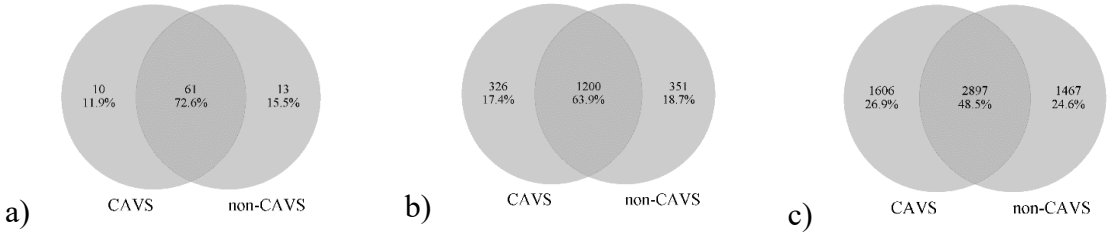


Figure 10. *Boxplot comparison of Shannon index between CAVS group and non-CAVS group. The horizontal axis shows the two categories being compared CAVS and non-CAVS. The values of the Shannon diversity index are shown between two groups*.

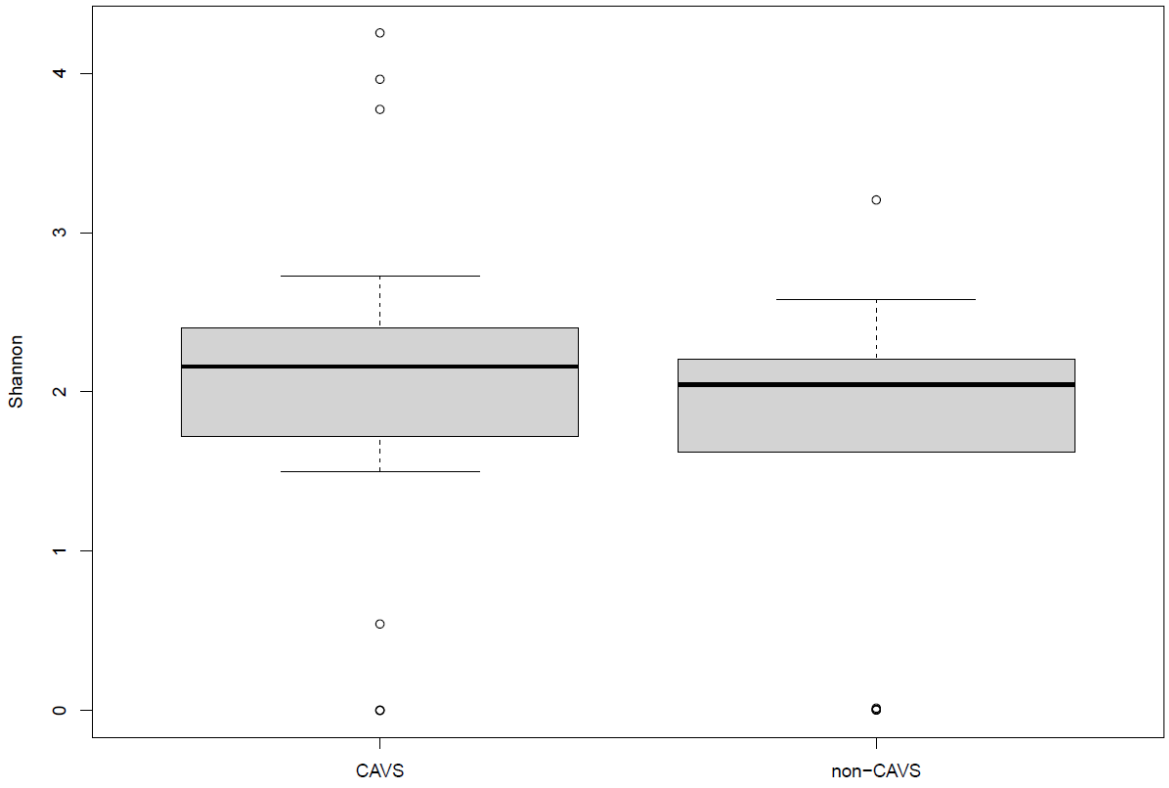


Figure 11. *Metabolic pathways between groups. Illustrates the distribution of various metabolic pathways between the CAVS and non-CAVS groups*.

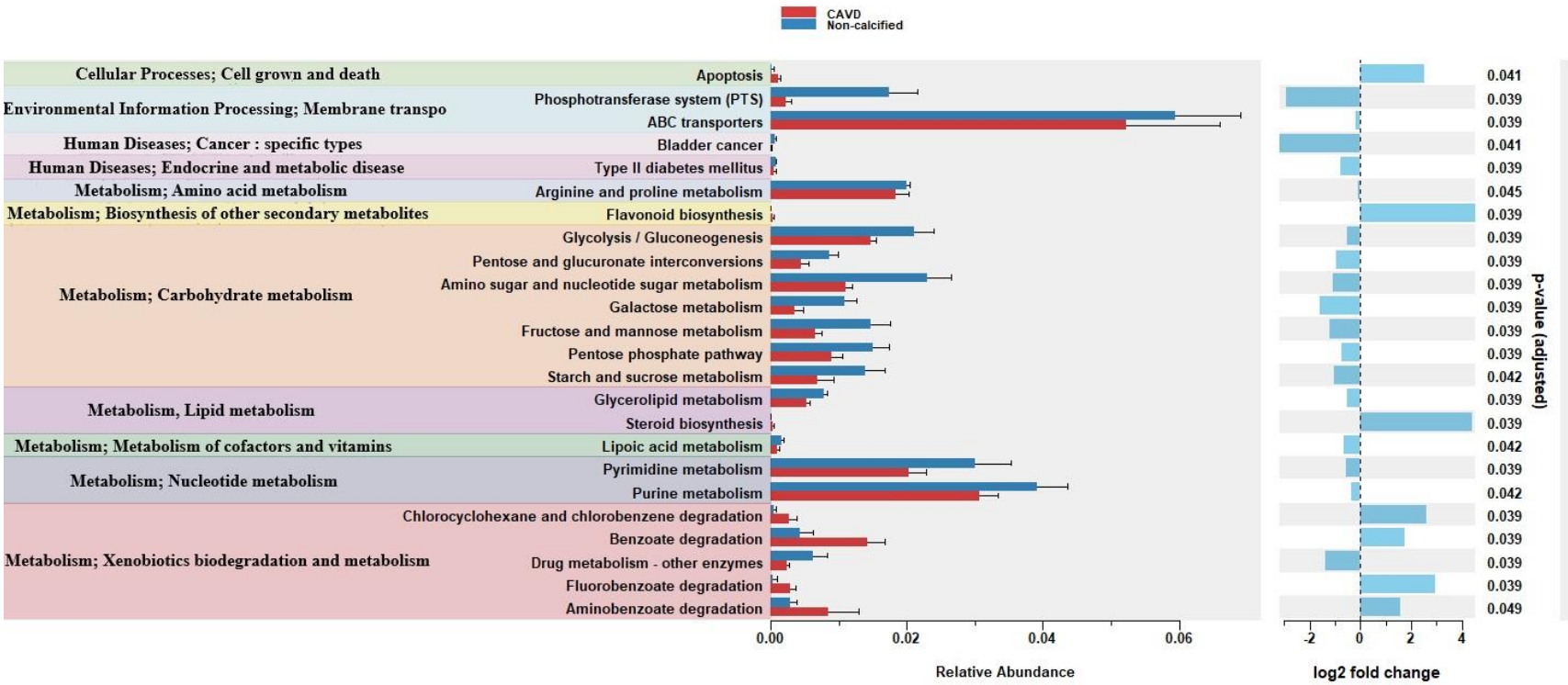


Table 5. *Data sets used for metagenomic analysis. The table summarizes the metagenomic data used, including information on the total number of samples analyzed, the sequencing platform employed, and the general categories of analyzed samples. Details regarding participant characteristics, such as age, sex, and specific references to the datasets*.

GEO ID	Country	n = 92	Platform	CAVS (n=23)	Non-CAVS (n=21)	Age	Sex	
							M	F
GSE138531(Kossar)	USA	6	HiSeq 2500	3	0	ND	--	--
GSE76718(Guauque)	Canada	27	HiSeq 2000	9	8	63.4±4.6	17	--
GSE148219(MacGrogan)	Spain	29	HiSeq 2500	7	8	53.3±20.5	14	1
GSE153555(Greene)	USA	30	HiSeq 2500	4	5	53.8±24.4	3	6

Table 6. *Number of total and classified reads in CAVS patients and non-CAVS individuals. The table provides general information about the overall read distribution across different groups and microbial categories.*

ID Sample CAVS	Bacterial reads	Viral reads	Fungal reads	Protozoan reads	ID Sample non-CAVS	Bacterial reads	Viral reads	Fungal reads	Protozoan reads
SRR12118630	11906	0	0	0	SRR12118617	15651	0	0	0
SRR12118632	25385	0	3	0	SRR12118620	10116	0	0	0
SRR12118634	14940	0	0	0	SRR12118622	10315	1	0	0
SRR12118636	9976	0	0	0	SRR12118624	12034	0	0	0
SRR3096626	5865	16	7	1	SRR12118626	19263	0	0	0
SRR3096627	4322	17	9	1	SRR3096635	5192	19	7	2
SRR3096628	9069	37	12	3	SRR3096636	5172	16	13	3
SRR3096629	5223	30	11	3	SRR3096637	10937	34	16	6
SRR3096630	2018	17	0	0	SRR3096638	4813	12	3	5
SRR3096631	1941	17	2	2	SRR3096639	1579	9	2	2
SRR3096632	6548	44	18	2	SRR3096640	2439	23	1	0
SRR3096633	1364	16	0	2	SRR3096641	7891	74	9	3
SRR3096634	9529	66	20	10	SRR3096642	12254	77	25	15
SRR10240188	1493668	342	2380	1786	SRR11497227	12382	321	64	13
SRR10240189	10270395	45	808	1141	SRR11497228	15061	361	55	7
SRR10240190	837550	649	3049	959	SRR11497229	2752	698	78	29
SRR11497230	1623	18	5	0	SRR11497239	6663	30	64	20
SRR11497231	1886	16	11	1	SRR11497240	5481	24	25	16
SRR11497232	3413	32	12	7	SRR11497241	1902	26	31	23
SRR11497234	10440	123	29	6	SRR11497246	819100	126	326	637
SRR11497235	4843	5	15	2	SRR11497247	725917	147	319	636
SRR11497236	5914	17	4	8	--	--	--	--	--
SRR11497237	5236	20	14	9	--	--	--	--	--
Mean	554046	66	279	171	Mean	81282	95	49	67
Median	5914	17	11	2	Median	10116	24	13	5
Std dev	2146402	146	793	464	Std dev	230325	171	94	189

Table 7. *Significantly different taxa between the CAVS and non-CAVS group. Summarizes the results of statistical analysis comparing the abundance of various taxonomic groups between CAVS and non-CAVS groups. Specific details, including exact taxa names, fold change values, p-values, and adjusted p-values*.

Level	Taxa	log2FoldChange	pvalue	padj
Genera	Standard (CAVS= 23, non-CAVS=21)			
	Sphingobacterium	-7.71	4.62E-08	3.88E-06
	Brevundimonas	-6.39	1.42E-07	5.97E-06
	Stutzerimonas	-7.02	2.25E-07	6.29E-06
	Salmonella	-7.68	3.59E-06	7.55E-05
	Novosphingobium	-4.84	4.73E-05	7.82E-04
	Yersinia	-9.77	5.59E-05	7.82E-04
	Rhizobium	-3.18	3.90E-04	4.68E-03
	Methylorubrum	-4.15	7.53E-04	7.91E-03
	Chryseobacterium	-3.48	1.33E-03	1.24E-02
	Microbacterium	-2.94	1.96E-03	1.65E-02
	Cupriavidus	-3.24	2.88E-03	2.20E-02
	Delftia	-3.83	3.30E-03	2.31E-02
	Curtobacterium	-3.38	3.60E-03	2.33E-02
	Vibrio	-2.38	3.92E-03	2.35E-02
	Pseudomonas	-2.51	5.40E-03	3.02E-02
	Caulobacter	-2.68	8.09E-03	4.21E-02
	Sphingobium	-3.32	8.52E-03	4.21E-02
	Greengenes			
	Cupriavidus	-26.17	6.33E-19	4.98E-17
	Sphingobacterium	-26.09	8.29E-19	4.98E-17
	Delftia	-26.88	6.81E-20	1.23E-17
	Sphingobium	-24.82	4.04E-17	1.82E-15
	Brevundimonas	-23.39	2.39E-15	8.62E-14
Specie	Standard			
	Yersinia pestis	-26.96	2.86E-20	3.64E-18
	Brucella melitensis	-24.21	1.24E-16	7.90E-15
	Chryseobacterium sp. PET-29	-22.87	5.37E-15	9.75E-14
	Brevundimonas sp. BT-123	-22.99	3.93E-15	8.47E-14
	Microbacterium sp. Y-01	-22.99	4.00E-15	8.47E-14
	Stutzerimonas kunmingensis	-23.68	5.70E-16	1.81E-14
	Sphingobium sp. PAMC28499	-23.84	3.61E-16	1.53E-14
	Pseudomonas sp. S150	-22.67	9.79E-15	1.38E-13
	Mesorhizobium japonicum	-22.74	7.91E-15	1.26E-13
	Anabaena sp. YBS01	-21.27	3.62E-13	4.60E-12
	Salmonella enterica	-7.62	1.43E-05	1.65E-04
	Burkholderia thailandensis	-7.47	4.67E-05	4.94E-04
	Acinetobacter sp. WCHA45	-11.83	5.15E-05	5.03E-04
	Stutzerimonas stutzeri	-6.92	2.73E-04	2.48E-03
	Sphingobacterium multivorum	-10.06	4.29E-04	3.63E-03
	Burkholderia mallei	-10.13	5.31E-04	4.21E-03
	Burkholderia cepacia	-7.2	2.72E-03	2.03E-02
	Burkholderia pseudomallei	-8.67	3.02E-03	2.08E-02
	Delftia acidovorans	-7.9	3.11E-03	2.08E-02
	Staphylococcus aureus	-2.68	3.82E-03	2.43E-02

Level	Taxa	log2FoldChange	pvalue	padj
	Acinetobacter junii	-6.37	5.15E-03	3.12E-02
	Brevundimonas diminuta	-7.87	6.55E-03	3.78E-02
	Microbacterium oxydans	-7.89	6.96E-03	3.84E-02
	Greengenes			
	Klebsiella oxytoca	29.84	3.65E-18	7.84E-17
	Salmonella enterica	30	2.43E-18	7.84E-17
	Trabulsiella farmeri	28.86	4.33E-17	6.20E-16
	Plesiomonas shigelloides	26.64	8.83E-15	6.33E-14
	Enterobacter cowanii	26.96	4.27E-15	3.68E-14
	Morganella morganii	27.04	3.49E-15	3.68E-14
	Haemophilus parainfluenzae	25.59	9.72E-14	5.23E-13
	Erwinia dispersa	26.22	2.33E-14	1.43E-13
	Brenneria quercina	24.38	1.30E-12	6.19E-12
	Brevundimonas diminuta	-12.93	1.97E-05	8.48E-05
	Sphingobacterium multivorum	-11.47	1.19E-04	4.64E-04
	Variovorax paradoxus	-10.82	2.52E-04	9.01E-04
	Acinetobacter schindleri	-10.53	4.22E-04	1.40E-03
	Pseudomonas veronii	-9.91	8.65E-04	2.66E-03
	Pseudomonas fragi	-9.98	1.13E-03	3.24E-03
	Methylobacterium hispanicum	-9.5	1.48E-03	3.99E-03
	Acinetobacter guillouiae	-9.39	1.71E-03	4.32E-03
	Aggregatibacter segnis	9.74	4.76E-03	1.08E-02
	Burkholderia gladioli	-9.28	5.01E-03	1.08E-02
	Serratia marcescens	9.1	4.82E-03	1.08E-02
	Serratia symbiotica	9.54	5.68E-03	1.16E-02
	Microbacterium lacticum	-8.92	7.02E-03	1.36E-02
	Sphingomonas yabuuchiae	-8.88	7.30E-03	1.36E-02
	Actinobacillus parahaemolyticus	8.48	1.45E-02	2.59E-02
	Corynebacterium kroppenstedtii	8.4	1.55E-02	2.67E-02
	Desulfovibrio aminophilus	8.31	1.67E-02	2.76E-02
	Sphingobium xenophagum	-7.87	1.74E-02	2.77E-02
	Pseudomonas balearica	-7.48	2.39E-02	3.67E-02
	Pseudomonas nitroreducens	-7.04	3.35E-02	4.97E-02

8. Conclusión general

En el desarrollo del proyecto del paisaje molecular y las comunidades microbianas asociadas con la estenosis aórtica por calcificación, identificamos genes candidatos potencialmente implicados en la enfermedad, a partir del análisis de la expresión diferencial de ARNm y ARNnc y de las variantes genéticas asociadas con la CAVS.. Estos genes se mapearon en vías moleculares específicas, revelando sus posibles funciones y modulación en CAVS, abriendo las puertas a terapias dirigidas. También se exploró el microbioma de tejidos de válvulas aórticas sanas y con CAVS, revelando variaciones en la diversidad y composición de microorganismos entre el estado patológico y normar de las válvulas, siendo las densidades microbianas más altas en el grupo CAVS, y la inferencia de las rutas metabólicas seguidas por los microorganismos identificados indica una tendencia a aumentar los procesos de degradación de compuestos aromáticos. Sugiere que la exposición a compuestos aromáticos podría ser un vínculo potencial para futuras investigaciones. Se identificó una posible superposición entre las vías moduladas por los genes identificados y las influenciadas por el microbioma, lo que sugiere mecanismos compartidos para las contribuciones genéticas y microbianas a CAVS, una indicación de que la microbiota podría estar involucrada en las alteraciones de las vías moleculares relacionadas con la enfermedad. Descifrar estas vías compartidas tiene un potencial terapéutico, lo que nos permite dirigirnos tanto a la predisposición genética como a la influencia del microbioma para el desarrollo de nuevas terapias CAVS.

Bibliografía

Abbood, S. J. A., Anvari, E., & Fateh, A. (2023). Association between interleukin-10 gene polymorphisms (rs1800871, rs1800872, and rs1800896) and severity of infection in different SARS-CoV-2 variants. Human genomics, 17(1), 19. https://doi.org/10.1186/s40246-023-00468-6

Ackah, R. L., Yasuhara, J., & Garg, V. (2023). Genetics of aortic valve disease. *Current Opinion in Cardiology*, *38*(3), 169–178. https://doi.org/10.1097/HCO.0000000000001028

Akdis, M., Aab, A., Altunbulakli, C., Azkur, K., Costa, R. A., Crameri, R., Duan, S., Eiwegger, T., Eljaszewicz, A., Ferstl, R., Frei, R., Garbani, M., Globinska, A., Hess, L., Huitema, C., Kubo, T., Komlosi, Z., Konieczna, P., Kovacs, N., … Akdis, C. A. (2016). Interleukins (from IL-1 to IL-38), interferons, transforming growth factor β, and TNF-α: Receptors, functions, and roles in diseases. Journal of Allergy and Clinical Immunology, 138(4), 984–1010. https://doi.org/10.1016/j.jaci.2016.06.033

Alushi, B., Curini, L., Christopher, M. R., Grubitzch, H., Landmesser, U., Amedei, A., & Lauten, A. (2020). Calcific Aortic Valve Disease-Natural History and Future Therapeutic Strategies. Frontiers in Pharmacology, 11(685), 1–12. https://doi.org/10.3389/fphar.2020.00685

Anger, T., Carson, W., Weyand, M., Daniel, W. G., Hoeher, M., & Garlichs, C. D. (2009). Atherosclerotic inflammation triggers osteogenic bone transformation in calcified and stenotic human aortic valves: still a matter of debate. Experimental and molecular pathology, 86(1), 10–17. https://doi.org/10.1016/j.yexmp.2008.11.001

Aurrecoechea, C., Barreto, A., Basenko, E. Y., Brestelli, J., Brunk, B. P., Cade, S., Crouch, K., Doherty, R., Falke, D., Fischer, S., Gajria, B., Harb, O. S., Heiges, M., Hertz-Fowler, C., Hu, S., Iodice, J., Kissinger, J. C., Lawrence, C., Li, W., … Zheng, J. (2017). EuPathDB: The eukaryotic pathogen genomics database resource. *Nucleic Acids Research*, *45*(D1), D581–D591. https://doi.org/10.1093/nar/gkw1105

Barrett, T., Wilhite, S. E., Ledoux, P., Evangelista, C., Kim, I. F., Tomashevsky, M., Marshall, K. A., Phillippy, K. H., Sherman, P. M., Holko, M., Yefanov, A., Lee, H., Zhang, N., Robertson, C. L., Serova, N., Davis, S., & Soboleva, A. (2013). NCBI GEO: Archive for functional genomics data sets--update. *Nucleic Acids Research*, *41*(Database issue), D991-995. https://doi.org/10.1093/nar/gks1193

Bartova, J., Sommerova, P., Lyuya-Mi, Y., Mysak, J., Prochazkova, J., Duskova, J., Janatova, T., & Podzimek, S. (2014). Periodontitis as a Risk Factor of Atherosclerosis. *Journal of Immunology Research*, *2014*, 1–9. https://doi.org/10.1155/2014/636893

Bateman, A., Martin, M.-J., Orchard, S., Magrane, M., Ahmad, S., Alpi, E., Bowler-Barnett, E. H., Britto, R., Bye-A-Jee, H., Cukura, A., Denny, P., Dogan, T., Ebenezer, T., Fan, J., Garmiri, P., da Costa Gonzales, L. J., Hatton-Ellis, E., Hussein, A., Ignatchenko, A., … Zhang, J. (2023). UniProt: the Universal Protein Knowledgebase in 2023. Nucleic Acids Research, 51(1), 523–531. https://doi.org/10.1093/nar/gkac1052

Bayram, A., Erdogan, M. B., Eksi, F., & Yamak, B. (2011). Demonstration of Chlamydophila pneumoniae, Mycoplasma pneumoniae, Cytomegalovirus, and Epstein-Barr virus in atherosclerotic coronary arteries, nonrheumatic calcific aortic and rheumatic stenotic mitral valves by polymerase chain reaction. *Anadolu Kardiyoloji Dergisi/The Anatolian Journal of Cardiology*. https://doi.org/10.5152/akd.2011.057

Bian, W., Wang, Z., Sun, C., & Zhang, D.-M. (2021). Pathogenesis and Molecular Immune Mechanism of Calcified Aortic Valve Disease. *Frontiers in Cardiovascular Medicine*, *8*, 765419. https://doi.org/10.3389/fcvm.2021.765419

Blaser, M. C., Kraler, S., Lüscher, T. F., & Aikawa, E. (2021). Multi-Omics Approaches to Define Calcific Aortic Valve Disease Pathogenesis. *Circulation Research*, *128*(9), 1371–1397. https://doi.org/10.1161/CIRCRESAHA.120.317979

Bolger, A. M., Lohse, M., & Usadel, B. (2014). Trimmomatic: A flexible trimmer for Illumina sequence data. *Bioinformatics*, *30*(15), 2114–2120. https://doi.org/10.1093/bioinformatics/btu170

Bosmans, J., Bleiziffer, S., Gerckens, U., Wenaweser, P., Brecker, S., Tamburino, C., & Linke, A. (2015). The Incidence and Predictors of Early- and Mid-Term Clinically Relevant Neurological Events After Transcatheter Aortic Valve Replacement in Real-World Patients. *Journal of the American College of Cardiology*, *66*(3), 209–217. https://doi.org/10.1016/j.jacc.2015.05.025

Bossé, Y., Miqdad, A., Fournier, D., Pépin, A., Pibarot, P., & Mathieu, P. (2009). Refining Molecular Pathways Leading to Calcific Aortic Valve Stenosis by Studying Gene Expression Profile of Normal and Calcified Stenotic Human Aortic Valves. Circulation: Cardiovascular Genetics, 2(5), 489–498. https://doi.org/10.1161/CIRCGENETICS.108.820795

Bourgeois, R., Bourgault, J., Despres, A. A., Perrot, N., Guertin, J., Girard, A., Mitchell, P. L., Gotti, C., Bourassa, S., Scipione, C. A., Gaudreault, N., Boffa, M. B., Koschinsky, M. L., Pibarot, P., Droit, A., Thériault, S., Mathieu, P., Bossé, Y., & Arsenault, B. J. (2021). Lipoprotein Proteomics and Aortic Valve Transcriptomics Identify Biological Pathways

Linking Lipoprotein(a) Levels to Aortic Stenosis. Metabolites, 11(7), 459. https://doi.org/10.3390/metabo11070459

Breitwieser, F. P., & Salzberg, S. L. (2020). Pavian: Interactive analysis of metagenomics data for microbiome studies and pathogen identification. *Bioinformatics (Oxford, England)*, *36*(4), 1303–1304. https://doi.org/10.1093/bioinformatics/btz715

Breyne, J., Juthier, F., Corseaux, D., Marechaux, S., Zawadzki, C., Jeanpierre, E., Ung, A., Ennezat, P. V., Susen, S., Van Belle, E., Le Marec, H., Vincentelli, A., Le Tourneau, T., & Jude, B. (2010). Atherosclerotic-like process in aortic stenosis: activation of the tissue factor-thrombin pathway and potential role through osteopontin alteration. Atherosclerosis, 213(2), 369–376. https://doi.org/10.1016/j.atherosclerosis.2010.07.047

Cambier, S., Gouwy, M., & Proost, P. (2023). The chemokines CXCL8 and CXCL12: molecular and functional properties, role in disease and efforts towards pharmacological intervention. Cellular & Molecular Immunology, 20(3), 217–251. https://doi.org/10.1038/s41423-023-00974-6

Cantor, E., Salas, R., Rosas, H., & Guauque-Olarte, S. (2021). Biological knowledge-slanted random forest approach for the classification of calcified aortic valve stenosis. BioData Mining, 14(35), 1–11. https://doi.org/10.1186/s13040-021-00269-4

Cardoso-Saldaña, G., Fragoso, J. M., Lale-Farjat, S., Torres-Tamayo, M., Posadas-Romero, C., Vargas-Alarcón, G., & Posadas-Sánchez, R. (2019). The rs10455872-G allele of the LPA gene is associated with high lipoprotein(a) levels and increased aortic valve calcium in a Mexican adult population. Genetics and molecular biology, 42(3), 519–525. https://doi.org/10.1590/1678-4685-GMB-2017-0371

Chen, H. Y., Engert, J. C., & Thanassoulis, G. (2019). Risk factors for valvular calcification. Current Opinion in Endocrinology, Diabetes & Obesity, 26(2), 96–102. https://doi.org/10.1097/MED.0000000000000471

Chen, H. Y., Cairns, B. J., Small, A. M., Burr, H. A., Ambikkumar, A., Martinsson, A., Thériault, S., Munter, H. M., Steffen, B., Zhang, R., Levinson, R. T., Shaffer, C. M., Rong, J., Sonestedt, E., Dufresne, L., Ljungberg, J., Näslund, U., Johansson, B., Ranatunga, D. K., Whitmer, R. A., … Thanassoulis, G. (2020). Association of FADS1/2 Locus Variants and Polyunsaturated Fatty Acids With Aortic Stenosis. JAMA cardiology, 5(6), 694–702. https://doi.org/10.1001/jamacardio.2020.0246

Chen, JH., Yip, CY. Y., Sone, ED., y Simmons, CA. (2009). Identification and characterization of aortic valve mesenchymal progenitor cells with robust osteogenic calcification potential. *The American Journal of Pathology*, *174*(3), 1109-1119. https://doi.org/10.2353/ajpath.2009.080750

Chen, P.-Y., Qin, L., & Simons, M. (2023). TGFβ signaling pathways in human health and disease. Frontiers in Molecular Biosciences, 10(1113061), 1–23. https://doi.org/10.3389/fmolb.2023.1113061

Cho, K. I., Sakuma, I., Sohn, I. S., Jo, S. H., & Koh, K. K. (2018). Inflammatory and metabolic mechanisms underlying the calcific aortic valve disease. In Atherosclerosis (Vol. 277, pp. 60–65). Elsevier Ireland Ltd. https://doi.org/10.1016/j.atherosclerosis.2018.08.029

Cho, S., Jang, I., Jun, Y., Yoon, S., Ko, M., Kwon, Y., Choi, I., Chang, H., Ryu, D., Lee, B., Kim, V. N., Kim, W., & Lee, S. (2012). miRGator v3.0: a microRNA portal for deep sequencing,

expression profiling and mRNA targeting. Nucleic Acids Research, 41(1), 252–257. https://doi.org/10.1093/nar/gks1168

Cochrane. (2020). Review Manager (RevMan). Version 5.4 (5.4; pp. 1–2). The Cochrane Collaboration. https://training.cochrane.org/online-learning/core-software/revman

Coffey, S., Williams, M. J., Phillips, L. V., Galvin, I. F., Bunton, R. W., & Jones, G. T. (2016). Integrated microRNA and messenger RNA analysis in aortic stenosis. Scientific reports, 6, 36904. https://doi.org/10.1038/srep36904

Coté, N., Mahmut, A., Bosse, Y., Couture, C., Pagé, S., Trahan, S., Boulanger, M.-C., Fournier, D., Pibarot, P., & Mathieu, P. (2013). Inflammation is associated with the remodeling of calcific aortic valve disease. *Inflammation*, *36*(3), 573–581. https://doi.org/10.1007/s10753-012-9579-6

Cotti, E., & Mercuro, G. (2015). Apical periodontitis and cardiovascular diseases: Previous findings and ongoing research. *International Endodontic Journal*, *48*(10), 926–932. https://doi.org/10.1111/iej.12506

Curini, L., Alushi, B., Christopher, M. R., Baldi, S., Di Gloria, L., Stefano, P., Laganà, A., Iannone, L., Grubitzsch, H., Landmesser, U., Ramazzotti, M., Niccolai, E., Lauten, A., & Amedei, A. (2023). The first taxonomic and functional characterization of human CAVD-associated microbiota. *Microbial Cell*, *10*(2), 36–48. https://doi.org/10.15698/mic2023.02.791

Cuschieri, S. (2019). The STROBE guidelines. Saudi Journal of Anaesthesia, 13(5), 31–34. https://doi.org/10.4103/sja.SJA_543_18

Davis, N. M., Proctor, D. M., Holmes, S. P., Relman, D. A., & Callahan, B. J. (2018). Simple statistical identification and removal of contaminant sequences in marker-gene and metagenomics data. Microbiome, 6(1), 226. https://doi.org/10.1186/s40168-018-0605-2

de Oliveira Sá, M. P. B., Cavalcanti, L. R. P., Perazzo, Á. M., Gomes, R. A. F., Clavel, M.-A., Pibarot, P., Biondi-Zoccai, G., Zhigalov, K., Weymann, A., Ruhparwar, A., & Lima, R. C. (2020). Calcific Aortic Valve Stenosis and Atherosclerotic Calcification. Current Atherosclerosis Reports, 22(2), 1–6. https://doi.org/10.1007/s11883-020-0821-7

de Santis, I. P., Lindenau, J. D., Ramos, R. B., Silva, T. R., Casanova, G., Oppermann, K., & Spritzer, P. M. (2020). C-reactive protein gene rs1205 polymorphism is associated with low-grade chronic inflammation in postmenopausal women. Women's midlife health, 6, 3. https://doi.org/10.1186/s40695-020-00051-2

DeSantis, T. Z., Hugenholtz, P., Larsen, N., Rojas, M., Brodie, E. L., Keller, K., Huber, T., Dalevi, D., Hu, P., & Andersen, G. L. (2006). Greengenes, a Chimera-Checked 16S rRNA Gene Database and Workbench Compatible with ARB. *Applied and Environmental Microbiology*, *72*(7), 5069–5072. https://doi.org/10.1128/AEM.03006-05

DeStefano, F., Anda, R. F., Kahn, H. S., Williamson, D. F., & Russell, C. M. (1993). Dental disease and risk of coronary heart disease and mortality. *BMJ*, *306*(6879), 688–691. https://doi.org/10.1136/bmj.306.6879.688

Dewhirst, F. E., Chen, T., Izard, J., Paster, B. J., Tanner, A. C., Yu, W. H., Lakshmanan, A., & Wade, W. G. (2010). The human oral microbiome. Journal of bacteriology, 192(19), 5002–5017. https://doi.org/10.1128/JB.00542-10

Dobaczewski, M., Chen, W., & Frangogiannis, N. G. (2011). Transforming growth factor (TGF)-β signaling in cardiac remodeling. Journal of Molecular and Cellular Cardiology, 51(4), 600–606. https://doi.org/10.1016/j.yjmcc.2010.10.033

Douglas, G. M., Maffei, V. J., Zaneveld, J. R., Yurgel, S. N., Brown, J. R., Taylor, C. M., Huttenhower, C., & Langille, M. G. I. (2020). PICRUSt2 for prediction of metagenome functions. Nature biotechnology, 38(6), 685–688. https://doi.org/10.1038/s41587-020-0548-6

Ducharme, V., Guauque-Olarte, S., Gaudreault, N., Pibarot, P., Mathieu, P., & Bossé, Y. (2013). NOTCH1 Genetic Variants in Patients with Tricuspid Calcific Aortic Valve Stenosis. The Journal of Heart Valve Disease, 22(1), 142–149.

Dweck, M. R., Boon, N. A., & Newby, D. E. (2012). Calcific Aortic Stenosis: A Disease of the Valve and the Myocardium. *Journal of the American College of Cardiology*, *60*(19), 1854–1863. https://doi.org/10.1016/j.jacc.2012.02.093

Engin, F., Yao, Z., Yang, T., Zhou, G., Bertin, T., Jiang, M. M., Chen, Y., Wang, L., Zheng, H., Sutton, R. E., Boyce, B. F., & Lee, B. (2008). Dimorphic effects of Notch signaling in bone homeostasis. Nature Medicine, 14(3), 299–305. https://doi.org/10.1038/nm1712

Ertas, F. S., Hasan, T., Ozdol, C., Gulec, S., Atmaca, Y., Tulunay, C., Karabulut, H., Kocum, H. T., Dincer, I., Kose, K. S., & Erol, C. (2007). Relationship Between Angiotensin-Converting Enzyme Gene Polymorphism and Severity of Aortic Valve Calcification. Mayo Clinic Proceedings, 82(8), 944–948. https://doi.org/10.4065/82.8.944

Fuster, V., Harrington, RA., Narula, J., y Eapen, ZJ. (2017). *Hurst's the heart: Vol. two volume set*. McGraw-Hill Education. https://pdfroom.com/books/hursts-the-heart/eKRd6XxA2Zp

García-Q., H., Carbonó-DelaHoz, E., & Barranco-Pérez, W. (2021). Diversidad beta del bosque seco tropical en el norte del Caribe colombiano. *Revista de la Academia Colombiana de Ciencias Exactas, Físicas y Naturales*. https://doi.org/10.18257/raccefyn.1267

Garg, V., Muth, A. N., Ransom, J. F., Schluterman, M. K., Barnes, R., King, I. N., Grossfeld, P. D., & Srivastava, D. (2005). Mutations in NOTCH1 cause aortic valve disease. Nature, 437(7056), 270–274. https://doi.org/10.1038/nature03940

Gaudreault, N., Ducharme, V., Lamontagne, M., Guauque-Olarte, S., Mathieu, P., Pibarot, P., & Bossé, Y. (2011). Replication of Genetic Association Studies in Aortic Stenosis in Adults. The American Journal of Cardiology, 108(9), 1305–1310. https://doi.org/10.1016/j.amjcard.2011.06.050

Godínez-Oviedo, A., Tamplin, M. L., Bowman, J. P., & Hernández-Iturriaga, M. (2024). Effects of intrinsic characteristics of Salmonella enterica strains isolated from foods and humans, and their interaction with food matrices during simulated gastric conditions. *International Journal of Food Microbiology*, *413*, 110584. https://doi.org/10.1016/j.ijfoodmicro.2024.110584

Gomila, M., Mulet, M., García-Valdés, E., & Lalucat, J. (2022). Genome-Based Taxonomy of the Genus Stutzerimonas and Proposal of S. frequens sp. Nov. And S. degradans sp. Nov. And Emended Descriptions of S. perfectomarina and S. chloritidismutans. *Microorganisms*, *10*(7), 1363. https://doi.org/10.3390/microorganisms10071363

Goumans, M.-J., & ten Dijke, P. (2018). TGF-β Signaling in Control of Cardiovascular Function. Cold Spring Harbor Perspectives in Biology, 10(a022210), 1–39. https://doi.org/10.1101/cshperspect.a022210

Greene, C. L., Jaatinen, K. J., Wang, H., Koyano, T. K., Bilbao, M. S., & Woo, Y. J. (2020). Transcriptional Profiling of Normal, Stenotic, and Regurgitant Human Aortic Valves. Genes, 11(789), 1–18. https://doi.org/10.3390/genes11070789

Guauque-Olarte, S., Droit, A., Tremblay-Marchand, J., Gaudreault, N., Kalavrouziotis, D., Dagenais, F., Seidman, J. G., Body, S. C., Pibarot, P., Mathieu, P., & Bossé, Y. (2016). RNA expression profile of calcified bicuspid, tricuspid, and normal human aortic valves by RNA sequencing. *Physiological Genomics*, *48*(10), 749–761. https://doi.org/10.1152/physiolgenomics.00041.2016

Guauque-Olarte, S., Messika-Zeitoun, D., Droit, A., Lamontagne, M., Tremblay-Marchand, J., Lavoie-Charland, E., Gaudreault, N., Arsenault, BJ., Dubé, MP., Tardif, JC., Body, SC., Seidman, JG., Boileau, C., Mathieu, P., Pibarot, P., y Bossé, Y. (2015). Calcium signaling pathway genes RUNX2 and CACNA1C are associated with calcific aortic valve disease. *Circulation. Cardiovascular Genetics*, *8*(6), 812-822. https://doi.org/10.1161/CIRCGENETICS.115.001145

Guddeti, R. R., Patil, S., Ahmed, A., Sharma, A., Aboeata, A., Lavie, C. J., & Alla, V. M. (2020). Lipoprotein(a) and calcific aortic valve stenosis: A systematic review. Progress in Cardiovascular Diseases, 63(4), 496–502. https://doi.org/10.1016/j.pcad.2020.06.002

Guo, H., Ingolia, N. T., Weissman, J. S., & Bartel, D. P. (2010). Mammalian microRNAs predominantly act to decrease target mRNA levels. Nature, 466(7308), 835–840. https://doi.org/10.1038/nature09267

Gupta, V. K., Paul, S., & Dutta, C. (2017). Geography, Ethnicity or Subsistence-Specific Variations in Human Microbiome Composition and Diversity. *Frontiers in Microbiology*, *8*, 1162. https://doi.org/10.3389/fmicb.2017.01162

Hadji, F., Boulanger, M. C., Guay, S. P., Gaudreault, N., Amellah, S., Mkannez, G., Bouchareb, R., Marchand, J. T., Nsaibia, M. J., Guauque-Olarte, S., Pibarot, P., Bouchard, L., Bossé, Y., & Mathieu, P. (2016). Altered DNA Methylation of Long Noncoding RNA H19 in Calcific Aortic Valve Disease Promotes Mineralization by Silencing NOTCH1. Circulation, 134(23), 1848–1862. https://doi.org/10.1161/CIRCULATIONAHA.116.023116

Han Y, Zhang J, Yang Z, Jian W, Zhu Y, Gao S, Liu Y, Li Y, He S, Zhang C, Li Y, You B, Liu J, Du J. Palmdelphin Deficiency Evokes NF-κB Signaling in Valvular Endothelial Cells and Aggravates Aortic Valvular Remodeling. JACC Basic Transl Sci. 2023 Aug 30;8(11):1457-1472. doi: 10.1016/j.jacbts.2023.06.004. PMID: 38093741; PMCID: PMC10714178.

Helgadottir, A., Thorleifsson, G., Gretarsdottir, S., Stefansson, OA., Tragante, V., Thorolfsdottir, RB., Jonsdottir, I., Bjornsson, T., Steinthorsdottir, V., Verweij, N., Nielsen, JB., Zhou, W., Folkersen, L., Martinsson, A., Heydarpour, M., Prakash, S., Oskarsson, G., Gudbjartsson, T., Geirsson, A., … Stefansson, K. (2018). Genome-wide analysis yields new loci associating with aortic valve stenosis. *Nature Communications*, *9*(1), 987. https://doi.org/10.1038/s41467-018-03252-6

Helske, S., Lindstedt, K. A., Laine, M., Mäyränpää, M., Werkkala, K., Lommi, J., Turto, H., Kupari, M., & Kovanen, P. T. (2004). Induction of local angiotensin II-producing systems in stenotic aortic valves. Journal of the American College of Cardiology, 44(9), 1859–1866. https://doi.org/10.1016/j.jacc.2004.07.054

Higgins, J., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M., & Welch, V. (2019). Cochrane Handbook for Systematic Reviews of Interventions (2nd ed., Vol. 1). John Wiley & Sons.

Higuchi, M. de L., Higuchi-Dos-Santos, M. H., Pierri, H., Palomino, S., Sambiase, N. V., Ramires, J. A. F., & Wajngarten, M. (2002). Mycoplasma pneumoniae and Chlamydia pneumoniae in calcified nodules of aortic stenotic valves. *Revista Do Instituto De Medicina Tropical De Sao Paulo*, *44*(4), 209–212. https://doi.org/10.1590/s0036-46652002000400005

Jang, S., Ishigami, K., Mergaert, P., & Kikuchi, Y. (2024). Ingested soil bacteria breach gut epithelia and prime systemic immunity in an insect. *Proceedings of the National Academy of Sciences*, *121*(11), e2315540121. https://doi.org/10.1073/pnas.2315540121

Jurasz, H., Pawłowski, T., & Perlejewski, K. (2021). Contamination Issue in Viral Metagenomics: Problems, Solutions, and Clinical Perspectives. Frontiers in microbiology, 12, 745076. https://doi.org/10.3389/fmicb.2021.745076

Kanehisa, M. (2000). KEGG: Kyoto Encyclopedia of Genes and Genomes. Nucleic Acids Research, 28(1), 27–30. https://doi.org/10.1093/nar/28.1.27

Kanehisa, M., Sato, Y., & Kawashima, M. (2022). KEGG mapping tools for uncovering hidden features in biological data. Protein Science, 31(1), 47–53. https://doi.org/10.1002/pro.4172

Kolltveit, K. M., Geiran, O., Tronstad, L., & Olsen, I. (n.d.). *M ultiple Bacteria in Calci c Aortic Valve Stenosis*.

Kossar, A. P., Anselmo, W., Grau, J. B., Liu, Y., Small, A., Carter, S. L., Salvador, L., Zhao, L., Cvijic, M. E., Li, Z., Yarde, M., Rioux, N., Rader, D. J., Levy, R. J., & Ferrari, G. (2020). Circulating and tissue matricellular RNA and protein expression in calcific aortic valve

disease. *Physiological Genomics*, *52*(4), 191–199. https://doi.org/10.1152/physiolgenomics.00104.2019

Kutikhin, A. G., Yuzhalin, A. E., Brusina, E. B., Ponasenko, A. V., Golovkin, A. S., & Barbarash, O. L. (2014). Genetic predisposition to calcific aortic stenosis and mitral annular calcification. Molecular Biology Reports, 41(9), 5645–5663. https://doi.org/10.1007/s11033-014-3434-9

Lafaurie, G. I., Neuta, Y., Ríos, R., Pacheco-Montealegre, M., Pianeta, R., Castillo, D. M., Herrera, D., Reyes, J., Diaz, L., Castillo, Y., Sanz, M., & Iniesta, M. (2022). Differences in the subgingival microbiome according to stage of periodontitis: A comparison of two geographic regions. PloS one, 17(8), e0273523. https://doi.org/10.1371/journal.pone.0273523

Laggerbauer, B., & Engelhardt, S. (2022). MicroRNAs as therapeutic targets in cardiovascular disease. Journal of Clinical Investigation, 132(11), 1–15. https://doi.org/10.1172/JCI159179

Lerman, D. A., Prasad, S., & Alotti, N. (2015). Calcific Aortic Valve Disease: Molecular Mechanisms And Therapeutic Approaches. European Cardiology Review, 10(2), 108–112. https://doi.org/10.15420/ecr.2015.10.2.108

Leung, L. Y., Chan, C. P. Y., Leung, Y. K., Jiang, H. L., Abrigo, J. M., Wang, D. F., Chung, J. S. H., Rainer, T. H., & Graham, C. A. (2014). Comparison of miR-124-3p and miR-16 for early diagnosis of hemorrhagic and ischemic stroke. Clinica Chimica Acta, 433, 139–144. https://doi.org/10.1016/j.cca.2014.03.007

Li, Y., Chen, Y., Li, J., Zhang, Z., Huang, C., Lian, G., Yang, K., Chen, S., Lin, Y., Wang, L., Huang, K., & Zeng, L. (2017). Co-delivery of microRNA-21 antisense oligonucleotides and gemcitabine using nanomedicine for pancreatic cancer therapy. Cancer science, 108(7), 1493–1503. https://doi.org/10.1111/cas.13267

Lindman, B. R., Clavel, M.-A., Mathieu, P., Iung, B., Lancellotti, P., Otto, C. M., & Pibarot, P. (2016). Calcific aortic stenosis. Nature Reviews Disease Primers, 2(16006), 1–28. https://doi.org/10.1038/nrdp.2016.6

Liu, R.-H., Ning, B., Ma, X.-E., Gong, W.-M., & Jia, T.-H. (2016). Regulatory roles of microRNA-21 in fibrosis through interaction with diverse pathways. Molecular Medicine Reports, 13(3), 2359–2366. https://doi.org/10.3892/mmr.2016.4834

Love, M. I., Huber, W., & Anders, S. (2014). Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. *Genome Biology*, *15*(12), 550. https://doi.org/10.1186/s13059-014-0550-8

Lu, J., Breitwieser, F. P., Thielen, P., & Salzberg, S. L. (2017). Bracken: Estimating species abundance in metagenomics data. *PeerJ Computer Science*, *3*, e104. https://doi.org/10.7717/peerj-cs.104

MacGrogan, D., Martínez-Poveda, B., Desvignes, J.-P., Fernandez-Friera, L., Gomez, M. J., Gil Vilariño, E., Callejas Alejano, S., Garcia-Pavia, P., Solis, J., Lucena, J., Salgado, D., Collod-Béroud, G., Faure, E., Théron, A., Torrents, J., Avierinos, J.-F., Montes, L., Dopazo, A., Fuster, V., … de la Pompa, J. L. (2020). Identification of a peripheral blood gene signature predicting aortic valve calcification. *Physiological Genomics*, *52*(12), 563–574. https://doi.org/10.1152/physiolgenomics.00034.2020

Mallah, M. A., Mallah, M. A., Liu, Y., Xi, H., Wang, W., Feng, F., & Zhang, Q. (2021). Relationship Between Polycyclic Aromatic Hydrocarbons and Cardiovascular Diseases: A Systematic Review. *Frontiers in Public Health*, *9*, 763706. https://doi.org/10.3389/fpubh.2021.763706

Matsui, M., Bouchareb, R., Storto, M., Hussain, Y., Gregg, A., Marx, S. O., & Pitt, G. S. (2022). Increased Ca2+ influx through CaV1.2 drives aortic valve calcification. JCI insight, 7(5), e155569. https://doi.org/10.1172/jci.insight.155569

McGovern, K., & Wilson, E. (2014). Role of Chemokines and Trafficking of Immune Cells in Parasitic Infections. Current Immunology Reviews, 9(3), 157–168. https://doi.org/10.2174/1573395509666131217000000

Misfeld, M., y Sievers, HH. (2007). Heart valve macro- and microstructure. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *362*(1484), 1421-1436. https://doi.org/10.1098/rstb.2007.2125

Moncla, LH.M., Briend, M., Bossé, Y. et al. Calcific aortic valve disease: mechanisms, prevention and treatment. Nat Rev Cardiol 20, 546–559 (2023). https://doi.org/10.1038/s41569-023-00845-7

Monroy-Muñoz, I., Muñoz-Medina, J., Fragoso, J., Santacruz-Tinoco, C., Sevilla-Montoya, R., Hidalgo-Bravo, A., Montes-Herrera, D., Bravo-Flores, E., & Angeles-Martínez, J. (2023). Genetic polymorphisms rs1800871 and rs1800872 of IL-10 gene are associated with dengue infection, especially with serotype 1 and DwoWS in Mexican population. Cytokine, 166, 156194. https://doi.org/10.1016/j.cyto.2023.156194

Moreno, C. E. (n.d.). *Métodos para medir la biodiversidad*.

Mourino-Alvarez, L., Baldan-Martin, M., Gonzalez-Calero, L., Martinez-Laborde, C., Sastre-Oliva, T., Moreno-Luna, R., Lopez-Almodovar, L. F., Sanchez, P. L., Fernandez-Aviles, F., Vivanco, F., Padial, L. R., Akerstrom, F., Alvarez-Llamas, G., de la Cuesta, F., & Barderas, M. G. (2016). Patients with calcific aortic stenosis exhibit systemic molecular evidence of ischemia, enhanced coagulation, oxidative stress and impaired cholesterol transport. International Journal of Cardiology, 225(1), 99–106. https://doi.org/10.1016/j.ijcard.2016.09.089

Nappi, F., Iervolino, A., Avtaar Singh, S. S., & Chello, M. (2021). MicroRNAs in Valvular Heart Diseases: Biological Regulators, Prognostic Markers and Therapeutical Targets. International Journal of Molecular Sciences, 22(12132), 1–18. https://doi.org/10.3390/ijms222212132

Nagy, E., Eriksson, P., Yousry, M., Caidahl, K., Ingelsson, E., Hansson, G. K., Franco-Cereceda, A., & Bäck, M. (2013). Valvular osteoclasts in calcification and aortic valve stenosis severity. International journal of cardiology, 168(3), 2264–2271. https://doi.org/10.1016/j.ijcard.2013.01.207

O'Brien, K. D. (2007). Epidemiology and genetics of calcific aortic valve disease. *Journal of Investigative Medicine: The Official Publication of the American Federation for Clinical Research*, *55*(6), 284–291. https://doi.org/10.2310/6650.2007.00010

Odom, A. R., Faits, T., Castro-Nallar, E., Crandall, K. A., & Johnson, W. E. (2023). Metagenomic profiling pipelines improve taxonomic classification for 16S amplicon sequencing data. *Scientific Reports*, *13*(1), 13957. https://doi.org/10.1038/s41598-023-40799-x

OHAT. (2019). Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. https://ntp.niehs.nih.gov/sites/default/files/ntp/ohat/pubs/handbookmarch2019_508.pdf

Oksanen J, Simpson G, Blanchet F, Kindt R, Legendre P, Minchin P, O'Hara R, Solymos P, Stevens M, Szoecs E, Wagner H, Barbour M, Bedward M, Bolker B, Borcard D, Carvalho G, Chirico M, De Caceres M, Durand S, Evangelista H, FitzJohn R, Friendly M, Furneaux B, Hannigan G, Hill M, Lahti L, McGlinn D, Ouellette M, Ribeiro Cunha E, Smith T, Stier A, Ter Braak C, Weedon J (2024). vegan: Community Ecology Package. R package version 2.6-5, https://github.com/vegandevs/vegan.

Oliveira, A. M., Morais, M. B. D., & Morais, T. B. (2012). A Novel and Potentially Valuable Exposure Measure: Escherichia coli in Oral Cavity and its Association with Child DayCare Center Attendance. *Journal of Tropical Pediatrics*, *58*(6), 517–520. https://doi.org/10.1093/tropej/fms025

Oliveira, F. A. F., Fernandes Forte, C. P., Silva, P. G. D. B., Lopes, C. D. B., Montenegro, R. C., Dos Santos, Â. K. C. R., Mota, M. R. L., Sousa, F. B., & Alves, A. P. N. N. (2019). Relationship of *Streptococcus mutans* with valvar cardiac tissue: A molecular and immunohistochemical study. *Journal of Oral Pathology & Medicine*, *48*(8), 745–753. https://doi.org/10.1111/jop.12929

Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan—a web and mobile app for systematic reviews. Systematic Reviews, 5(210), 1–10. https://doi.org/10.1186/s13643-016-0384-4

Ozkan, Ozcelik, Yildiz, & Budak. (2019). Lipoprotein(a) Gene Polymorphism Increases a Risk Factor for Aortic Valve Calcification. Journal of Cardiovascular Development and Disease, 6(31), 1–9. https://doi.org/10.3390/jcdd6030031

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ, 372(71), 1–9. https://doi.org/10.1136/bmj.n71

Park, J. Y., Seo, H., Kang, C.-S., Shin, T.-S., Kim, J. W., Park, J.-M., Kim, J. G., & Kim, Y.-K. (2022). Dysbiotic change in gastric microbiome and its functional implication in gastric carcinogenesis. *Scientific Reports*, *12*(1), 4285. https://doi.org/10.1038/s41598-022-08288-9

Pierri, H., Higuchi-dos-Santos, M. H., Higuchi, M. D. L., Palomino, S., Sambiase, N. V., Demarchi, L. M. M., Rodrigues, G. H. D. P., Nussbacher, A., Ramires, J. A. F., & Wajngarten, M. (2006). Density of Chlamydia pneumoniae is increased in fibrotic and calcified areas of degenerative aortic stenosis. *International Journal of Cardiology*, *108*(1), 43–47. https://doi.org/10.1016/j.ijcard.2005.04.022

Pinto, G., & Fragasso, G. (2022). Aortic valve stenosis: drivers of disease progression and drug targets for therapeutic opportunities. Expert Opinion on Therapeutic Targets, 26(7), 633–644. https://doi.org/10.1080/14728222.2022.2118576

Qiao, E., Huang, Z., & Wang, W. (2022). Exploring potential genes and pathways related to calcific aortic valve disease. Gene, 808(145987), 1–10. https://doi.org/10.1016/j.gene.2021.145987

R Core Team 2019. R: A language and environment for statistical computing. [Internet]. R Foundation for Statistical Computing. Vienna, Austria; 2019. https://www.r-project.org/.

Raddatz, M. A., Madhur, M. S., & Merryman, W. D. (2019). Adaptive immune cells in calcific aortic valve disease. American Journal of Physiology-Heart and Circulatory Physiology, 317(1), 141–155. https://doi.org/10.1152/ajpheart.00100.2019

Radke, P. W., Ortlepp, J. R., Merkelbach-Bruse, S., Messmer, B. J., Kaiser, A., Kronenberger, S., Handt, S., & Hanrath, P. (2002). Prevalence of cytomegalovirus in nonrheumatic stenotic aortic valves. *The American Journal of Cardiology*, *89*(4), 477–479. https://doi.org/10.1016/S0002-9149(01)02277-9

Rathan, S., Ankeny, C. J., Arjunon, S., Ferdous, Z., Kumar, S., Fernandez Esmerats, J., Heath, J. M., Nerem, R. M., Yoganathan, A. P., & Jo, H. (2016). Identification of side- and shear-dependent microRNAs regulating porcine aortic valve pathogenesis. Scientific Reports, 6(25397), 1–16. https://doi.org/10.1038/srep25397

Rodriguez-Esteban, R., & Jiang, X. (2017). Differential gene expression in disease: a comparison between high-throughput studies and the literature. BMC medical genomics, 10(1), 59. https://doi.org/10.1186/s12920-017-0293-y

Rysä, J. (2020). Novel insights into the molecular basis of calcific aortic valve disease. Journal of Thoracic Disease, 12(11), 6419–6421. https://doi.org/10.21037/jtd-20-1669

Salter, S. J., Cox, M. J., Turek, E. M., Calus, S. T., Cookson, W. O., Moffatt, M. F., Turner, P., Parkhill, J., Loman, N. J., & Walker, A. W. (2014). Reagent and laboratory contamination can critically impact sequence-based microbiome analyses. BMC biology, 12, 87. https://doi.org/10.1186/s12915-014-0087-z

Sayers, E. W., Beck, J., Bolton, E. E., Brister, J. R., Chan, J., Comeau, D. C., Connor, R., DiCuccio, M., Farrell, C. M., Feldgarden, M., Fine, A. M., Funk, K., Hatcher, E., Hoeppner, M., Kane, M., Kannan, S., Katz, K. S., Kelly, C., Klimke, W., … Sherry, S. T. (2024). Database resources of the National Center for Biotechnology Information. Nucleic Acids Research, 52(1), 33–43. https://doi.org/10.1093/nar/gkad1044

Schlotter, F., Halu, A., Goto, S., Blaser, MC., Body, SC., Lee, LH., Higashi, H., DeLaughter, DM., Hutcheson, JD., Vyas, P., Pham, T., Rogers, MA., Sharma, A., Seidman, CE., Loscalzo, J., Seidman, JG., Aikawa, M., Singh, SA., y Aikawa, E. (2018). Spatiotemporal Multi-Omics mapping generates a molecular atlas of the aortic valve and reveals networks driving disease. *Circulation*, *138*(4), 377-393.

Schulz, K. F., Altman, D. G., & Moher, D. (2010). CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Medicine, 8(18), 1–9. https://doi.org/10.1186/1741-7015-8-18

Shea, B. J., Reeves, B. C., Wells, G., Thuku, M., Hamel, C., Moran, J., Moher, D., Tugwell, P., Welch, V., Kristjansson, E., & Henry, D. A. (2017). AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ, 358(j4008), 1–9. https://doi.org/10.1136/bmj.j4008

Shi, Z., Li, X., Zhang, L., Luo, Y., Shrestha, B., & Hu, X. (2021). Potential novel modules and hub genes as prognostic candidates of thyroid cancer by weighted gene co-expression network analysis. International Journal of General Medicine, 14, 9433–9444. https://doi.org/10.2147/IJGM.S329128

Siedlecki, S. L. (2024). Confidence Interval and Odds Ratio: What Is It and How Should It Be Interpreted? Clinical Nurse Specialist, 38(1), 11–14. https://doi.org/10.1097/NUR.0000000000000787

Socransky, S. S., & Haffajee, A. D. (2005). Periodontal microbial ecology. *Periodontology 2000*, *38*(1), 135–187. https://doi.org/10.1111/j.1600-0757.2005.00107.x

Strong, M. J., Xu, G., Morici, L., Splinter Bon-Durant, S., Baddoo, M., Lin, Z., Fewell, C., Taylor, C. M., & Flemington, E. K. (2014). Microbial contamination in next generation sequencing: implications for sequence-based analysis of clinical samples. PLoS pathogens, 10(11), e1004437. https://doi.org/10.1371/journal.ppat.1004437

Sun, J.-Y., Hua, Y., Shen, H., Qu, Q., Kan, J.-Y., Kong, X.-Q., Sun, W., & Shen, Y.-Y. (2021). Identification of key genes in calcific aortic valve disease via weighted gene co-expression network analysis. BMC Medical Genomics, 14(135), 1–12. https://doi.org/10.1186/s12920-021-00989-w

Sun, L., Rajamannan, N. M., & Sucosky, P. (2013). Defining the role of fluid shear stress in the expression of early signaling markers for calcific aortic valve disease. *PloS One*, *8*(12), e84433. https://doi.org/10.1371/journal.pone.0084433

Svensson, S., Abrahamsson, A., Rodriguez, G. V., Olsson, A.-K., Jensen, L., Cao, Y., & Dabrosin, C. (2015). CCL2 and CCL5 Are Novel Therapeutic Targets for Estrogen-Dependent Breast Cancer. Clinical Cancer Research, 21(16), 3794–3805. https://doi.org/10.1158/1078-0432.CCR-15-0204

Szklarczyk, D., Gable, A. L., Lyon, D., Junge, A., Wyder, S., Huerta-Cepas, J., Simonovic, M., Doncheva, N. T., Morris, J. H., Bork, P., Jensen, L. J., & Mering, C. von. (2019). STRING

v11: protein–protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. Nucleic Acids Research, 47(1), 607–613. https://doi.org/10.1093/nar/gky1131

Teng, P., Xu, X., Ni, C., Yan, H., Sun, Q., Zhang, E., & Ni, Y. (2020). Identification of key genes in calcific aortic valve disease by integrated bioinformatics analysis. Medicine, 99(29), 1–9. https://doi.org/10.1097/MD.0000000000021286

Thanassoulis, G. (2016). Lipoprotein (a) in calcific aortic valve disease: from genomics to novel drug target for aortic stenosis. Journal of Lipid Research, 57(6), 917–924. https://doi.org/10.1194/jlr.R051870

Thanassoulis, G., Campbell, C. Y., Owens, D. S., Smith, J. G., Smith, A. V., Peloso, G. M., Kerr, K. F., Pechlivanis, S., Budoff, M. J., Harris, T. B., Malhotra, R., O'Brien, K. D., Kamstrup, P. R., Nordestgaard, B. G., Tybjaerg-Hansen, A., Allison, M. A., Aspelund, T., Criqui, M. H., Heckbert, S. R., … Post, W. S. (2013). Genetic Associations with Valvular Calcification and Aortic Stenosis. New England Journal of Medicine, 368(6), 503–512. https://doi.org/10.1056/NEJMoa1109034

Thériault, S., Dina, C., Messika-Zeitoun, D., Le Scouarnec, S., Capoulade, R., Gaudreault, N., Rigade, S., Li, Z., Simonet, F., Lamontagne, M., Clavel, M.-A., Arsenault, B. J., Boureau, A.-S., Lecointe, S., Baron, E., Bonnaud, S., Karakachoff, M., Charpentier, E., Fellah, I., … Schott, J.-J. (2019). Genetic Association Analyses Highlight IL6, ALPL, and NAV1 As 3 New Susceptibility Genes Underlying Calcific Aortic Valve Stenosis. *Circulation. Genomic and Precision Medicine*, *12*(10), e002617. https://doi.org/10.1161/CIRCGEN.119.002617

Vieceli Dalla Sega, F., Fortini, F., Severi, P., Rizzo, P., Gardi, I., Cimaglia, P., Rapezzi, C., Tavazzi, L., & Ferrari, R. (2022). Cardiac Calcifications: Phenotypes, Mechanisms, Clinical and Prognostic Implications. *Biology*, *11*(3), Article 3. https://doi.org/10.3390/biology11030414

Wang, P., Zhuang, L., Zhang, J., Fan, J., Luo, J., Chen, H., Wang, K., Liu, L., Chen, Z., & Meng, Z. (2013). The serum miR-21 level serves as a predictor for the chemosensitivity of advanced pancreatic cancer, and miR-21 expression confers chemoresistance by targeting FasL. Molecular oncology, 7(3), 334–345. https://doi.org/10.1016/j.molonc.2012.10.011

Wang, Y.-T., Li, Y., Ma, Y.-T., Yang, Y.-N., Ma, X., Li, X.-M., Liu, F., & Chen, B.-D. (2018). Association between apolipoprotein B genetic polymorphism and the risk of calcific aortic stenosis in Chinese subjects, in Xinjiang, China. Lipids in Health and Disease, 17(40), 1–7. https://doi.org/10.1186/s12944-018-0696-6

Wingett, S. W., & Andrews, S. (2018). FastQ Screen: A tool for multi-genome mapping and quality control. F1000Research, 7, 1338. https://doi.org/10.12688/f1000research.15931.2

Wood, D. E., Lu, J., & Langmead, B. (2019). Improved metagenomic analysis with Kraken 2. *Genome Biology*, *20*(1), 257. https://doi.org/10.1186/s13059-019-1891-0

Wypasek, E., Potaczek, D., & Undas, A. (2015). Association of the C-Reactive Protein Gene (CRP) rs1205 C>T Polymorphism with Aortic Valve Calcification in Patients with Aortic Stenosis. International Journal of Molecular Sciences, 16(10), 23745–23759. https://doi.org/10.3390/ijms161023745

Yang, C., Mai, J., Cao, X., Burberry, A., Cominelli, F., & Zhang, L. (2023). ggpicrust2: An R package for PICRUSt2 predicted functional profile analysis and visualization. *Bioinformatics*, *39*(8), btad470. https://doi.org/10.1093/bioinformatics/btad470

Yoshiba, S., Nakagawa, H., Kuwata, H., Nabuchi, A., Yaso, A., & Shirota, T. (2023). Metagenomic analysis of oral plaques and aortic valve tissues reveals oral bacteria associated with aortic stenosis. *Clinical Oral Investigations*, *27*(8), 4335–4344. https://doi.org/10.1007/s00784-023-05053-8

Yuan, D., Ahamed, A., Burgin, J., Cummins, C., Devraj, R., Gueye, K., Gupta, D., Gupta, V., Haseeb, M., Ihsan, M., Ivanov, E., Jayathilaka, S., Kadhirvelu, V. B., Kumar, M., Lathi, A., Leinonen, R., McKinnon, J., Meszaros, L., O'Cathail, C., … Cochrane, G. (2024). The European Nucleotide Archive in 2023. *Nucleic Acids Research*, *52*(D1), D92–D97. https://doi.org/10.1093/nar/gkad1067

Zeng, Z., Lan, T., Wei, Y., & Wei, X. (2022). CCL5/CCR5 axis in human diseases and related treatments. Genes & Diseases, 9(1), 12–27. https://doi.org/10.1016/j.gendis.2021.08.004

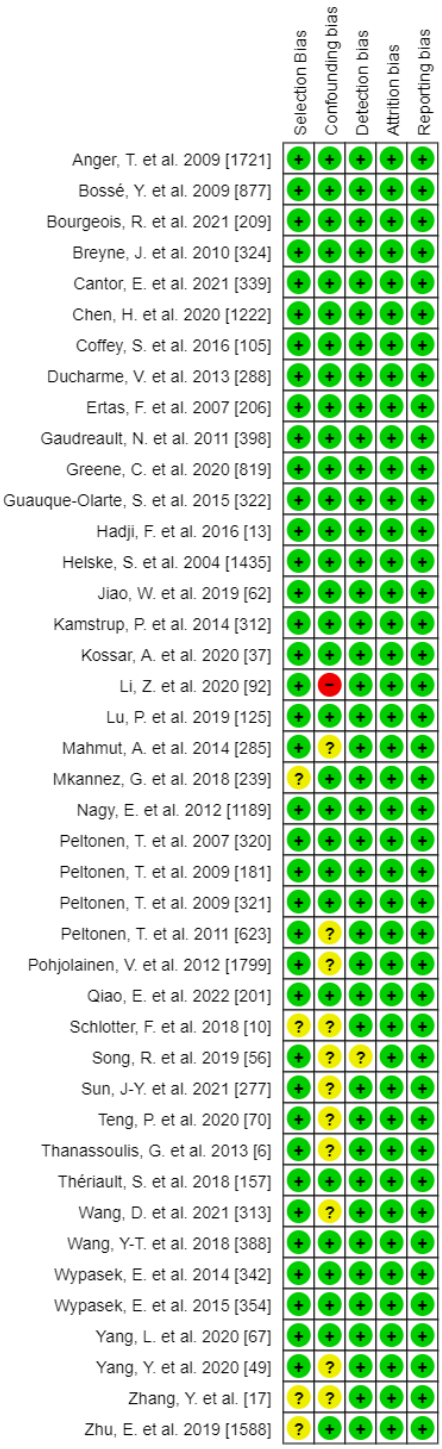
Zhang, Y., Ying, X., He, Y., Jiang, L., Zhang, S., Bartra, S. S., Plano, G. V., Klena, J. D., Skurnik, M., Chen, H., Cai, H., & Chen, T. (2020). Invasiveness of the Yersinia pestis ail protein contributes to host dissemination in pneumonic and oral plague. *Microbial Pathogenesis*, *141*, 103993. https://doi.org/10.1016/j.micpath.2020.103993

Zhu, E., Liu, Z., He, W., Deng, B., Shu, X., He, Z., Wu, X., Ke, X., & Nie, R. (2019). CC chemokine receptor 2 functions in osteoblastic transformation of valvular interstitial cells. Life Sciences, 228(1), 72–84. https://doi.org/10.1016/j.lfs.2019.04.050

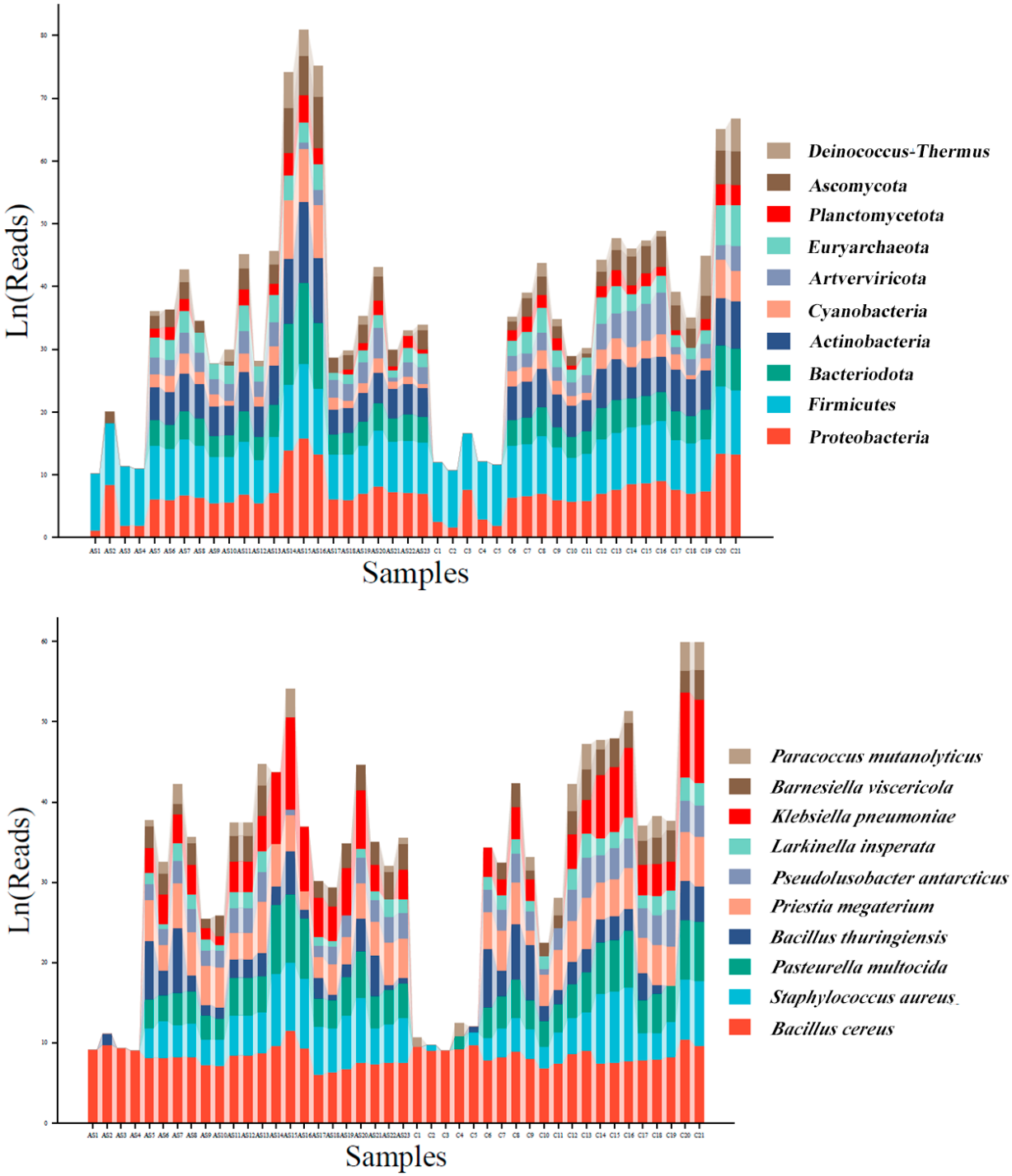
Zhu, Y., Zheng, M., Song, D., Ye, L., & Wang, X. (2015). Global comparison of chromosome X genes of pulmonary telocytes with mesenchymal stem cells, fibroblasts, alveolar type II cells, airway epithelial cells, and lymphocytes. Journal of Translational Medicine, 13(318), 1–11. https://doi.org/10.1186/s12967-015-0669-8

ANEXOS

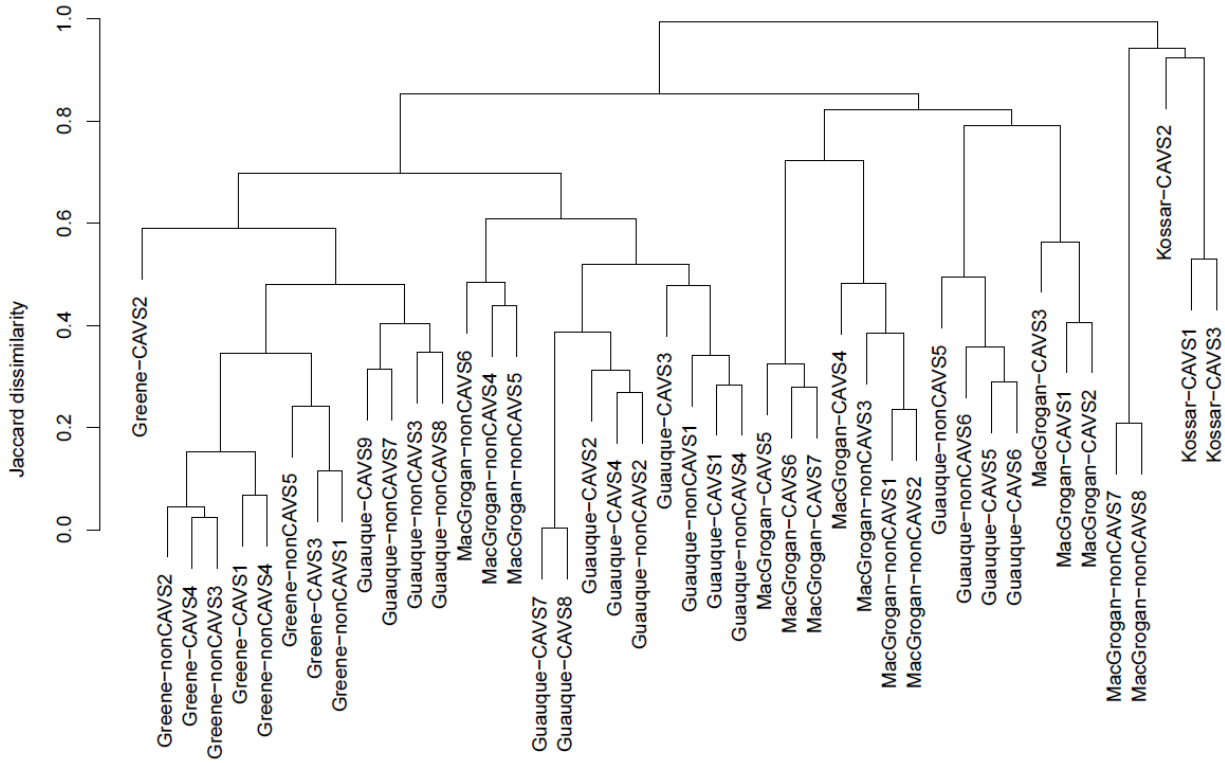
Supplementary 1. Supplementary Figure 1. Risk of bias for each article included in the present systematic review.



Supplementary 2. Supplementary Figure 2. Abundance of microorganisms for phyla and species is shown. The top 10 microorganisms with the highest number of samples and readings obtained after classification are shown. “AS” corresponds to the CAVS group and “C” corresponds to the non-CAVS group. The samples are listed according to the sequence followed in table 6 of the present document.



Supplementary 3. Supplementary Figure 3. Jaccard index of similarity between all samples, both CAVS and non-CAVS, aggregated by dataset and condition. CAVS denotes samples with calcific aortic valve stenosis, while non-CAVS denotes samples without calcific aortic valve stenosis. The author clearly identifies the dataset names, along with the condition and sample count for each dataset.



Supplementary 4. Supplementary table 1. Quality assessment of included papers. The criteria established according to STROBE and CONSORT 2010 guidelines guide are distributed in a matrix of presence and absence, with the criterion in question marked as present or absent in the article. The final column presents the total fulfilment of all the criteria established for each article.

Article	Item grade															Total
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Anger, T et al., 2009	1	1	1	1	0	1	1	0	1	0	1	0	1	1	0	10
Bossé et al., 2009	1	1	1	1	1	1	0	1	0	1	0	0	1	1	1	11
Bourgeois et al., 2021	1	1	1	1	1	1	0	1	0	1	1	0	0	1	1	11
Breyne et al., 2010	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	14
Cantor et al., 2021	1	1	1	1	0	0	1	1	0	1	1	0	1	1	0	10
Chen et al., 2020	1	1	1	1	1	1	1	1	0	0	0	0	1	1	1	11
Coffey et al., 2016	1	1	1	0	0	1	0	1	0	1	1	1	1	1	0	10
Ducharme et al., 2013	1	1	1	1	0	1	1	1	0	0	1	0	0	1	1	10
Ertas et al., 2007	1	1	1	1	1	1	0	1	0	1	1	0	0	1	1	11
Gaudreault et al., 2011	1	1	1	1	1	1	0	1	0	1	1	0	0	1	1	11
Greene et al., 2020	1	1	1	1	1	1	0	1	1	1	0	0	1	1	1	12
Guauque-Olarte et al., 2015	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	13
Hadji et al., 2016	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	14
Helske et al., 2004	1	1	1	1	1	1	0	1	0	1	0	0	1	1	0	10
Jiao et al., 2019	1	1	1	1	0	1	0	1	0	0	1	1	1	1	1	11
Kamstrup et al., 2014	1	1	1	1	1	1	1	1	0	1	1	0	0	1	0	11
Kossar et al., 2020	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	14
Li et al., 2020	1	1	1	1	1	1	0	1	0	1	1	1	1	1	0	12
Lu et al., 2019	1	1	1	1	0	1	1	1	0	1	0	1	1	1	0	11
Mahmut et al., 2014	1	1	1	1	0	1	0	1	0	0	1	1	1	1	0	10
Mkannez et al., 2018	1	1	1	1	1	1	1	1	0	1	1	0	0	1	1	12
Nagy et al., 2012	1	1	1	1	1	1	0	1	0	0	0	0	1	1	1	10
Peltonen et al., 2011	1	1	1	1	1	1	0	1	0	1	0	0	1	1	1	11
Peltonen et al., 2009	1	1	1	1	0	0	0	1	0	1	1	1	1	1	0	10
Peltonen et al., 2009	1	1	1	1	0	1	1	1	0	1	1	1	1	1	1	13
Peltonen et al., 2007	1	1	1	1	0	1	0	1	0	1	1	0	1	1	0	10
Pohjolainen et al., 2012	1	1	1	1	0	1	0	1	0	0	1	1	0	1	1	10
Qiao et al., 2022	1	1	1	1	1	1	0	1	0	0	1	1	0	1	0	10
Schlotter et al., 2018	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	14
Song et al., 2019	1	0	1	1	1	1	0	1	1	0	1	1	1	1	1	12
Sun et al., 2021	1	1	1	0	1	1	0	1	0	1	1	1	1	1	0	11
Teng et al., 2020	1	1	1	1	0	1	1	0	0	1	1	1	1	1	0	11
Thanassoulis et al., 2013	1	1	1	0	1	1	1	0	1	1	1	1	1	1	0	12
Thériault et al., 2018	1	1	1	1	0	1	0	1	0	0	1	1	1	1	0	10
Wang et al 2021	1	1	1	1	0	1	0	1	0	1	1	0	1	1	0	10
Wang et al 2018	1	1	1	1	1	1	0	1	0	1	1	0	1	1	0	11
Wypasek et al., 2014	1	1	1	1	0	1	0	0	0	1	1	0	1	1	1	10
Wypasek et al., 2015	1	1	1	1	0	1	1	1	0	1	0	0	1	1	0	10
Yang et al., 2020	1	1	1	0	0	1	0	1	0	0	1	1	1	1	1	10
Yang et al., 2020	1	1	1	1	1	1	1	1	0	0	1	1	1	1	0	12
Zhang and Ma, 2019	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	14
Zhu et al., 2019	1	1	1	1	1	1	0	1	0	1	0	0	1	1	0	10

(1) answer the research question of the present systematic review (genetic variants, mRNA, miRNA and proteins on CAVD) presenting specific results for varians that influence the mechanisms related to CAVD, (2) Indicate the study's design with a commonly used term in the title or the abstract, (3) Provide in the abstract an informative and balanced summary of what was done and what was found, (4) State specific objectives, including any prespecified hypotheses, (5) Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, (6) Describes the selected sample: cellular, tissues or sequences of animal or humans. Protein obtained and the intervention for each group, and size, (7) Clearly define all outcomes and potential confounders. Give diagnostic criteria, if applicable, (8) For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group, (9) Describe any efforts to address potential sources of bias, (10) Explain how the study size was arrived at (cases-controls), (11) Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why, (12) Describe all statistical methods, including those used to control for confounding, (13) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (case-controls), (14) Summarize key results with reference to this review question, (15) Discuss limitations of the study, considering sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.

Supplementary 5. Supplementary table 2. List of differentially expressed genes between CAVS and Non-CAVS. It reports 510 upregulated genes and 399 downregulated genes. The column indicates the validated gene symbol according to the NCBI and Uniprot databases. The sense and authors of each gene are indicated in the respective columns, along with the diagnosis and aortic valve configuration for the samples used by the different authors.

Gene	Sense	Author	Diagnostic	Configuration
A2M	upregulated	Qiao et al. 2022	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
ABCA8	downregulated	Bossé et al. 2009	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
ABCA9	downregulated	Bossé et al. 2009	AS	TAV
ABCG1	upregulated	Bossé et al. 2009	AS	TAV
ABLIM1	downregulated	Qiao et al. 2022	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
ABTB2	downregulated	Bossé et al. 2009	AS	TAV
ACACB	downregulated	Zhu et al. 2019	AS	BAV/TAV
ACADVL	downregulated	Zhang y Ma. 2019	AS	BAV/TAV
ACAN	downregulated	Bossé et al. 2009	AS	TAV
		Kossar et al. 2020	AS	TAV
ACAP1	downregulated	Bossé et al. 2009	AS	TAV
ACE	upregulated	Helske et al. 2004	AS	BAV/TAV/CAV
ACE2	downregulated	Peltonen et al. 2011	AS	BAV/TAV
ACSM3	downregulated	Bossé et al. 2009	AS	TAV
ADAM12	upregulated	Bossé et al. 2009	AS	TAV
ADAM19	upregulated	Bossé et al. 2009	AS	TAV
ADAM28	upregulated	Bossé et al. 2009	AS	TAV
ADAM8	upregulated	Bossé et al. 2009	AS	TAV
ADAMTS15	downregulated	Zhu et al. 2019	AS	BAV/TAV
ADAMTS5	upregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
ADCYAP1	upregulated	Bossé et al. 2009	AS	TAV
ADGRB3	downregulated	Bossé et al. 2009	AS	TAV
ADGRE2	upregulated	Zhu et al. 2019	AS	BAV/TAV
ADGRG2	downregulated	Qiao et al. 2022	AS	TAV
ADH1A	downregulated	Bossé et al. 2009	AS	TAV
ADH1B	downregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
ADRB1	downregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
AFAP1-AS1	upregulated	Hadji et al. 2016	AS	TAV
AFF1	downregulated	Bossé et al. 2009	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
AGTR1	downregulated	Bossé et al. 2009	AS	TAV
		Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
		Peltonen et al. 2011	AS	BAV/TAV
AGTR2	downregulated	Peltonen et al. 2011	AS	BAV/TAV
AIF1	upregulated	Qiao et al. 2022	AS	TAV
AIF1L	downregulated	Bossé et al. 2009	AS	TAV
AKAP12	downregulated	Bossé et al. 2009	AS	TAV
AKAP13	downregulated	Bossé et al. 2009	AS	TAV
ALDH1L1	downregulated	Greene et al. 2020	AS	BAV/TAV
AMER2	downregulated	Zhu et al. 2019	AS	BAV/TAV
AMPD3	upregulated	Bossé et al. 2009	AS	TAV
		Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
ANGPT2	upregulated	Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
ANGPTL2	upregulated	Bossé et al. 2009	AS	TAV
ANGPTL7	downregulated	Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
		Zhang y Ma. 2019	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
ANK3	downregulated	Bossé et al. 2009	AS	TAV

Gene	Sense	Author	Diagnostic	Configuration
ANKRD10	upregulated	Bossé et al. 2009	AS	TAV
ANLN	upregulated	Bossé et al. 2009	AS	TAV
ANO3	downregulated	Bossé et al. 2009	AS	TAV
ANPEP	upregulated	Qiao et al. 2022	AS	TAV
AOAH	upregulated	Qiao et al. 2022	AS	TAV
AOC3	upregulated	Anger et al. 2009	AS	TAV
AOX1	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
APOBEC3B	upregulated	Bossé et al. 2009	AS	TAV
APOas1	downregulated	Hadji et al. 2016	AS	TAV
APOC1	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
APOL6	downregulated	Bossé et al. 2009	AS	TAV
AQP7P1	downregulated	Greene et al. 2020	AS	BAV/TAV
AQP7P2	downregulated	Greene et al. 2020	AS	BAV/TAV
AQP7P3	downregulated	Greene et al. 2020	AS	BAV/TAV
AQP7P4	downregulated	Greene et al. 2020	AS	BAV/TAV
AR	downregulated	Zhu et al. 2019	AS	BAV/TAV
ARFGEF3	downregulated	Zhu et al. 2019	AS	BAV/TAV
ARHGAP15	upregulated	Bossé et al. 2009	AS	TAV
ARHGAP30	upregulated	Teng et al. 2020	AS	BAV/TAV
		Zhang y Ma. 2019	AS	BAV/TAV
ARHGAP9	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
ARHGDIA	upregulated	Bossé et al. 2009	AS	TAV
ARHGEF26	downregulated	Bossé et al. 2009	AS	TAV
ARID5B	upregulated	Bossé et al. 2009	AS	TAV
ARL4C	upregulated	Bossé et al. 2009	AS	TAV
		Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
ART4	downregulated	Bossé et al. 2009	AS	TAV
ATOH8	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
ATOSA	downregulated	Bossé et al. 2009	AS	TAV
ATP11B	downregulated	Bossé et al. 2009	AS	TAV
ATP6V0D2	upregulated	Cantor et al. 2021	AS	TAV
ATP8A1	downregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
B2M	upregulated	Kossar et al. 2020	AS	TAV
B4GALT5	upregulated	Bossé et al. 2009	AS	TAV
BAMBI	downregulated	Qiao et al. 2022	AS	TAV
BASP1	upregulated	Bossé et al. 2009	AS	TAV
BBLN	upregulated	Bossé et al. 2009	AS	TAV
BCAR3	downregulated	Qiao et al. 2022	AS	TAV
BCAT1	upregulated	Sun et al. 2021	AS	BAV/TAV
BCL11B	upregulated	Bossé et al. 2009	AS	TAV
BCL3	upregulated	Bossé et al. 2009	AS	TAV
BCL6	downregulated	Bossé et al. 2009	AS	TAV
BCLAF1	downregulated	Bossé et al. 2009	AS	TAV
BCO2	downregulated	Bossé et al. 2009	AS	TAV
BCOR	upregulated	Bossé et al. 2009	AS	TAV
BDKRB2	upregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
BEX2	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
BGN	upregulated	Bossé et al. 2009	AS	TAV
BIRC6	upregulated	Bossé et al. 2009	AS	TAV
BMX	downregulated	Bossé et al. 2009	AS	TAV
BRINP3	downregulated	Bossé et al. 2009	AS	TAV
BTC	downregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
BTG1	upregulated	Bossé et al. 2009	AS	TAV
BTK	upregulated	Qiao et al. 2022	AS	TAV

Gene	Sense	Author	Diagnostic	Configuration
C16orf54	upregulated	Bossé et al. 2009	AS	TAV
C1orf162	upregulated	Qiao et al. 2022	AS	TAV
C1orf21	downregulated	Bossé et al. 2009	AS	TAV
C1QA	upregulated	Kossar et al. 2020	AS	TAV
C1QC	upregulated	Teng et al. 2020	AS	BAV/TAV
C1QTNF5	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
C2orf88	downregulated	Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
C5orf46	upregulated	Qiao et al. 2022	AS	TAV
C6	downregulated	Qiao et al. 2022	AS	TAV
		Sun et al. 2021	AS	BAV/TAV
		Teng et al. 2020	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
C7	downregulated	Qiao et al. 2022	AS	TAV
C8orf88	downregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
CA12	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Sun et al. 2021	AS	BAV/TAV
		Zhang y Ma. 2019	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
CAB39L	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
CACNA1C	upregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
CACNAH1	upregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
CADM1	upregulated	Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
CADM2	downregulated	Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
CADM3	downregulated	Bossé et al. 2009	AS	TAV
CARHSP1	upregulated	Bossé et al. 2009	AS	TAV
CASP1	upregulated	Anger et al. 2009	AS	TAV
CASP10	downregulated	Anger et al. 2009	AS	TAV
CASP8	downregulated	Anger et al. 2009	AS	TAV
CAVIN2	downregulated	Bossé et al. 2009	AS	TAV
CBLN1	downregulated	Cantor et al. 2021	AS	TAV
		Greene et al. 2020	AS	BAV/TAV
		Qiao et al. 2022	AS	TAV
CBLN4	upregulated	Greene et al. 2020	AS	BAV/TAV
CBX3	upregulated	Bossé et al. 2009	AS	TAV
CCDC181	upregulated	Bossé et al. 2009	AS	TAV
CCDC80	upregulated	Bossé et al. 2009	AS	TAV
CCL14	upregulated	Bossé et al. 2009	AS	TAV
CCL15	upregulated	Bossé et al. 2009	AS	TAV
CCL23	upregulated	Bossé et al. 2009	AS	TAV
CCL26	upregulated	Anger et al. 2009	AS	TAV
CCL4	upregulated	Bossé et al. 2009	AS	TAV
		Yang et al. 2020	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
CCL5	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
		Yang et al. 2020	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
CCN4	upregulated	Bossé et al. 2009	AS	TAV
CCN5	downregulated	Qiao et al. 2022	AS	TAV
CCNC	upregulated	Anger et al. 2009	AS	TAV
CCND2	downregulated	Anger et al. 2009	AS	TAV
CCNG1	downregulated	Anger et al. 2009	AS	TAV
CCR2	upregulated	Zhu et al. 2019	AS	BAV/TAV
CCR5	upregulated	Bossé et al. 2009	AS	TAV
CCR7	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
CCT7	downregulated	Yang et al. 2020	AS	BAV/TAV

Gene	Sense	Author	Diagnostic	Configuration
CD14	upregulated	Kossar et al. 2020	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
CD209	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
CD226	downregulated	Bossé et al. 2009	AS	TAV
CD247	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
CD248	upregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
CD27	upregulated	Qiao et al. 2022	AS	TAV
CD28	upregulated	Bossé et al. 2009	AS	TAV
CD300A	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
CD300LF	upregulated	Bossé et al. 2009	AS	TAV
CD3G	upregulated	Bossé et al. 2009	AS	TAV
CD44	upregulated	Bossé et al. 2009	AS	TAV
CD48	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
CD53	upregulated	Qiao et al. 2022	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
CD72	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
CD74	upregulated	Teng et al. 2020	AS	BAV/TAV
		Zhang y Ma. 2019	AS	BAV/TAV
CD79A	upregulated	Cantor et al. 2021	AS	TAV
CD84	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
CD86	upregulated	Zhu et al. 2019	AS	BAV/TAV
CDC7	upregulated	Bossé et al. 2009	AS	TAV
CDH19	downregulated	Bossé et al. 2009	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
		Zhang y Ma. 2019	AS	BAV/TAV
CDH6	upregulated	Greene et al. 2020	AS	BAV/TAV
CDK1	upregulated	Bossé et al. 2009	AS	TAV
CDK4	downregulated	Yang et al. 2020	AS	BAV/TAV
CDKN3	upregulated	Bossé et al. 2009	AS	TAV
CDO1	downregulated	Bossé et al. 2009	AS	TAV
CECR2	downregulated	Bossé et al. 2009	AS	TAV
CELF2	downregulated	Bossé et al. 2009	AS	TAV
CEMIP	upregulated	Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
CEP55	upregulated	Bossé et al. 2009	AS	TAV
CERCAM	upregulated	Bossé et al. 2009	AS	TAV
CERKL	upregulated	Bossé et al. 2009	AS	TAV
CFD	downregulated	Qiao et al. 2022	AS	TAV
CFL1	upregulated	Bossé et al. 2009	AS	TAV
CGNL1	downregulated	Zhu et al. 2019	AS	BAV/TAV
CHAD	downregulated	Qiao et al. 2022	AS	TAV
CHODL	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
CHST7	downregulated	Qiao et al. 2022	AS	TAV
CHST9	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
CIDEC	downregulated	Qiao et al. 2022	AS	TAV
CKLF3	downregulated	Anger et al. 2009	AS	TAV
CKS2	upregulated	Bossé et al. 2009	AS	TAV
CLC	upregulated	Bossé et al. 2009	AS	TAV
CLDN11	downregulated	Bossé et al. 2009	AS	TAV

Gene	Sense	Author	Diagnostic	Configuration
		Qiao et al. 2022	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
CLDN5	upregulated	Qiao et al. 2022	AS	TAV
CLEC3B	downregulated	Bossé et al. 2009	AS	TAV
CLEC7A	upregulated	Zhu et al. 2019	AS	BAV/TAV
CLK4	downregulated	Bossé et al. 2009	AS	TAV
CLSTN2	downregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
CMA1	upregulated	Greene et al. 2020	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
CMYA5	downregulated	Qiao et al. 2022	AS	TAV
CNP	downregulated	Peltonen et al. 2007	AS	BAV/TAV
CNR1	downregulated	Bossé et al. 2009	AS	TAV
CNTFR	downregulated	Greene et al. 2020	AS	BAV/TAV
CNTN1	downregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
CNTN4	downregulated	Bossé et al. 2009	AS	TAV
COBL	downregulated	Bossé et al. 2009	AS	TAV
COL15A1	upregulated	Bossé et al. 2009	AS	TAV
		Sun et al. 2021	AS	BAV/TAV
COL18A1	upregulated	Bossé et al. 2009	AS	TAV
COL1A2	upregulated	Sun et al. 2021	AS	BAV/TAV
COL4A1	upregulated	Bossé et al. 2009	AS	TAV
		Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
COL4A2	upregulated	Bossé et al. 2009	AS	TAV
		Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
COL4A3	downregulated	Bossé et al. 2009	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
COL4A4	downregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
COL4A5	downregulated	Zhu et al. 2019	AS	BAV/TAV
COL5A1	upregulated	Bossé et al. 2009	AS	TAV
		Sun et al. 2021	AS	BAV/TAV
COL5A2	upregulated	Bossé et al. 2009	AS	TAV
		Sun et al. 2021	AS	BAV/TAV
COL6A2	upregulated	Bossé et al. 2009	AS	TAV
COL9A3	downregulated	Bossé et al. 2009	AS	TAV
COLGALT2	downregulated	Qiao et al. 2022	AS	TAV
COMP	upregulated	Qiao et al. 2022	AS	TAV
CORIN	downregulated	Bossé et al. 2009	AS	TAV
CORO1A	upregulated	Bossé et al. 2009	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
		Zhang y Ma. 2019	AS	BAV/TAV
COTL1	upregulated	Qiao et al. 2022	AS	TAV
CPAMD8	downregulated	Bossé et al. 2009	AS	TAV
CPVL	upregulated	Bossé et al. 2009	AS	TAV
CR1	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
CR1L	upregulated	Bossé et al. 2009	AS	TAV
CRTAC1	upregulated	Qiao et al. 2022	AS	TAV
CSE1L	downregulated	Yang et al. 2020	AS	BAV/TAV
CSF1R	upregulated	Qiao et al. 2022	AS	TAV
CSF3	upregulated	Anger et al. 2009	AS	TAV
CSK	upregulated	Qiao et al. 2022	AS	TAV
CST6	upregulated	Qiao et al. 2022	AS	TAV
CST7	upregulated	Bossé et al. 2009	AS	TAV
		Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
CTSB	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
CTSC	upregulated	Bossé et al. 2009	AS	TAV
CTSD	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
CTSZ	upregulated	Bossé et al. 2009	AS	TAV

Gene	Sense	Author	Diagnostic	Configuration
CTTNBP2	downregulated	Bossé et al. 2009	AS	TAV
CX3CR1	upregulated	Qiao et al. 2022	AS	TAV
CXCL1	upregulated	Bossé et al. 2009	AS	TAV
CXCL10	upregulated	Yang et al. 2020	AS	BAV/TAV
CXCL12	upregulated	Bossé et al. 2009	AS	TAV
		Kossar et al. 2020	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
CXCL14	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
CXCL9	upregulated	Qiao et al. 2022	AS	TAV
CXCR1	upregulated	Anger et al. 2009	AS	TAV
CXCR3	upregulated	Bossé et al. 2009	AS	TAV
CXCR4	upregulated	Yang et al. 2020	AS	BAV/TAV
CYBA	upregulated	Teng et al. 2020	AS	BAV/TAV
		Zhang y Ma. 2019	AS	BAV/TAV
CYP27B1	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
CYP4B1	downregulated	Bossé et al. 2009	AS	TAV
		Greene et al. 2020	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
CYTH4	upregulated	Qiao et al. 2022	AS	TAV
DDIT4L	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
DENND2A	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
DENND2D	upregulated	Bossé et al. 2009	AS	TAV
DHRS9	upregulated	Bossé et al. 2009	AS	TAV
DIO2	upregulated	Bossé et al. 2009	AS	TAV
DKK2	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
DKK3	downregulated	Bossé et al. 2009	AS	TAV
DLG2	upregulated	Bossé et al. 2009	AS	TAV
DLGAP5	upregulated	Bossé et al. 2009	AS	TAV
DNER	downregulated	Greene et al. 2020	AS	BAV/TAV
DOCK10	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
DOCK8	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
DOCK9	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
DOK3	upregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
DOK6	downregulated	Bossé et al. 2009	AS	TAV
DPP4	upregulated	Bossé et al. 2009	AS	TAV
DPY19L2	downregulated	Bossé et al. 2009	AS	TAV
DTL	upregulated	Bossé et al. 2009	AS	TAV
DUSP1	downregulated	Qiao et al. 2022	AS	TAV
DUSP14	upregulated	Qiao et al. 2022	AS	TAV
ECE1	downregulated	Peltonen et al. 2009	severe AS	BAV/TAV
ECHDC2	downregulated	Qiao et al. 2022	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
EDNRA	upregulated	Bossé et al. 2009	AS	TAV
		Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
		Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
EGFR	downregulated	Bossé et al. 2009	AS	TAV
EHBP1	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Sun et al. 2021	AS	BAV/TAV
		Zhang y Ma. 2019	AS	BAV/TAV
EIF2S1	downregulated	Yang et al. 2020	AS	BAV/TAV
EIF5A	upregulated	Bossé et al. 2009	AS	TAV
ELOVL2	downregulated	Bossé et al. 2009	AS	TAV
EMILIN1	upregulated	Bossé et al. 2009	AS	TAV

Gene	Sense	Author	Diagnostic	Configuration
EMILIN2	upregulated	Qiao et al. 2022	AS	TAV
EMILIN3	downregulated	Bossé et al. 2009	AS	TAV
ENPEP	upregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
ENPP1	upregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
ENPP2	upregulated	Qiao et al. 2022	AS	TAV
		Sun et al. 2021	AS	BAV/TAV
		Zhang y Ma. 2019	AS	BAV/TAV
EPB41L4B	downregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
EPB41L5	downregulated	Bossé et al. 2009	AS	TAV
EPHB1	downregulated	Greene et al. 2020	AS	BAV/TAV
ERBB3	downregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
		Teng et al. 2020	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
ESM1	upregulated	Greene et al. 2020	AS	BAV/TAV
		Qiao et al. 2022	AS	TAV
ESR1	downregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
ETNK2	downregulated	Kossar et al. 2020	AS	TAV
EVI2A	upregulated	Qiao et al. 2022	AS	TAV
EVI2B	upregulated	Qiao et al. 2022	AS	TAV
EVI5	downregulated	Bossé et al. 2009	AS	TAV
EYA1	downregulated	Bossé et al. 2009	AS	TAV
F10	downregulated	Qiao et al. 2022	AS	TAV
F13B	upregulated	Bossé et al. 2009	AS	TAV
F5	downregulated	Teng et al. 2020	AS	BAV/TAV
		Zhang y Ma. 2019	AS	BAV/TAV
FAM107A	downregulated	Bossé et al. 2009	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
FAM163A	downregulated	Greene et al. 2020	AS	BAV/TAV
FAM20A	upregulated	Bossé et al. 2009	AS	TAV
		Sun et al. 2021	AS	BAV/TAV
		Teng et al. 2020	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
FAM43A	upregulated	Bossé et al. 2009	AS	TAV
FAM83D	upregulated	Zhu et al. 2019	AS	BAV/TAV
FAP	upregulated	Bossé et al. 2009	AS	TAV
FAT1	upregulated	Qiao et al. 2022	AS	TAV
FBLN5	downregulated	Qiao et al. 2022	AS	TAV
FCGBP	upregulated	Qiao et al. 2022	AS	TAV
FCGR1A	upregulated	Bossé et al. 2009	AS	TAV
		Sun et al. 2021	AS	BAV/TAV
FCGR2A	upregulated	Zhang y Ma. 2019	AS	BAV/TAV
FCMR	upregulated	Qiao et al. 2022	AS	TAV
FEZ1	downregulated	Zhang y Ma. 2019	AS	BAV/TAV
FGF1	upregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
FGF7	upregulated	Bossé et al. 2009	AS	TAV
FGF7P3	upregulated	Bossé et al. 2009	AS	TAV
FGF7P6	upregulated	Bossé et al. 2009	AS	TAV
FGFBP2	downregulated	Qiao et al. 2022	AS	TAV
FGFR3	downregulated	Bossé et al. 2009	AS	TAV
FGL2	downregulated	Qiao et al. 2022	AS	TAV
FHL2	upregulated	Qiao et al. 2022	AS	TAV
FHOD3	upregulated	Bossé et al. 2009	AS	TAV
FKBP11	upregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
FKBP1A	upregulated	Bossé et al. 2009	AS	TAV
FKBP5	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
FMO2	downregulated	Bossé et al. 2009	AS	TAV
FMO3	upregulated	Qiao et al. 2022	AS	TAV
FN1	upregulated	Bossé et al. 2009	AS	TAV
		Sun et al. 2021	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
FNDC1	upregulated	Bossé et al. 2009	AS	TAV

Gene	Sense	Author	Diagnostic	Configuration
		Qiao et al. 2022	AS	TAV
		Sun et al. 2021	AS	BAV/TAV
FOXO1	downregulated	Zhang y Ma. 2019	AS	BAV/TAV
FOXO3	downregulated	Bossé et al. 2009	AS	TAV
FOXP2	downregulated	Bossé et al. 2009	AS	TAV
FPR1	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
		Yang et al. 2020	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
FPR3	upregulated	Qiao et al. 2022	AS	TAV
FRAS1	downregulated	Bossé et al. 2009	AS	TAV
FRMD3	downregulated	Bossé et al. 2009	AS	TAV
FRRS1L	downregulated	Zhu et al. 2019	AS	BAV/TAV
FRZB	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
FST	upregulated	Qiao et al. 2022	AS	TAV
Furin	downregulated	Peltonen et al. 2007	AS	BAV/TAV
FXYD1	downregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
FYB	upregulated	Bossé et al. 2009	AS	TAV
		Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
		Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
GADD45G	downregulated	Bossé et al. 2009	AS	TAV
GALNT15	downregulated	Bossé et al. 2009	AS	TAV
GALNT3	upregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
GAP43	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
GATA5	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
GNLY	upregulated	Bossé et al. 2009	AS	TAV
GPC5	downregulated	Bossé et al. 2009	AS	TAV
GPM6A	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
GPM6B	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
GPR146	upregulated	Bossé et al. 2009	AS	TAV
GPR160	upregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
GPR18	upregulated	Bossé et al. 2009	AS	TAV
GPR68	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
GPRASP1	upregulated	Wang et al. 2021	AS	BAV/TAV
GPRIN3	upregulated	Zhu et al. 2019	AS	BAV/TAV
GPSM3	upregulated	Qiao et al. 2022	AS	TAV
GPX3	downregulated	Greene et al. 2020	AS	BAV/TAV
GSC	upregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
GSN	downregulated	Qiao et al. 2022	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
GUCY1A1	upregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
GUCY1B1	upregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
GZMH	upregulated	Bossé et al. 2009	AS	TAV
H19	upregulated	Bossé et al. 2009	AS	TAV
		Greene et al. 2020	AS	BAV/TAV
		Hadji et al. 2016	AS	TAV
H4C3	upregulated	Kossar et al. 2020	AS	TAV
HAND2-AS1	downregulated	Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
HAPLN3	upregulated	Qiao et al. 2022	AS	TAV
HBA1	upregulated	Bossé et al. 2009	AS	TAV

Gene	Sense	Author	Diagnostic	Configuration
		Greene et al. 2020	AS	BAV/TAV
HBA2	upregulated	Bossé et al. 2009	AS	TAV
HBB	upregulated	Bossé et al. 2009	AS	TAV
		Greene et al. 2020	AS	BAV/TAV
HCG11	downregulated	Bossé et al. 2009	AS	TAV
HCK	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
HCLS1	upregulated	Qiao et al. 2022	AS	TAV
HCST	upregulated	Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
HDC	upregulated	Bossé et al. 2009	AS	TAV
HIBCH	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
HIF1A	upregulated	Greene et al. 2020	AS	BAV/TAV
HIF3A	downregulated	Bossé et al. 2009	AS	TAV
		Greene et al. 2020	AS	BAV/TAV
HIRA	downregulated	Bossé et al. 2009	AS	TAV
HK3	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
HLA-DMB	upregulated	Bossé et al. 2009	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
		Zhang y Ma. 2019	AS	BAV/TAV
HLA-DOA	upregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
		Teng et al. 2020	AS	BAV/TAV
HLA-DOB	upregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
HLA-DPA1	upregulated	Bossé et al. 2009	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
HLA-DPB2	upregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
HLA-DQA1	upregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
HLA-DQB1	upregulated	Bossé et al. 2009	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
HLA-DRA	upregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
		Kossar et al. 2020	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
HMGCLL1	downregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
HMMR	upregulated	Bossé et al. 2009	AS	TAV
HOXD4	upregulated	Bossé et al. 2009	AS	TAV
HPR	downregulated	Bossé et al. 2009	AS	TAV
HPSE	upregulated	Bossé et al. 2009	AS	TAV
HRH1	upregulated	Bossé et al. 2009	AS	TAV
		Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
HS3ST1	downregulated	Bossé et al. 2009	AS	TAV
HS3ST2	upregulated	Bossé et al. 2009	AS	TAV
HSD17B13	downregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
HSPA6	upregulated	Bossé et al. 2009	AS	TAV
HTR4	downregulated	Bossé et al. 2009	AS	TAV
		Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
HTRA1	upregulated	Qiao et al. 2022	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
HTRA4	upregulated	Bossé et al. 2009	AS	TAV
HYAL1	downregulated	Bossé et al. 2009	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
ICA1L	downregulated	Bossé et al. 2009	AS	TAV
ID2	downregulated	Bossé et al. 2009	AS	TAV
ID2B	downregulated	Bossé et al. 2009	AS	TAV
IFI35	downregulated	Anger et al. 2009	AS	TAV
IFI6	upregulated	Bossé et al. 2009	AS	TAV
		Kossar et al. 2020	AS	TAV
IFITM3	upregulated	Anger et al. 2009	AS	TAV
IFNA8	upregulated	Anger et al. 2009	AS	TAV

Gene	Sense	Author	Diagnostic	Configuration
IFRD1	upregulated	Anger et al. 2009	AS	TAV
IGDCC4	upregulated	Bossé et al. 2009	AS	TAV
IGF1	upregulated	Bossé et al. 2009	AS	TAV
IGFBP2	upregulated	Teng et al. 2020	AS	BAV/TAV
IGFBP4	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
IGHG1	upregulated	Bossé et al. 2009	AS	TAV
IGHG2	upregulated	Bossé et al. 2009	AS	TAV
IGHG3	upregulated	Bossé et al. 2009	AS	TAV
IGHM	upregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
IGKC	upregulated	Zhu et al. 2019	AS	BAV/TAV
IGKV1-17	upregulated	Zhu et al. 2019	AS	BAV/TAV
IGKV1-5	upregulated	Bossé et al. 2009	AS	TAV
IGKV1D-13	upregulated	Zhu et al. 2019	AS	BAV/TAV
IGKV1OR2-108	upregulated	Zhu et al. 2019	AS	BAV/TAV
IGKV4-1	upregulated	Zhu et al. 2019	AS	BAV/TAV
IGL	upregulated	Bossé et al. 2009	AS	TAV
IGLJ3	upregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
IGLL1	upregulated	Qiao et al. 2022	AS	TAV
IGLL3P	upregulated	Sun et al. 2021	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
IGLV2-14	upregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
IGLV3-10	upregulated	Zhu et al. 2019	AS	BAV/TAV
IGLV3-25	upregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
IGLV4-3	upregulated	Bossé et al. 2009	AS	TAV
IGSF11	downregulated	Bossé et al. 2009	AS	TAV
		Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
IGSF4	upregulated	Bossé et al. 2009	AS	TAV
IL10RA	downregulated	Anger et al. 2009	AS	TAV
IL11	upregulated	Greene et al. 2020	AS	BAV/TAV
IL12	downregulated	Anger et al. 2009	AS	TAV
IL12RB1	upregulated	Anger et al. 2009	AS	TAV
IL16	upregulated	Anger et al. 2009	AS	TAV
IL17C	downregulated	Anger et al. 2009	AS	TAV
IL17D	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
		Zhang y Ma. 2019	AS	BAV/TAV
IL1B	upregulated	Bossé et al. 2009	AS	TAV
IL1RN	upregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
IL21R	upregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
IL2RB	upregulated	Bossé et al. 2009	AS	TAV
IL4	downregulated	Anger et al. 2009	AS	TAV
IL4I1	upregulated	Bossé et al. 2009	AS	TAV
IL6	upregulated	Bossé et al. 2009	AS	TAV
ILKAP	upregulated	Bossé et al. 2009	AS	TAV
ING3	downregulated	Bossé et al. 2009	AS	TAV
IP6K3	downregulated	Bossé et al. 2009	AS	TAV
IRF4	downregulated	Anger et al. 2009	AS	TAV
IRF6	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
IRF8	upregulated	Qiao et al. 2022	AS	TAV
IRX3	downregulated	Bossé et al. 2009	AS	TAV
ISM1	upregulated	Bossé et al. 2009	AS	TAV
ITGA4	upregulated	Bossé et al. 2009	AS	TAV
		Yang et al. 2020	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
ITGA9	downregulated	Bossé et al. 2009	AS	TAV
ITGAV	upregulated	Bossé et al. 2009	AS	TAV
ITGAX	upregulated	Bossé et al. 2009	AS	TAV

Gene	Sense	Author	Diagnostic	Configuration
		Teng et al. 2020	AS	BAV/TAV
ITGB2	upregulated	Yang et al. 2020	AS	BAV/TAV
		Zhang y Ma. 2019	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
ITGB7	upregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
ITK	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Sun et al. 2021	AS	BAV/TAV
ITM2A	downregulated	Qiao et al. 2022	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
ITPRID2	downregulated	Bossé et al. 2009	AS	TAV
JAK3	upregulated	Bossé et al. 2009	AS	TAV
KANK1	downregulated	Zhu et al. 2019	AS	BAV/TAV
KCNJ15	upregulated	Bossé et al. 2009	AS	TAV
KCNJ6	upregulated	Greene et al. 2020	AS	BAV/TAV
KCNK17	downregulated	Bossé et al. 2009	AS	TAV
KCNN4	upregulated	Bossé et al. 2009	AS	TAV
		Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
KCNT1	downregulated	Greene et al. 2020	AS	BAV/TAV
KDELR2	upregulated	Sun et al. 2021	AS	BAV/TAV
KIF11	upregulated	Bossé et al. 2009	AS	TAV
KIF21A	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
KIF5C	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
KLF15	downregulated	Bossé et al. 2009	AS	TAV
KLF4	downregulated	Qiao et al. 2022	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
KLF9	downregulated	Bossé et al. 2009	AS	TAV
KLHL6	upregulated	Bossé et al. 2009	AS	TAV
KLRB1	upregulated	Bossé et al. 2009	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
KLRC1	upregulated	Bossé et al. 2009	AS	TAV
KLRC2	upregulated	Bossé et al. 2009	AS	TAV
KMO	upregulated	Bossé et al. 2009	AS	TAV
KMT2A	downregulated	Bossé et al. 2009	AS	TAV
KRT17	upregulated	Qiao et al. 2022	AS	TAV
KYNU	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
L1CAM	downregulated	Bossé et al. 2009	AS	TAV
LAIR1	upregulated	Bossé et al. 2009	AS	TAV
LAMA2	downregulated	Bossé et al. 2009	AS	TAV
LAMA3	downregulated	Bossé et al. 2009	AS	TAV
LAMC3	downregulated	Bossé et al. 2009	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
LBP	upregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
LCK	upregulated	Bossé et al. 2009	AS	TAV
		Sun et al. 2021	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
LCP1	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
LCP2	upregulated	Bossé et al. 2009	AS	TAV
LDAF1	downregulated	Bossé et al. 2009	AS	TAV
LDLR	upregulated	Anger et al. 2009	AS	TAV
LEPR	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
LIFR	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV

Gene	Sense	Author	Diagnostic	Configuration
LILRB1	upregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
LILRB2	upregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
LILRB4	upregulated	Bossé et al. 2009	AS	TAV
LIMCH1	downregulated	Zhang y Ma. 2019	AS	BAV/TAV
LINC00844	downregulated	Zhu et al. 2019	AS	BAV/TAV
LINC01094	upregulated	Zhu et al. 2019	AS	BAV/TAV
LINC01614	upregulated	Zhu et al. 2019	AS	BAV/TAV
LMO3	downregulated	Bossé et al. 2009	AS	TAV
LOC102723407	upregulated	Bossé et al. 2009	AS	TAV
LOC374443	upregulated	Bossé et al. 2009	AS	TAV
LONRF2	downregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
LOXL2	upregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
LPAR1	downregulated	Qiao et al. 2022	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
LPL	downregulated	Kossar et al. 2020	AS	TAV
LRATD2	downregulated	Bossé et al. 2009	AS	TAV
LRP1	upregulated	Bossé et al. 2009	AS	TAV
LRP1B	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
LRRC15	upregulated	Bossé et al. 2009	AS	TAV
		Greene et al. 2020	AS	BAV/TAV
		Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
LRRC32	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
LSP1	upregulated	Bossé et al. 2009	AS	TAV
LST1	upregulated	Qiao et al. 2022	AS	TAV
LTB	upregulated	Bossé et al. 2009	AS	TAV
		Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
		Teng et al. 2020	AS	BAV/TAV
LUM	upregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
		Kossar et al. 2020	AS	TAV
		Qiao et al. 2022	AS	TAV
LY6H	upregulated	Greene et al. 2020	AS	BAV/TAV
LY9	upregulated	Bossé et al. 2009	AS	TAV
LY96	upregulated	Qiao et al. 2022	AS	TAV
LYN	upregulated	Qiao et al. 2022	AS	TAV
LYZ	upregulated	Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
MAB21L1	downregulated	Bossé et al. 2009	AS	TAV
MAGEA4	downregulated	Bossé et al. 2009	AS	TAV
MAL	downregulated	Bossé et al. 2009	AS	TAV
MALAT1	upregulated	Bossé et al. 2009	AS	TAV
MAMDC2	downregulated	Qiao et al. 2022	AS	TAV
MAP2	downregulated	Bossé et al. 2009	AS	TAV
MAP2K6	downregulated	Bossé et al. 2009	AS	TAV
MAP3K7CL	upregulated	Qiao et al. 2022	AS	TAV
MAPK13	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
MAPT	downregulated	Bossé et al. 2009	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
MAS1	downregulated	Peltonen et al. 2011	AS	BAV/TAV
MASP1	downregulated	Bossé et al. 2009	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
		Zhang y Ma. 2019	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
MATN2	downregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
MCTP1	upregulated	Bossé et al. 2009	AS	TAV
MEF2A	downregulated	Bossé et al. 2009	AS	TAV
MEIS2	downregulated	Bossé et al. 2009	AS	TAV

Gene	Sense	Author	Diagnostic	Configuration
		Qiao et al. 2022	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
MEIS3P1	downregulated	Zhang y Ma. 2019	AS	BAV/TAV
MFAP2	upregulated	Bossé et al. 2009	AS	TAV
MFAP5	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
MGST1	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
MMP10	upregulated	Anger et al. 2009	AS	TAV
MMP19	upregulated	Anger et al. 2009	AS	TAV
MMP7	upregulated	Bossé et al. 2009	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
MOXD1	upregulated	Bossé et al. 2009	AS	TAV
MPPED2	downregulated	Qiao et al. 2022	AS	TAV
MS4A1	upregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
MS4A14	upregulated	Bossé et al. 2009	AS	TAV
MTSS1	upregulated	Bossé et al. 2009	AS	TAV
MTURN	downregulated	Qiao et al. 2022	AS	TAV
MTUS1	downregulated	Bossé et al. 2009	AS	TAV
MXI1	downregulated	Zhang y Ma. 2019	AS	BAV/TAV
MXRA5	upregulated	Qiao et al. 2022	AS	TAV
MYO10	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
MYO1D	upregulated	Qiao et al. 2022	AS	TAV
MYO1F	upregulated	Qiao et al. 2022	AS	TAV
MYO5A	upregulated	Bossé et al. 2009	AS	TAV
MYO5C	upregulated	Bossé et al. 2009	AS	TAV
MYRIP	downregulated	Bossé et al. 2009	AS	TAV
MZB1	upregulated	Qiao et al. 2022	AS	TAV
		Sun et al. 2021	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
NAALAD2	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
NABP1	upregulated	Qiao et al. 2022	AS	TAV
NAIP	upregulated	Bossé et al. 2009	AS	TAV
NAP1L2	downregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
NBEA	downregulated	Zhu et al. 2019	AS	BAV/TAV
NCAM1	downregulated	Bossé et al. 2009	AS	TAV
NCOR2	upregulated	Bossé et al. 2009	AS	TAV
NDRG2	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
NDRG4	downregulated	Bossé et al. 2009	AS	TAV
NEDD1	upregulated	Bossé et al. 2009	AS	TAV
NEK6	upregulated	Bossé et al. 2009	AS	TAV
NELL2	upregulated	Greene et al. 2020	AS	BAV/TAV
NETO2	downregulated	Bossé et al. 2009	AS	TAV
NEURL2	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
NFIA	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
NFKB1	downregulated	Anger et al. 2009	AS	TAV
NID2	upregulated	Bossé et al. 2009	AS	TAV
NMES1	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
NOTCH3	upregulated	Qiao et al. 2022	AS	TAV

Gene	Sense	Author	Diagnostic	Configuration
NPAS3	downregulated	Bossé et al. 2009	AS	TAV
NPL	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
NPR1	downregulated	Peltonen et al. 2007	AS	BAV/TAV
NPR2	downregulated	Peltonen et al. 2007	AS	BAV/TAV
NPY	downregulated	Greene et al. 2020	AS	BAV/TAV
		Qiao et al. 2022	AS	TAV
NR4A2	downregulated	Zhu et al. 2019	AS	BAV/TAV
NRP2	upregulated	Bossé et al. 2009	AS	TAV
NSG1	downregulated	Qiao et al. 2022	AS	TAV
NTN4	downregulated	Qiao et al. 2022	AS	TAV
NTRK2	downregulated	Bossé et al. 2009	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
NUDT10	downregulated	Bossé et al. 2009	AS	TAV
NUSAP1	upregulated	Bossé et al. 2009	AS	TAV
NXPH4	upregulated	Greene et al. 2020	AS	BAV/TAV
OIP5-AS1	downregulated	Hadji et al. 2016	AS	TAV
OLFML2A	downregulated	Qiao et al. 2022	AS	TAV
OLR1	upregulated	Qiao et al. 2022	AS	TAV
OPCML	downregulated	Bossé et al. 2009	AS	TAV
OR51E1	upregulated	Greene et al. 2020	AS	BAV/TAV
OSP	upregulated	Breyne et al. 2010	AS	BAV/TAV
OSR1	downregulated	Qiao et al. 2022	AS	TAV
OSR2	upregulated	Bossé et al. 2009	AS	TAV
OTC	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
OXTR	upregulated	Qiao et al. 2022	AS	TAV
P2RX6	downregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
P2RY12	downregulated	Bossé et al. 2009	AS	TAV
P2RY14	downregulated	Bossé et al. 2009	AS	TAV
P4HB	upregulated	Bossé et al. 2009	AS	TAV
PAMR1	downregulated	Qiao et al. 2022	AS	TAV
PAPOLA	downregulated	Bossé et al. 2009	AS	TAV
PARVG	upregulated	Teng et al. 2020	AS	BAV/TAV
PAXBP1	downregulated	Bossé et al. 2009	AS	TAV
PCDH1	upregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
PCDH11Y	downregulated	Bossé et al. 2009	AS	TAV
PCDH12	upregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
		Qiao et al. 2022	AS	TAV
PCDH20	downregulated	Bossé et al. 2009	AS	TAV
PCDH9	downregulated	Bossé et al. 2009	AS	TAV
PCDHB14	downregulated	Bossé et al. 2009	AS	TAV
PCDHB5	downregulated	Bossé et al. 2009	AS	TAV
PCLAF	upregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
PCSK1	upregulated	Bossé et al. 2009	AS	TAV
PDE3B	downregulated	Bossé et al. 2009	AS	TAV
PDIA5	upregulated	Bossé et al. 2009	AS	TAV
PDPN	upregulated	Bossé et al. 2009	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
PDZK1	downregulated	Bossé et al. 2009	AS	TAV
PEBP4	downregulated	Bossé et al. 2009	AS	TAV
PFN1	upregulated	Bossé et al. 2009	AS	TAV
PGM5	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
PGRMC1	downregulated	Teng et al. 2020	AS	BAV/TAV
PHF17	downregulated	Bossé et al. 2009	AS	TAV
PHKA1	downregulated	Bossé et al. 2009	AS	TAV
PI15	upregulated	Zhu et al. 2019	AS	BAV/TAV
PIAS1	downregulated	Bossé et al. 2009	AS	TAV
PIK3AP1	upregulated	Qiao et al. 2022	AS	TAV
PIK3CG	upregulated	Yang et al. 2020	AS	BAV/TAV
PIK3R1	downregulated	Bossé et al. 2009	AS	TAV

Gene	Sense	Author	Diagnostic	Configuration
PILRA	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
PIM1	upregulated	Qiao et al. 2022	AS	TAV
PIM2	upregulated	Qiao et al. 2022	AS	TAV
PIR	downregulated	Bossé et al. 2009	AS	TAV
PKHD1L1	downregulated	Bossé et al. 2009	AS	TAV
		Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
PKIA	downregulated	Bossé et al. 2009	AS	TAV
PKP2	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
PLA1A	downregulated	Qiao et al. 2022	AS	TAV
PLA2G4A	downregulated	Bossé et al. 2009	AS	TAV
		Mahmut et al. 2014	AS	BAV/TAV
PLA2G5	downregulated	Bossé et al. 2009	AS	TAV
		Mahmut et al. 2014	AS	BAV/TAV
PLCE1	downregulated	Bossé et al. 2009	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
PLCH1	downregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
PLD3	upregulated	Bossé et al. 2009	AS	TAV
PLEK	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
PLEK2	upregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
PLEKHA6	downregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
PLEKHB1	downregulated	Bossé et al. 2009	AS	TAV
PLEKHG1	upregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
PLEKHS1	upregulated	Greene et al. 2020	AS	BAV/TAV
PLLP	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
PLOD2	upregulated	Bossé et al. 2009	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
PLPP3	downregulated	Mkannez et al. 2018	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
PLVAP	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
PLXNC1	upregulated	Bossé et al. 2009	AS	TAV
PMP22	downregulated	Zhang y Ma. 2019	AS	BAV/TAV
PNKD	upregulated	Bossé et al. 2009	AS	TAV
PNMT	downregulated	Cantor et al. 2021	AS	TAV
PNP	upregulated	Qiao et al. 2022	AS	TAV
POF1B	downregulated	Bossé et al. 2009	AS	TAV
POU2F2	upregulated	Bossé et al. 2009	AS	TAV
PPAR	upregulated	Anger et al. 2009	AS	TAV
PPM1H	downregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
PPP1R1B	downregulated	Greene et al. 2020	AS	BAV/TAV
PPP1R9A	downregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
PPP4R2	upregulated	Bossé et al. 2009	AS	TAV
PRDM1	upregulated	Zhu et al. 2019	AS	BAV/TAV
PRG1	upregulated	Bossé et al. 2009	AS	TAV
PRIMA1	downregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
PRINS	upregulated	Hadji et al. 2016	AS	TAV
PRLR	downregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
PRND	upregulated	Greene et al. 2020	AS	BAV/TAV
		Qiao et al. 2022	AS	TAV

Gene	Sense	Author	Diagnostic	Configuration
		Zhu et al. 2019	AS	BAV/TAV
PRSS23	downregulated	Bossé et al. 2009	AS	TAV
PRSS35	upregulated	Bossé et al. 2009	AS	TAV
		Greene et al. 2020	AS	BAV/TAV
PRTFDC1	downregulated	Qiao et al. 2022	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
PSMD9	downregulated	Yang et al. 2020	AS	BAV/TAV
PTCHD1	downregulated	Bossé et al. 2009	AS	TAV
PTENP1-AS	downregulated	Hadji et al. 2016	AS	TAV
PTGER2	upregulated	Bossé et al. 2009	AS	TAV
PTGER4	upregulated	Qiao et al. 2022	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
PTGS2	downregulated	Qiao et al. 2022	AS	TAV
PTHLH	downregulated	Bossé et al. 2009	AS	TAV
PTPRB	downregulated	Bossé et al. 2009	AS	TAV
PTPRC	upregulated	Bossé et al. 2009	AS	TAV
PTPRG	downregulated	Bossé et al. 2009	AS	TAV
PWWP3B	downregulated	Bossé et al. 2009	AS	TAV
		Cantor et al. 2021	AS	TAV
		Greene et al. 2020	AS	BAV/TAV
		Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
PXDN	upregulated	Bossé et al. 2009	AS	TAV
PXDNL	downregulated	Bossé et al. 2009	AS	TAV
QSER1	upregulated	Bossé et al. 2009	AS	TAV
RADX	downregulated	Bossé et al. 2009	AS	TAV
		Sun et al. 2021	AS	BAV/TAV
RAN	downregulated	Yang et al. 2020	AS	BAV/TAV
RANBP9	upregulated	Bossé et al. 2009	AS	TAV
RAP2B	upregulated	Bossé et al. 2009	AS	TAV
RARRES1	upregulated	Bossé et al. 2009	AS	TAV
RASAL3	upregulated	Qiao et al. 2022	AS	TAV
RASGEF1A	upregulated	Bossé et al. 2009	AS	TAV
RASGRP3	upregulated	Qiao et al. 2022	AS	TAV
RBL2	downregulated	Bossé et al. 2009	AS	TAV
RBM22	upregulated	Bossé et al. 2009	AS	TAV
RBM25	downregulated	Bossé et al. 2009	AS	TAV
RBMS3	downregulated	Zhang y Ma. 2019	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
REN	downregulated	Peltonen et al. 2011	AS	BAV/TAV
RERG	downregulated	Bossé et al. 2009	AS	TAV
RFX8	upregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
RGS1	upregulated	Yang et al. 2020	AS	BAV/TAV
RGS13	upregulated	Bossé et al. 2009	AS	TAV
RGS16	upregulated	Bossé et al. 2009	AS	TAV
RGS19	upregulated	Qiao et al. 2022	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
RGS4	upregulated	Qiao et al. 2022	AS	TAV
RHAG	downregulated	Greene et al. 2020	AS	BAV/TAV
RHOB	downregulated	Qiao et al. 2022	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
RHOBTB3	downregulated	Qiao et al. 2022	AS	TAV
RMST	downregulated	Bossé et al. 2009	AS	TAV
RNASE2	upregulated	Bossé et al. 2009	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
RNF180	downregulated	Bossé et al. 2009	AS	TAV
ROR2	upregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
RORA	downregulated	Bossé et al. 2009	AS	TAV
RPL23A	upregulated	Yang et al. 2020	AS	BAV/TAV
RPS12P5	downregulated	Greene et al. 2020	AS	BAV/TAV
RRM2	upregulated	Bossé et al. 2009	AS	TAV
RUNX1	upregulated	Bossé et al. 2009	AS	TAV
RUNX1-IT1	upregulated	Bossé et al. 2009	AS	TAV
RUNX2	upregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV

Gene	Sense	Author	Diagnostic	Configuration
		Zhu et al. 2019	AS	BAV/TAV
RUNX3	upregulated	Bossé et al. 2009	AS	TAV
S100A11	upregulated	Bossé et al. 2009	AS	TAV
S100B	downregulated	Bossé et al. 2009	AS	TAV
SALL1	downregulated	Bossé et al. 2009	AS	TAV
SAMD3	upregulated	Bossé et al. 2009	AS	TAV
SAMSN1	upregulated	Bossé et al. 2009	AS	TAV
SASH3	upregulated	Qiao et al. 2022	AS	TAV
SCN7A	downregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
SCO2	upregulated	Qiao et al. 2022	AS	TAV
SDC1	upregulated	Zhu et al. 2019	AS	BAV/TAV
SEL1L3	upregulated	Qiao et al. 2022	AS	TAV
SELENBP1	downregulated	Qiao et al. 2022	AS	TAV
SERPINA1	upregulated	Bossé et al. 2009	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
		Zhang y Ma. 2019	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
SERPINE1	upregulated	Bossé et al. 2009	AS	TAV
SESTD1	downregulated	Qiao et al. 2022	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
SFRP1	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
SFRP2	upregulated	Qiao et al. 2022	AS	TAV
SGCE	upregulated	Sun et al. 2021	AS	BAV/TAV
SGSM1	downregulated	Teng et al. 2020	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
SH2D1A	upregulated	Bossé et al. 2009	AS	TAV
SH3KBP1	upregulated	Zhang y Ma. 2019	AS	BAV/TAV
SH3RF2	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
SIGLEC7	upregulated	Bossé et al. 2009	AS	TAV
sIL-1RAcP	downregulated	Anger et al. 2009	AS	TAV
SLAMF7	upregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
SLC11A1	upregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
SLC14A1	downregulated	Bossé et al. 2009	AS	TAV
SLC15A2	downregulated	Bossé et al. 2009	AS	TAV
SLC16A10	upregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
SLC16A3	upregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
SLC16A6	upregulated	Bossé et al. 2009	AS	TAV
SLC20A1	upregulated	Sun et al. 2021	AS	BAV/TAV
		Zhang y Ma. 2019	AS	BAV/TAV
SLC27A6	downregulated	Greene et al. 2020	AS	BAV/TAV
SLC2A3	upregulated	Bossé et al. 2009	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
SLC2A5	upregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
SLC39A8	upregulated	Bossé et al. 2009	AS	TAV
SLC45A2	upregulated	Zhu et al. 2019	AS	BAV/TAV
SLC5A4	downregulated	Teng et al. 2020	AS	BAV/TAV
SLC6A16	downregulated	Bossé et al. 2009	AS	TAV
SLCO4A1	downregulated	Bossé et al. 2009	AS	TAV
SLITRK5	downregulated	Bossé et al. 2009	AS	TAV
SLP1	upregulated	Teng et al. 2020	AS	BAV/TAV
SMCO4	upregulated	Qiao et al. 2022	AS	TAV
SMOC2	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
		Zhang y Ma. 2019	AS	BAV/TAV

Gene	Sense	Author	Diagnostic	Configuration
SMTNL2	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
SNAP91	downregulated	Bossé et al. 2009	AS	TAV
SNRPD3	downregulated	Yang et al. 2020	AS	BAV/TAV
SNX1	downregulated	Zhang y Ma. 2019	AS	BAV/TAV
SOCS3	upregulated	Bossé et al. 2009	AS	TAV
		Kossar et al. 2020	AS	TAV
SOD2	upregulated	Bossé et al. 2009	AS	TAV
SOS1	downregulated	Bossé et al. 2009	AS	TAV
SOST	downregulated	Teng et al. 2020	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
Sox11	downregulated	Anger et al. 2009	AS	TAV
Sox18	downregulated	Anger et al. 2009	AS	TAV
SOX2-OT	downregulated	Hadji et al. 2016	AS	TAV
Sox30	upregulated	Anger et al. 2009	AS	TAV
SPATA22	downregulated	Bossé et al. 2009	AS	TAV
SPHK1	upregulated	Bossé et al. 2009	AS	TAV
SPOCK2	upregulated	Bossé et al. 2009	AS	TAV
SPOCK3	downregulated	Bossé et al. 2009	AS	TAV
SPON1	downregulated	Zhang y Ma. 2019	AS	BAV/TAV
SPON2	upregulated	Bossé et al. 2009	AS	TAV
SPRY2	downregulated	Qiao et al. 2022	AS	TAV
SPSB1	upregulated	Qiao et al. 2022	AS	TAV
SPTBN1	downregulated	Zhang y Ma. 2019	AS	BAV/TAV
SRGN	upregulated	Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
SSTR1	downregulated	Bossé et al. 2009	AS	TAV
SSX2IP	downregulated	Bossé et al. 2009	AS	TAV
ST6GALNAC1	downregulated	Bossé et al. 2009	AS	TAV
ST8SIA4	upregulated	Zhu et al. 2019	AS	BAV/TAV
STAT4	upregulated	Bossé et al. 2009	AS	TAV
STC1	upregulated	Qiao et al. 2022	AS	TAV
STEAP1	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
STON2	downregulated	Bossé et al. 2009	AS	TAV
STXBP6	downregulated	Bossé et al. 2009	AS	TAV
SUGCT	upregulated	Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
SUGGT	upregulated	Teng et al. 2020	AS	BAV/TAV
SULF1	upregulated	Qiao et al. 2022	AS	TAV
SURF4	downregulated	Sun et al. 2021	AS	BAV/TAV
SYBU	downregulated	Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
SYK	upregulated	Qiao et al. 2022	AS	TAV
SYN2	downregulated	Bossé et al. 2009	AS	TAV
SYTL2	upregulated	Zhang y Ma. 2019	AS	BAV/TAV
SYTL4	downregulated	Bossé et al. 2009	AS	TAV
TAC1	downregulated	Bossé et al. 2009	AS	TAV
TAGLN	upregulated	Zhang y Ma. 2019	AS	BAV/TAV
TARP	upregulated	Bossé et al. 2009	AS	TAV
TASOR2	downregulated	Bossé et al. 2009	AS	TAV
TBX2	upregulated	Qiao et al. 2022	AS	TAV
TBXA2R	upregulated	Bossé et al. 2009	AS	TAV
TCERG1	downregulated	Bossé et al. 2009	AS	TAV
TENM3	downregulated	Bossé et al. 2009	AS	TAV
TESC	upregulated	Bossé et al. 2009	AS	TAV
TEX11	downregulated	Bossé et al. 2009	AS	TAV
TFPI2	downregulated	Bossé et al. 2009	AS	TAV
TGFA	upregulated	Bossé et al. 2009	AS	TAV
TGFB1	upregulated	Anger et al. 2009	AS	TAV
TGFB2	upregulated	Anger et al. 2009	AS	TAV
TGM2	upregulated	Bossé et al. 2009	AS	TAV
THBS1	upregulated	Bossé et al. 2009	AS	TAV
THEMIS	upregulated	Bossé et al. 2009	AS	TAV

Gene	Sense	Author	Diagnostic	Configuration
THEMIS2	upregulated	Bossé et al. 2009	AS	TAV
THRSP	downregulated	Bossé et al. 2009	AS	TAV
THSD4	downregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
TIMD4	upregulated	Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
TIMP3	downregulated	Anger et al. 2009	AS	TAV
TIMPs	downregulated	Anger et al. 2009	AS	TAV
TIPARP	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
TLCD4	downregulated	Zhu et al. 2019	AS	BAV/TAV
TLR7	upregulated	Qiao et al. 2022	AS	TAV
TLR8	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
TM4SF18	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
TM7SF2	downregulated	Greene et al. 2020	AS	BAV/TAV
TMC6	upregulated	Bossé et al. 2009	AS	TAV
TMEFF2	downregulated	Bossé et al. 2009	AS	TAV
TMEM100	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
TMEM108	downregulated	Bossé et al. 2009	AS	TAV
TMEM119	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
TMEM132C	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
TMEM158	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Sun et al. 2021	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
TMEM163	upregulated	Bossé et al. 2009	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
TMEM200A	upregulated	Bossé et al. 2009	AS	TAV
		Greene et al. 2020	AS	BAV/TAV
		Qiao et al. 2022	AS	TAV
		Sun et al. 2021	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
TMEM245	downregulated	Bossé et al. 2009	AS	TAV
TMEM38A	downregulated	Bossé et al. 2009	AS	TAV
TMEM51	upregulated	Qiao et al. 2022	AS	TAV
TMOD1	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
Tnf	downregulated	Anger et al. 2009	AS	TAV
TNFAIP8L1	upregulated	Bossé et al. 2009	AS	TAV
TNFRSF11B	upregulated	Zhang y Ma. 2019	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
TNFRSF12A	upregulated	Bossé et al. 2009	AS	TAV
TNFSF15	upregulated	Greene et al. 2020	AS	BAV/TAV
TNRC6B	downregulated	Bossé et al. 2009	AS	TAV
TOP2A	upregulated	Bossé et al. 2009	AS	TAV
TPD52L1	downregulated	Qiao et al. 2022	AS	TAV
TPPP	downregulated	Bossé et al. 2009	AS	TAV
TPSAB1	upregulated	Qiao et al. 2022	AS	TAV
TRAF3	upregulated	Anger et al. 2009	AS	TAV
TRAF3IP3	upregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
TRAF4a	upregulated	Anger et al. 2009	AS	TAV
TRAT1	upregulated	Bossé et al. 2009	AS	TAV
TRBC1	upregulated	Bossé et al. 2009	AS	TAV
		Sun et al. 2021	AS	BAV/TAV

Gene	Sense	Author	Diagnostic	Configuration
TRBV19	upregulated	Bossé et al. 2009	AS	TAV
TRBV21-1	upregulated	Bossé et al. 2009	AS	TAV
TRBV3-1	upregulated	Bossé et al. 2009	AS	TAV
TRBV5-4	upregulated	Bossé et al. 2009	AS	TAV
TRDN	downregulated	Bossé et al. 2009	AS	TAV
TREM2	upregulated	Qiao et al. 2022	AS	TAV
TRGC2	upregulated	Bossé et al. 2009	AS	TAV
TRGV2	upregulated	Bossé et al. 2009	AS	TAV
TRGV9	upregulated	Bossé et al. 2009	AS	TAV
TRHDE	downregulated	Bossé et al. 2009	AS	TAV
		Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhu et al. 2019	AS	BAV/TAV
TRHDE-AS1	downregulated	Guauque-Olarte et al. 2015	Mild/Severe AS	TAV
TRIM2	downregulated	Bossé et al. 2009	AS	TAV
TRIM59	upregulated	Bossé et al. 2009	AS	TAV
TRPM3	downregulated	Bossé et al. 2009	AS	TAV
TSC22D3	downregulated	Bossé et al. 2009	AS	TAV
TSPAN13	upregulated	Bossé et al. 2009	AS	TAV
TSPAN8	downregulated	Bossé et al. 2009	AS	TAV
		Qiao et al. 2022	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
		Zhu et al. 2019	AS	BAV/TAV
TSPYL5	downregulated	Qiao et al. 2022	AS	TAV
TTC12	downregulated	Bossé et al. 2009	AS	TAV
TUBA1A	upregulated	Yang et al. 2020	AS	BAV/TAV
TUBAL3	downregulated	Bossé et al. 2009	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
TYROBP	upregulated	Qiao et al. 2022	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
UBASH3B	upregulated	Bossé et al. 2009	AS	TAV
UGCG	upregulated	Bossé et al. 2009	AS	TAV
ULK4P1	upregulated	Bossé et al. 2009	AS	TAV
UNC5A	upregulated	Greene et al. 2020	AS	BAV/TAV
USP14	downregulated	Yang et al. 2020	AS	BAV/TAV
USP53	downregulated	Bossé et al. 2009	AS	TAV
VAMP8	upregulated	Qiao et al. 2022	AS	TAV
VAV1	upregulated	Qiao et al. 2022	AS	TAV
VDR	upregulated	Bossé et al. 2009	AS	TAV
VMP1	upregulated	Qiao et al. 2022	AS	TAV
VWF	upregulated	Qiao et al. 2022	AS	TAV
		Teng et al. 2020	AS	BAV/TAV
		Yang et al. 2020	AS	BAV/TAV
		Zhang y Ma. 2019	AS	BAV/TAV
WAS	upregulated	Qiao et al. 2022	AS	TAV
		Zhang y Ma. 2019	AS	BAV/TAV
WASF2	downregulated	Bossé et al. 2009	AS	TAV
WDR17	downregulated	Bossé et al. 2009	AS	TAV
WFDC1	upregulated	Qiao et al. 2022	AS	TAV
WLS	downregulated	Qiao et al. 2022	AS	TAV
WNK3	downregulated	Zhu et al. 2019	AS	BAV/TAV
WSB1	downregulated	Bossé et al. 2009	AS	TAV
XCL2	upregulated	Bossé et al. 2009	AS	TAV
XKR4	downregulated	Bossé et al. 2009	AS	TAV
XRCC6	upregulated	Yang et al. 2020	AS	BAV/TAV
ZBTB16	downregulated	Bossé et al. 2009	AS	TAV
ZC2HC1A	downregulated	Bossé et al. 2009	AS	TAV
ZMYND11	downregulated	Bossé et al. 2009	AS	TAV
ZNF124	upregulated	Bossé et al. 2009	AS	TAV
ZYX	upregulated	Bossé et al. 2009	AS	TAV

Supplementary 6. Supplementary table 3. List of the 252 miRNAs identified after full text review. Gene Target predicted by miRGator 3.0 and differentially expressed among the reviewed articles are shown. Upregulated genes are shown in bold. *Gene targets indicated by the authors.

miRNA	sense of expression	Gene target	Author	Configuration
MIR1	Downregulated	**PNP**,TIMP3,**CTSC**,**PIM1**,TRIM2	Coffey et al, 2016	TAV
MIR103a-3p	Downregulated	--	Coffey et al, 2016	TAV
MIR106a-5p	Downregulated	**RUNX1**	Coffey et al, 2016	TAV
	N.D.	**RUNX1**,CXCL8*	Qiao et al, 2022	TAV
MIR106b-3p	Downregulated	--	Coffey et al, 2016	TAV
MIR107	Downregulated	NFIA,**HIF1A**	Coffey et al, 2016	TAV
MIR1180-3p	Downregulated	--	Coffey et al, 2016	TAV
MIR1185-1-3p	N.D.	VCAM1*	Qiao et al, 2022	TAV
MIR1185-2-3p	N.D.	VCAM1*	Qiao et al, 2022	TAV
MIR1202	Downregulated	--	Coffey et al, 2016	TAV
MIR1205	N.D.	**SYK***	Qiao et al, 2022	TAV
MIR1207-5p	Downregulated	--	Coffey et al, 2016	TAV
MIR1225-5p	Downregulated	--	Coffey et al, 2016	TAV
MIR122-5p	Downregulated	NCAM1, CCNG1	Coffey et al, 2016	TAV
MIR124-3p	Downregulated	CDK4,**NEK6**,CHODL,GSN,**LDLR**,**MYO10**,SURF4	Coffey et al, 2016	TAV
MIR1245	Downregulated	--	Jiao et al, 2019	TAV
MIR1246	Downregulated	--	Coffey et al, 2016	TAV
MIR125b-2-3p	Downregulated	--	Coffey et al, 2016	TAV
		--	Qiao et al, 2022	TAV
MIR1263	Upregulated	--	Coffey et al, 2016	TAV
MIR1271-5p	Downregulated	--	Coffey et al, 2016	TAV
MIR1275	Upregulated	--	Coffey et al, 2016	TAV
MIR1277-5p	N.D.	VCAM*,**CXCL12***	Qiao et al, 2022	TAV
MIR128-3p	Downregulated	--	Coffey et al, 2016	TAV
MIR1284	N.D.	VCAM1*	Qiao et al, 2022	TAV
MIR1287-5p	Downregulated	--	Coffey et al, 2016	TAV
			Qiao et al, 2022	TAV
MIR1294	N.D.	CXCL8*	Qiao et al, 2022	TAV
MIR130a-5p	N.D.	VCAM*,**CXCL12***	Qiao et al, 2022	TAV
MIR1323	N.D.	**PLEK***	Qiao et al, 2022	TAV
MIR133a-3p	Downregulated	--	Coffey et al, 2016	TAV
MIR133b	Downregulated	KLF15	Coffey et al, 2016	TAV
			Qiao et al, 2022	TAV

miRNA	sense of expression	Gene target	Author	Configuration
MIR137	N.D.	-- KIT*	Qiao et al, 2022	TAV TAV
MIR138	Downregulated	--	Lu et al, 2019 Qiao et al, 2022	TAV TAV
MIR139-5p	Downregulated	--	Coffey et al, 2016	TAV
MIR140-3p	Downregulated	--	Coffey et al, 2016	TAV
MIR141-3p	N.D.	**TGFB2**,**CXCL12***,**PLEK***	Qiao et al, 2022	TAV
MIR142	Upregulated	--	Schlotter et al, 2018	TAV
MIR143-3p	Upregulated	--	Coffey et al, 2016	TAV
MIR144-3p	N.D.	**CXCL12***	Qiao et al, 2022	TAV
MIR146a-5p	N.D.	**CDKN3**,EGFR,NFKB1,**CXCR4**,ATOH8,**CCL5***	Qiao et al, 2022	TAV
MIR146b-5p	N.D.	NFKB1,**CCL5***	Qiao et al, 2022	TAV
MIR149-3p	N.D.	**CSF1R***	Qiao et al, 2022	TAV
MIR149-5p	Downregulated	--	Coffey et al, 2016 Qiao et al, 2022	TAV TAV
MIR155	Upregulated	--	Bossé et al, 2009	TAV
MIR155-5p	N.D.	PAPOLA,AGTR1,**FGF7**,LPL,**MYO10**,**BCAT1**,PHF17,**RUNX2**,**CSF1R***	Qiao et al, 2022	TAV
MIR16-5p	Downregulated	**KCNN4**,PTGS2,**CA12**,**IFRD1**,EGFR,**ARHGDIA**,**SLC16A3**	Coffey et al, 2016	TAV
MIR17-5p	Downregulated	RBL2,CCND2,**THBS1**,**RUNX1**	Coffey et al, 2016 Qiao et al, 2022	TAV TAV
MIR181a-2-3p	Downregulated	--	Coffey et al, 2016	TAV
MIR181a-5p	N.D.	ESR1,SPP1*	Qiao et al, 2022	TAV
MIR181b-5p	N.D.	ESR1,TIMP3,SPP1*	Qiao et al, 2022	TAV
MIR181c-5p	N.D.	SPP1*	Qiao et al, 2022	TAV
MIR181d-5p	N.D.	SPP1*	Qiao et al, 2022	TAV
MIR1825	N.D.	KIT*	Qiao et al, 2022	TAV
MIR182-5p	Downregulated	TSC22D3,FOXO1	Coffey et al, 2016	TAV
MIR185-5p	Downregulated	--	Coffey et al, 2016	TAV
MIR18a-5p	Downregulated	ESR1,**THBS1**	Coffey et al, 2016	TAV
MIR18b-5p	Downregulated	ESR1	Coffey et al, 2016	TAV
MIR190a-3p	N.D.	VCAM1*	Qiao et al, 2022	TAV
MIR191-5p	Downregulated	--	Coffey et al, 2016	TAV
MIR192-5p	Downregulated	--	Coffey et al, 2016	TAV
MIR193b-3p	N.D.	ESR1,KIT*	Qiao et al, 2022	TAV
MIR194-5p	Downregulated	--	Coffey et al, 2016	TAV
MIR195	Downregulated	**VWF**	Yang et al	BAV - TAV
MIR1973	Downregulated	--	Coffey et al, 2016	TAV
MIR197-3p	Downregulated	-- **SYK***	Coffey et al, 2016 Qiao et al, 2022	TAV TAV

miRNA	sense of expression	Gene target	Author	Configuration
MIR199a-3p	Upregulated	**CD44**	Coffey et al, 2016	TAV
MIR199a-5p	Upregulated	--	Coffey et al, 2016	TAV
MIR199b-3p	Upregulated	--	Coffey et al, 2016	TAV
MIR19b-3p	Downregulated	ESR1	Coffey et al, 2016	TAV
MIR200a-3p	N.D.	**CXCL12***, **PLEK***	Qiao et al, 2022	TAV
MIR200c-3p	Downregulated	**FN1**	Coffey et al, 2016	TAV
MIR204	Downregulated	**IL11**,**SERPINE1**,MEIS2,**IL1B**,**CTSC**	Song et al	TAV
MIR206	Downregulated	ESR1,**NOTCH3**,TAC1	Coffey et al, 2016	TAV
MIR20a-5p	Downregulated	**HIF1A**,RBL2,**THBS1**,**RUNX1**,CCND2	Coffey et al, 2016	TAV
MIR20b-5p	Downregulated	ESR1,BAMBI,**HIF1A**	Coffey et al, 2016	TAV
MIR21-5p	Upregulated	TIMP3,**TGFB1**,**SLC16A10**	Coffey et al, 2016	TAV
MIR2110	Downregulated	--	Coffey et al, 2016	TAV
MIR2117	N.D.	SPP1*	Qiao et al, 2022	TAV
MIR214-3p	Downregulated	--	Coffey et al, 2016	TAV
MIR216a-5p	Upregulated	--	Coffey et al, 2016	TAV
MIR221-3p	N.D.	**NAIP**,ESR1,**CORO1A**,**CXCL12***,KIT*	Qiao et al, 2022	TAV
	Upregulated	**NAIP**,ESR1,**CORO1A**	Coffey et al, 2016	TAV
MIR222-3p	N.D.	ESR1,**SOD2**,**CORO1A**,KIT*	Qiao et al, 2022	TAV
	Upregulated	ESR1,**SOD2**,**CORO1A**	Coffey et al, 2016	TAV
MIR22-3p	N.D.	ESR1,**CSF1R***	Qiao et al, 2022	TAV
MIR224-3p	N.D.	**TLR8***	Qiao et al, 2022	TAV
MIR23a-3p	N.D.	VCAM*,**CXCL12***	Qiao et al, 2022	TAV
MIR23b-3p	N.D.	VCAM*,**CXCL12***	Qiao et al, 2022	TAV
MIR23c	N.D.	VCAM*,**CXCL12***	Qiao et al, 2022	TAV
MIR24-2	N.D.	FURIN,**TGFB1**,CDK4	Kossar et al, 2020	TAV
MIR27a-3p	N.D.	SPRY2,FOXO1,**RUNX1**,SYK*	Qiao et al, 2022	TAV
MIR27a-5p	Upregulated	--	Coffey et al, 2016	TAV
MIR27b-3p	N.D.	**EDNRA**,**SYK***	Qiao et al, 2022	TAV
	Upregulated	**EDNRA**	Coffey et al, 2016	TAV
MIR296-3p	N.D.	**CX3CR1***	Qiao et al, 2022	TAV
MIR302a-3p	N.D.	CDK4,TAC1,CXCL8*	Qiao et al, 2022	TAV
MIR302c-3p	N.D.	ESR1,CXCL8*	Qiao et al, 2022	TAV
MIR302d-3p	N.D.	CCND2,NR4A2,CXCL8*	Qiao et al, 2022	TAV
MIR30d-5p	Downregulated	--	Coffey et al, 2016	TAV
MIR30e-5p	Downregulated	--	Coffey et al, 2016	TAV
MIR3120-3p	N.D.	**TLR8***	Qiao et al, 2022	TAV
MIR3124-5p	Upregulated	--	Coffey et al, 2016	TAV

miRNA	sense of expression	Gene target	Author	Configuration
MIR3128	Upregulated	--	Coffey et al, 2016	TAV
MIR3129-5p	N.D.	**CXCL12***	Qiao et al, 2022	TAV
MIR31-5p	N.D.	**CXCL12***,PPBP*	Qiao et al, 2022	TAV
	Upregulated	**CXCL12**	Coffey et al, 2016	TAV
MIR3162-5p	Downregulated	--	Coffey et al, 2016	TAV
MIR3178	Upregulated	--	Coffey et al, 2016	TAV
MIR3197	Upregulated	--	Coffey et al, 2016	TAV
MIR320a	Downregulated	TAC1	Coffey et al, 2016	TAV
	N.D.	TAC1,**CXCL12***,**CCR7***	Qiao et al, 2022	TAV
MIR320b	Downregulated	--	Coffey et al, 2016	TAV
	N.D.	**CXCL12***,**CCR7***	Qiao et al, 2022	TAV
MIR320c	Downregulated	--	Coffey et al, 2016	TAV
	N.D.	**CCR7***	Qiao et al, 2022	TAV
MIR320d	N.D.	**CCR7***	Qiao et al, 2022	TAV
MIR324-3p	Downregulated	--	Coffey et al, 2016	TAV
MIR328-3p	Downregulated	--	Coffey et al, 2016	TAV
MIR335-5p	Upregulated	**RUNX2**	Coffey et al, 2016	TAV
MIR339-3p	Downregulated	--	Coffey et al, 2016	TAV
MIR339-5p	Downregulated	BCL6	Coffey et al, 2016	TAV
MIR340-5p	N.D.	KIT*	Qiao et al, 2022	TAV
MIR34a-5p	N.D.	**CD44**,CDK4,KIT*,**CSF1R***	Qiao et al, 2022	TAV
	Upregulated	**CD44**,CDK4	Coffey et al, 2016	TAV
MIR3606-3p	N.D.	CXCL8*	Qiao et al, 2022	TAV
MIR3617-5p	N.D.	KIT*	Qiao et al, 2022	TAV
MIR3681-5p	N.D.	CCR1*	Qiao et al, 2022	TAV
MIR369-3p	N.D.	CXCL8*	Qiao et al, 2022	TAV
MIR376a-2-5p	N.D.	CXCL8*	Qiao et al, 2022	TAV
MIR378a-3p	Downregulated	--	Coffey et al, 2016	TAV
MIR378a-5p	Downregulated	--	Coffey et al, 2016	TAV
MIR378c	Downregulated	--	Coffey et al, 2016	TAV
MIR381-3p	Upregulated	--	Coffey et al, 2016	TAV
			Qiao et al, 2022	TAV
MIR3915	N.D.	**PLEK***	Qiao et al, 2022	TAV
MIR3941	N.D.	KIT*	Qiao et al, 2022	TAV
MIR3978	N.D.	**SYK***	Qiao et al, 2022	TAV
MIR422a	Downregulated	--	Coffey et al, 2016	TAV
	N.D.	**CCR7***	Qiao et al, 2022	TAV
MIR4251	N.D.	SPP1*	Qiao et al, 2022	TAV

miRNA	sense of expression	Gene target	Author	Configuration
MIR4253	Downregulated	--	Coffey et al, 2016	TAV
MIR425-5p	Downregulated	--	Coffey et al, 2016	TAV
MIR4262	N.D.	SPP1*	Qiao et al, 2022	TAV
MIR4282	N.D.	CXCL8*	Qiao et al, 2022	TAV
MIR4284	Downregulated	--	Coffey et al, 2016	TAV
MIR4290	N.D.	**SYK***	Qiao et al, 2022	TAV
MIR432-5p	N.D.	**CCR7***	Qiao et al, 2022	TAV
MIR4429	N.D.	**CCR7***	Qiao et al, 2022	TAV
MIR4458	N.D.	**CCR7***	Qiao et al, 2022	TAV
MIR4474-3p	N.D.	**HCK***	Qiao et al, 2022	TAV
MIR448	N.D.	**CXCL12***	Qiao et al, 2022	TAV
MIR4481	N.D.	**FPR1***	Qiao et al, 2022	TAV
MIR4492	Downregulated	--	Jiao et al, 2019	TAV
MIR449C	Downregulated	--	Jiao et al, 2019	TAV
MIR4500	N.D.	**CCR7***	Qiao et al, 2022	TAV
MIR4516	N.D.	**PLEK***	Qiao et al, 2022	TAV
MIR451a	Downregulated	--	Coffey et al, 2016	TAV
MIR4524a-3p	N.D.	PPBP*	Qiao et al, 2022	TAV
MIR455-3p	Upregulated	--	Coffey et al, 2016	TAV
MIR4686	N.D.	**PLEK***	Qiao et al, 2022	TAV
MIR4687-3p	N.D.	CXCL8*	Qiao et al, 2022	TAV
MIR4692	N.D.	VCAM1*	Qiao et al, 2022	TAV
MIR4699-3p	N.D.	CXCL8*	Qiao et al, 2022	TAV
MIR4701-3p	N.D.	**SYK***	Qiao et al, 2022	TAV
MIR4715-5p	N.D.	**TLR7***	Qiao et al, 2022	TAV
MIR4717 5p	N.D.	VCAM1*	Qiao et al, 2022	TAV
MIR4722-3p	N.D.	**SYK***	Qiao et al, 2022	TAV
MIR4725-3p	N.D.	**CCL5***	Qiao et al, 2022	TAV
MIR4739	Upregulated	--	Jiao et al, 2019	TAV
MIR4745-5p	N.D.	**FPR1***	Qiao et al, 2022	TAV
MIR4753-3p	N.D.	SPP1*	Qiao et al, 2022	TAV
MIR4769-3p	N.D.	PPBP*	Qiao et al, 2022	TAV
MIR4773	N.D.	CCR1*	Qiao et al, 2022	TAV
MIR4774-3p	Upregulated	--	Jiao et al, 2019	TAV
MIR4789-3p	N.D.	KIT*	Qiao et al, 2022	TAV
MIR4795-3p	N.D.	CCR1*	Qiao et al, 2022	TAV
MIR486-3p	Downregulated	--	Coffey et al, 2016	TAV
	N.D.	**PLEK***	Qiao et al, 2022	TAV
MIR486-5p	Downregulated	--	Coffey et al, 2016	TAV
MIR491-5p	Downregulated	--	Coffey et al, 2016	TAV
MIR493-5p	N.D.	CXCL8*	Qiao et al, 2022	TAV
MIR495-5p	N.D.	VCAM1*	Qiao et al, 2022	TAV
MIR5003-5p	N.D.	SPP1*	Qiao et al, 2022	TAV
MIR500a-3p	Downregulated	--	Coffey et al, 2016	TAV
MIR500a-5p	Downregulated	--	Coffey et al, 2016	TAV
			Qiao et al, 2022	TAV
MIR5010-3p	N.D.	**CX3CR1***	Qiao et al, 2022	TAV
MIR5011	Upregulated	--	Hadji et al, 2016	TAV

miRNA	sense of expression	Gene target	Author	Configuration
MIR5011-5p	N.D.	VCAM1*	Qiao et al, 2022	TAV
MIR501-3p	Downregulated	--	Coffey et al, 2016	TAV
	N.D.	CCR1*	Qiao et al, 2022	TAV
MIR502-3p	Downregulated	--	Coffey et al, 2016	TAV
			Qiao et al, 2022	TAV
MIR5095	N.D.	**CCL5***	Qiao et al, 2022	TAV
MIR513a-3p	N.D.	CXCL8*	Qiao et al, 2022	TAV
MIR513b-3p	N.D.	**CXCL12***	Qiao et al, 2022	TAV
MIR513c-3p	N.D.	CXCL8*	Qiao et al, 2022	TAV
MIR513c-5p	N.D.	VCAM1*	Qiao et al, 2022	TAV
MIR518c-5p	N.D.	CCR1*	Qiao et al, 2022	TAV
MIR5192	N.D.	**TYROBP***	Qiao et al, 2022	TAV
MIR5194	N.D.	**CCR7***,**CCL5***	Qiao et al, 2022	TAV
MIR520a-5p	N.D.	**TLR7***	Qiao et al, 2022	TAV
MIR520b	N.D.	CXCL8*	Qiao et al, 2022	TAV
MIR520d-5p	N.D.	VCAM1*	Qiao et al, 2022	TAV
MIR522-3p	N.D.	**TLR8***	Qiao et al, 2022	TAV
MIR525-5p	N.D.	**TLR7***	Qiao et al, 2022	TAV
MIR532-3p	Downregulated	--	Coffey et al, 2016	TAV
MIR532-5p	Downregulated	**RUNX3**	Coffey et al, 2016	TAV
MIR541-3p	N.D.	**TYROBP***	Qiao et al, 2022	TAV
MIR545-3p	N.D.	**LRP1**,VCAM1*	Qiao et al, 2022	TAV
MIR548a-3p	Upregulated	--	Coffey et al, 2016	TAV
MIR548au-3p	N.D.	VCAM1*	Qiao et al, 2022	TAV
MIR548v	N.D.	KIT*	Qiao et al, 2022	TAV
MIR550a-3-5p	N.D.	**CX3CR1***	Qiao et al, 2022	TAV
MIR550a-3p	Upregulated	--	Coffey et al, 2016	TAV
MIR550a-5p	N.D.	**CX3CR1***	Qiao et al, 2022	TAV
MIR550b-2-5p	N.D.	**CX3CR1***	Qiao et al, 2022	TAV
MIR5572	N.D.	**CX3CR1***	Qiao et al, 2022	TAV
MIR561-5p	N.D.	VCAM1*	Qiao et al, 2022	TAV
MIR5692a	N.D.	CXCL8*	Qiao et al, 2022	TAV
MIR5706	N.D.	CXCL8*	Qiao et al, 2022	TAV
MIR574-3p	Downregulated	--	Coffey et al, 2016	TAV
MIR583	N.D.	KIT*	Qiao et al, 2022	TAV
MIR586	N.D.	**TLR7***	Qiao et al, 2022	TAV
MIR607	N.D.	CXCL8*	Qiao et al, 2022	TAV
MIR6074	N.D.	VCAM1*	Qiao et al, 2022	TAV
MIR6124	N.D.	CCR1*	Qiao et al, 2022	TAV
MIR6132	N.D.	**SYK***	Qiao et al, 2022	TAV
MIR625-5p	Downregulated	--	Coffey et al, 2016	TAV
MIR629-5p	Downregulated	--	Coffey et al, 2016	TAV
	N.D.	CCR1*	Qiao et al, 2022	TAV
MIR638	Upregulated	--	Jiao et al, 2019	TAV
MIR641	N.D.	KIT*	Qiao et al, 2022	TAV
MIR6513-5p	N.D.	**TLR8***	Qiao et al, 2022	TAV
MIR652-3p	Downregulated	--	Coffey et al, 2016	TAV
MIR654-5p	N.D.	**TYROBP***	Qiao et al, 2022	TAV

miRNA	sense of expression	Gene target	Author	Configuration
MIR664-5p	Downregulated	--	Coffey et al, 2016	TAV
MIR665	Downregulated	--	Coffey et al, 2016	TAV
MIR671-5p	N.D.	KIT*	Qiao et al, 2022	TAV
MIR6718-5p	N.D.	**PLEK***	Qiao et al, 2022	TAV
MIR6722-3p	N.D.	**PLEK***	Qiao et al, 2022	TAV
MIR675	Upregulated	--	Schlotter et al, 2018	TAV
MIR6764-3p	N.D.	**CCR7***	Qiao et al, 2022	TAV
MIR6806	Downregulated	--	Jiao et al, 2019	TAV
MIR6849-5p	N.D.	CCR1*	Qiao et al, 2022	TAV
MIR6870-5p	N.D.	**CSF1R***	Qiao et al, 2022	TAV
MIR7110	Downregulated	--	Sun et al, 2021	BAV - TAV
MIR7-5p	N.D.	EGFR,**CXCL12***	Qiao et al, 2022	TAV
MIR765	N.D.	**CXCL12***	Qiao et al, 2022	TAV
MIR766-3p	Downregulated	--	Coffey et al, 2016	TAV
MIR8087	Downregulated	--	Jiao et al, 2019 Qiao et al, 2022	TAV TAV
MIR885-5p	Downregulated	--	Coffey et al, 2016	TAV
MIR889-3p	N.D.	CXCL8*	Qiao et al, 2022	TAV
MIR92a-3p	Downregulated	**THBS1**	Coffey et al, 2016	TAV
MIR933	Downregulated	--	Coffey et al, 2016	TAV
MIR93-5p	Downregulated	--	Coffey et al, 2016	TAV
MIR939-5p	Downregulated	--	Coffey et al, 2016 Qiao et al, 2022	TAV TAV
MIR98-5p	N.D.	**CCR7***	Qiao et al, 2022	TAV
MIR99a-5p	Downregulated	FGFR3,**SERPINE1**	Coffey et al, 2016	TAV
MIRLET7A1 5p	N.D.	CCND2,**PRDM1**,NFKB1,**SLC20A1**,CASP8,**IL6**,**CCR7***	Qiao et al, 2022	TAV
MIRLET7B	N.D.	**BIRC6**,PGRMC1,**PRDM1**,**PXDN**,**THBS1**,**CCR7***	Qiao et al, 2022	TAV
MIRLET7C 5p	N.D.	**CCR7***	Qiao et al, 2022	TAV
MIRLET7E 5p	N.D.	**CCR7***	Qiao et al, 2022	TAV
MIRLET7F1	Upregulated	**PRDM1**	Coffey et al, 2016	TAV
MIRLET7F2 3p	N.D.	VCAM1*	Qiao et al, 2022	TAV
MIRLET7F2 5p	N.D.	**CCR7***	Qiao et al, 2022	TAV
MIRLET7G 5p	N.D.	**COL1A2**,**CCR7***	Qiao et al, 2022	TAV
MIRLET7I	Upregulated	--	Coffey et al, 2016	TAV
MIRLET7I 5p	N.D.	**CCR7***	Qiao et al, 2022	TAV

Supplementary 7. Supplementary table 4. List of significant pathways (FDR<0.05). Differentially expressed genes according to literature review are shown. Genes in bold are regulated by any of the differentially expressed miRNA identified. Genes with a list one associated variant are marked with an asterisk.

ID	Pathway	FDR	Matching genes accord to list extracted from the systematic review
hsa04060	Cytokine-cytokine receptor interaction	1.92e-09	IL2RB,**TGFB1***,CSF3, IL10RA,IL4,IL17C,**CCR7**,IL1RN,**IL1B**,**IL11**,CD27,**CSF1R**,CCR2,CCR5,CXCR1,TNFRSF11B,IL17D,IL16,CXCL10,TNFRSF12A,LEPR,CXCL14,IL21R,**CX3CR1**,CXCL9,XCL2,CXCR3,TNFSF15,CNTFR,IFNA8,CCL26,CXCL1,**CXCL12**,IL6,CXCR4,LIFR,TNF,LTB,IL12RB1,**CCL5**,CCL4,PRLR,CCL15
hsa04151	PI3K-Akt signaling pathway	1.92e-09	IL2RB,COMP,CSF3,NFKB1,IL4,**CDK4**,CHAD,**THBS1**,ITGAV,**CCND2**,**VWF**,**RBL2**,ITGA9,ITGB7,ERBB3,FGF7,**EGFR**,NTRK2,**CSF1R**,COL1A2,COL6A2,ANGPT2,LAMA3,COL4A5,FOXO3,**FGFR3**,PIK3AP1,**FN1**,COL4A2,LAMC3,LPAR1,**SYK**,COL4A1,IFNA8,IGF1,COL4A3,COL4A4,ITGA4,SOS1,IL6,LAMA2,TGFA,PIK3CG,PIK3R1,JAK3,LOC102723407,FGF1,PRLR,COL9A3
hsa04512	ECM-receptor interaction	2.14e-09	COMP,CHAD,**THBS1**,ITGAV,**VWF**,ITGA9,ITGB7,COL1A2,COL6A2,LAMA3,COL4A5,**FN1**,COL4A2,LAMC3,COL4A1,SDC1,HMMR,COL4A3,COL4A4,ITGA4,**CD44**,LAMA2,FRAS1,COL9A3
hsa04061	Viral protein interaction with cytokine and cytokine receptor	1.83e-07	IL2RB, IL10RA,**CCR7**,**CSF1R**,CCR2,CCR5,CXCR1,CXCL10,CXCL14,**CX3CR1**,CXCL9,XCL2,CXCR3,CCL26,CXCL1,**CXCL12**,IL6,CXCR4,TNF,**CCL5**,CCL4,CCL15
hsa05152	Tuberculosis	3.81e-07	CD74,MAPK13,LBP,**CORO1A**,**TGFB1***,NFKB1,IL10RA,CYP27B1*,CTSD,**IL1B**,FCGR2A,ATP6V0D2,CASP10,CLEC7A,SPHK1,CD209,CASP8,FCGR1A,**SYK**,IFNA8,LSP1,ITGB2,CD14,IL6,TNF,CR1L,ITGAX,LOC102723407
hsa05200	Pathways in cancer	4.61e-07	IL2RB,**TGFB1***,NFKB1,IL4,PTGER2,GADD45G,**CDK4**,ITGAV,**CCND2**,**NOTCH3**,FGF7,**EGFR**,**CSF1R**,**RUNX1**,PTGER4,**EDNRA**,LAMA3,COL4A5,ZBTB16,**FGFR3**,**FN1**,STAT4,CASP8,COL4A2,LAMC3,**PTGS2**,**PIM1**,LPAR1,AR,CKS2,COL4A1,PIM2,**FOXO1**,IFNA8,TRAF3,IGF1,**CXCL12**,MGST1,COL4A3,COL4A4,SOS1,IL6,RASGRP3,CXCR4,AGTR1,LAMA2,TGFA,**ESR1**,PIK3R1,JAK3,**HIF1A**,BDKRB2,IL12RB2,FGF1
hsa04380	Osteoclast differentiation	8.68e-07	LCP2,MAPK13,**TGFB1***,NFKB1,CYBA,**TYROBP**,**IL1B**,FCGR2A,**CSF1R**,TNFRSF11B,LILRB1,SOCS3,FCGR1A,TREM2,**SYK**,LILRB4,LILRB2,FHL2,TNF,PIK3R1,MAP2K6,LCK,BTK
hsa04933	AGE-RAGE signaling pathway in diabetic complications	1.94e-06	MAPK13,**TGFB1***,**SERPINE1**,NFKB1,**CDK4**,**IL1B**,COL1A2,COL4A5,**FN1**,COL4A2,PLCE1,**PIM1**,COL4A1,**FOXO1**,COL4A3,COL4A4,IL6,TNF,AGTR1,PIK3R1
hsa04062	Chemokine signaling pathway	2.09e-06	NFKB1,**CCR7**,CCR2,CCR5,CXCR1,CXCL10,CXCL14,FOXO3,**CX3CR1**,CXCL9,XCL2,CXCR3,**HCK**,WAS,CCL26,CXCL1,**CXCL12**,SOS1,CXCR4,ITK,PIK3CG,PIK3R1,LYN,JAK3,VAV1,**CCL5**,CCL4,CCL15
hsa04620	Toll-like receptor signaling pathway	2.79e-06	MAPK13,LBP,NFKB1,**IL1B**,LY96,CXCL10,**TLR8**,CD86,CASP8,CXCL9,IFNA8,**TLR7**,TRAF3,CD14,IL6,TNF,PIK3R1,MAP2K6,**CCL5**,CCL4
hsa05144	Malaria	2.93e-06	**TGFB1***,COMP,CSF3,KLRB1,LRP1,HBA2,**THBS1**,**IL1B**,SDC1,ITGB2,IL6,TNF,CR1L,HBB
hsa05146	Amoebiasis	2.93e-06	**TGFB1***,NFKB1,**IL1B**,COL1A2,LAMA3,COL4A5,**FN1**,COL4A2,LAMC3,COL4A1,CXCL1,COL4A3,COL4A4,ITGB2,CD14,IL6,TNF,LAMA2,PIK3R1,LOC102723407
hsa04510	Focal adhesion	3.49e-06	COMP,CHAD,**THBS1**,ITGAV,**CCND2**,**VWF**,ITGA9,ITGB7,**EGFR**,COL1A2,COL6A2,ZYX,LAMA3,COL4A5,**FN1**,COL4A2,LAMC3,COL4A1,IGF1,COL4A3,COL4A4,ITGA4,SOS1,PARVG,LAMA2,PIK3R1,VAV1,COL9A3
hsa05165	Human papillomavirus infection	6.97e-06	COMP,NFKB1,**CDK4**,CHAD,**THBS1**,ITGAV,**CCND2**,**VWF**,**RBL2**,**NOTCH3**,ITGA9,ITGB7,**EGFR**,ATP6V0D2,COL1A2,COL6A2,PTGER4,LAMA3,COL4A5,**FN1**,CASP8,COL4A2,LAMC3,**PTGS2**,COL4A1,DLG2,**FOXO1**,IFNA8,TRAF3,COL4A3,COL4A4,ITGA4,SOS1,TNF,LAMA2,PIK3R1,COL9A3
hsa04630	JAK-STAT signaling pathway	9.52e-06	IL2RB,CSF3,IL10RA,IL4,**CCND2**,**IL11**,**EGFR**,IL17D,SOCS3,LEPR,IL21R,STAT4,**PIM1**,AOX1,CNTFR,IFNA8,SOS1,IL6,LIFR,PIK3R1,JAK3,PIAS1.IL12RB1,PRLR
hsa04659	Th17 cell differentiation	2.60e-05	MAPK13,IL2RB,**TGFB1***,NFKB1,IL4,RORA,**IL1B**,**RUNX1**,IL17D,IL21R,CD247,IRF4,IL6,CD3G,JAK3,**HIF1A**,IL12RB1,LCK
hsa04064	NF-kappa B signaling pathway	3.04e-05	LBP,NFKB1,GADD45G,**IL1B**,LY96,**PTGS2**,**SYK**,TRAF3,CXCL1,**CXCL12,**CD14,TNF,LTB,LYN,LCK, LOC102723407,CCL4,BTK

ID	Pathway	FDR	Matching genes accord to list extracted from the systematic review
hsa04666	Fc gamma R-mediated phagocytosis	3.04e-05	FCGR2A,SPHK1,PLA2G4A,FCGR1A,PLPP3,**GSN**,**SYK**,**HCK**,WAS,PTPRC,**MYO10**,PIK3R1,LYN,CFL1,VAV1, LOC102723407,WASF2
hsa05222	Small cell lung cancer	3.54e-05	NFKB1,GADD45G,**CDK4**,ITGAV,LAMA3,COL4A5,**FN1**,COL4A2,LAMC3,**PTGS2**,CKS2,COL4A1,TRAF3,COL4A3,COL4A4,LAMA2,PIK3R1
hsa04610	Complement and coagulation cascades	3.61e-05	**SERPINE1**,**VWF**,C6,C7,**A2M**,F13B,F5,C1QC,C1QA,F10,ITGB2,SERPINA1,CR1L,BDKRB2,ITGAX,CFD
hsa05134	Legionellosis	5.03e-05	NFKB1,**IL1B**,HSPA6,CLK4,CASP8,CXCL1,ITGB2,CD14,IL6,TNF,CR1L,**NAIP**,CASP1
hsa04614	Renin-angiotensin system	5.57e-05	CMA1,ENPEP,REN,**ACE***,ANPEP,AGTR2,ACE2,AGTR1,MAS1
hsa04924	Renin secretion	5.80e-05	PTGER2,CACNA1C,REN,PDE3B,**ACE***,GUCY1A1,PTGER4,**EDNRA**,CTSB,NPR1,ADRB1,AGTR1,GUCY1B1,ADCYAP1
hsa04662	B cell receptor signaling pathway	7.26e-05	CD79A,NFKB1,CD72,LILRB1,PIK3AP1,**SYK**,LILRB4,LILRB2,SOS1,RASGRP3,PIK3R1,LYN,VAV1,LOC102723407,BTK
hsa04640	Hematopoietic cell lineage	8.28e-05	CSF3,IL4,**IL1B**,**IL11**,**CSF1R**,ANPEP,FCGR1A,ITGA4,CD14,IL6,**CD44**,TNF,CR1L,CD3G,MS4A1,LOC102723407
hsa05140	Leishmaniasis	8.28e-05	MAPK13,**TGFB1***,NFKB1,IL4,CYBA,**IL1B**,FCGR2A,**PTGS2**,FCGR1A,ITGA4,ITGB2,TNF,CR1L,LOC102723407
hsa05169	Epstein-Barr virus infection	0.00011	MAPK13,NFKB1,GADD45G,**CDK4**,**CCND2**,CXCL10,CASP8,CD247,**SYK**,IFNA8,TRAF3,**RUNX3**,NCOR2,IL6,**CD44**,TNF,PIK3R1,LYN,CD3G,JAK3,MAP2K6,LOC102723407,BTK,B2M
hsa04664	Fc epsilon RI signaling pathway	0.00017	LCP2,MAPK13,IL4,PLA2G4A,**SYK**,SOS1,TNF,PIK3R1,LYN,MAP2K6,VAV1,LOC102723407,BTK
hsa05142	Chagas disease	0.00017	MAPK13,**TGFB1***,**SERPINE1**,NFKB1,**IL1B**,**ACE***,CASP8,CD247,C1QC,C1QA,IL6,TNF,PIK3R1,CD3G,BDKRB2,**CCL5**
hsa05202	Transcriptional misregulation in cancer	0.00017	IL2RB,NFKB1,ID2,GADD45G,**CCND2**,ITGB7,**CSF1R**,**RUNX1**,CD86,ZBTB16,BCL11B,FCGR1A,**RUNX2**,**FOXO1**,IGF1,AFF1,**BCL6**,CD14,IL6,KMT2A,LOC102723407,EYA1
hsa05130	Pathogenic Escherichia coli infection	0.00019	CLDN11,MAPK13,NFKB1,CYTH4,MYO5C,**IL1B**,FCGR2A,HCLS1,MYO1D,CASP8,LPAR1,TUBAL3,MYO5A,CLDN5,IL6,TNF,**MYO10**,**NAIP**,CASP1,TUBA1A,LOC102723407,WASF2,MYO1F
hsa04974	Protein digestion and absorption	0.00021	COL1A2,COL6A2,COL4A5,COL18A1,COL4A2,DPP4,**SLC16A10**,COL5A1,COL5A2,COL15A1,COL4A1,COL4A3,COL4A4,ACE2,COL9A3,**KCNN4**
hsa05205	Proteoglycans in cancer	0.0003	MAPK13,**TGFB1***,**THBS1**,ITGAV,**TIMP3**,LUM,ERBB3,**EGFR**,ANK3,COL1A2,HCLS1,**FN1**,PLCE1,SDC1,IGF1,HPSE,SOS1,**CD44**,TNF,**ESR1**,PIK3R1,**HIF1A**,VAV1
hsa05323	Rheumatoid arthritis	0.00038	**TGFB1***,**IL1B**,**IL11**,ATP6V0D2,CD28,CD86,CXCL1,**CXCL12**,ITGB2,IL6,TNF,LTB,**CCL5**,LOC102723407
hsa04650	Natural killer cell mediated cytotoxicity	0.00043	LCP2,HCST,**TYROBP**,CD247,SH2D1A,**SYK**,IFNA8,KLRC2,ITGB2,SOS1,TNF,PIK3R1,KLRC1,VAV1,LCK,LOC102723407,CD48
hsa05133	Pertussis	0.00043	MAPK13,NFKB1,**IL1B**,IRF8,LY96,C1QC,C1QA,ITGB2,CD14,IL6,TNF,CFL1,CASP1
hsa04672	Intestinal immune network for IgA production	0.00044	**TGFB1***,IL4,ITGB7,CD28,CD86,**CXCL12**,ITGA4,IL6,CXCR4,LOC102723407
hsa05163	Human cytomegalovirus infection	0.00049	MAPK13, IL10RA,NFKB1,PTGER2,**CDK4**,ITGAV,**IL1B**,**EGFR**,CCR5,PTGER4,CASP8,AKAP13,**PTGS2**,IFNA8,**CXCL12**,SOS1,IL6,CXCR4,TNF,PIK3R1,MAP2K6,**CCL5**,CCL4,B2M
hsa04668	TNF signaling pathway	0.00053	BCL3,MAPK13,NFKB1,**IL1B**,CASP10,CXCL10,SOCS3,CASP8,**PTGS2**,TRAF3,CXCL1,IL6,TNF,PIK3R1,MAP2K6,**CCL5**
hsa05135	Yersinia infection	0.00054	LCP2,MAPK13,NFKB1,**IL1B**,FCGR2A,**FN1**,WAS,ITGA4,IL6,TNF,PIK3R1,CASP1,MAP2K6,VAV1,LCK,WASF2,LOC102723407
hsa04660	T cell receptor signaling pathway	0.00057	LCP2,MAPK13,NFKB1,IL4,**CDK4**,CD28,CD247,SOS1,ITK,TNF,PTPRC,PIK3R1,CD3G,VAV1,LCK
hsa04625	C-type lectin receptor signaling pathway	0.00061	BCL3,MAPK13,NFKB1,**IL1B**,CLEC7A,IL17D,CD209,CASP8,**PTGS2**,**SYK**,LSP1,IL6,TNF,PIK3R1,CASP1

ID	Pathway	FDR	Matching genes accord to list extracted from the systematic review
hsa04657	IL-17 signaling pathway	0.00073	MAPK13,CSF3,NFKB1,IL4,IL17C,**IL1B**,IL17D,CXCL10,CASP8,**PTGS2**,TRAF3,CXCL1,IL6,TNF
hsa05145	Toxoplasmosis	0.00073	MAPK13,**TGFB1***,NFKB1,IL10RA,LY96,CCR5,HSPA6,LAMA3,CASP8,LAMC3,TNF,LAMA2,PIK3CG,**LDLR**,MAP2K6
hsa04611	Platelet activation	0.0012	LCP2,MAPK13,**VWF**,VAMP8,FCGR2A,GUCY1A1,COL1A2,P2RY12,PLA2G4A,**SYK**,TBXA2R,PIK3CG,GUCY1B1,PIK3R1,LYN,BTK
hsa05162	Measles	0.0014	IL2RB,NFKB1,EIF2S1,**CDK4**,**CCND2**,**IL1B**,HSPA6,CD209,CD28,CASP8,IFNA8,**TLR7**,TRAF3,IL6,PIK3R1,CD3G,JAK3
hsa04810	Regulation of actin cytoskeleton	0.0015	PFN1,ITGAV,ITGA9,ITGB7,FGF7,**EGFR**,**FGFR3**,**FN1**,**GSN**,LPAR1,**CXCL12**,ITGA4,ITGB2,SOS1,CXCR4,PIK3R1,CFL1,BDKRB2,ITGAX,VAV1,FGF1, WASF2
hsa05321	Inflammatory bowel disease	0.0033	**TGFB1***,NFKB1,IL4,RORA,**IL1B**,IL21R,STAT4,IL6,TNF,IL12RB1
hsa04514	Cell adhesion molecules	0.004	CLDN11,ITGAV,ITGA9,ITGB7,CD28,CD86,L1CAM,SDC1,IGSF11,ITGA4,ITGB2,CLDN5,PTPRC,CNTN1,CD226,**NCAM1**
hsa04658	Th1 and Th2 cell differentiation	0.004	MAPK13,IL2RB,NFKB1,IL4,**NOTCH3**,STAT4,CD247,**RUNX3**,CD3G,JAK3,,IL12RB1,LCK
hsa04145	Phagosome	0.0047	**CORO1A**,COMP,**THBS1**,ITGAV,CYBA,FCGR2A,ATP6V0D2,CLEC7A,OLR1,CD209,FCGR1A,TUBAL3,ITGB2,CD14,TUBA1A,LOC102723407
hsa04015	Rap1 signaling pathway	0.005	LCP2,MAPK13,PFN1,**THBS1**,FGF7,**EGFR**,**CSF1R**,ANGPT2,**FGFR3**,CNR1,PLCE1,LPAR1,IGF1,ITGB2,RASGRP3,PIK3R1,MAP2K6,**FPR1**,VAV1,FGF1
hsa05167	Kaposi sarcoma-associated herpesvirus infection	0.0052	MAPK13,NFKB1,**CDK4**,CCR5,ANGPT2,CD86,CASP8,**PTGS2**,**SYK**,**HCK**,IFNA8,TRAF3,CXCL1,IL6,PIK3CG,PIK3R1,LYN,**HIF1A**,MAP2K6
hsa04010	MAPK signaling pathway	0.0065	MAPK13,**TGFB1***,NFKB1,DUSP1,GADD45G,**IL1B**,CACNA1C,ERBB3,FGF7,**EGFR**,NTRK2,**CSF1R**,HSPA6,ANGPT2,**FGFR3**,MAPT,PLA2G4A,IGF1,SOS1,CD14,RASGRP3,TNF,TGFA,MAP2K6,FGF1
hsa05221	Acute myeloid leukemia	0.0069	NFKB1,**CSF1R**,**RUNX1**,ZBTB16,FCGR1A,**PIM1**,PIM2,SOS1,CD14,PIK3R1
hsa05143	African trypanosomiasis	0.0099	HBA2,**IL1B**,IL6,TNF,HPR,HBB,LOC102723407
hsa04068	FoxO signaling pathway	0.0106	MAPK13,**TGFB1***,GADD45G,**CCND2**,**RBL2**,**EGFR**,**FOXO1**,FOXO3,IGF1,**BCL6**,SOS1,IL6,PIK3R1,**SOD2**
hsa04115	p53 signaling pathway	0.0106	**SERPINE1**,GADD45G,**CDK4**,**THBS1**,**CCND2**,**CCNG1**,CASP8,RRM2,IGF1,CDK1
hsa05131	Shigellosis	0.0108	MAPK13,PFN1,NFKB1,CYTH4,**IL1B**,**EGFR**,HK3,HCLS1,CBX3,FOXO3,PLCE1,**FOXO1**,CD14,**CD44**,TNF,PIK3R1,**NAIP**,CASP1,**CCL5**,WASF2
hsa05340	Primary immunodeficiency	0.0108	CD79A,IGLL1,PTPRC,JAK3,LCK,BTK,LOC102723407
hsa05160	Hepatitis C	0.011	CLDN11,NFKB1,EIF2S1,**CDK4**,**EGFR**,CXCL10,SOCS3,CASP8,IFNA8,TRAF3,SOS1,CLDN5,TNF,PIK3R1,PIAS1,**LDLR**
hsa05410	Hypertrophic cardiomyopathy	0.0128	**TGFB1***,ITGAV,ITGA9,CACNA1C,ITGB7,**ACE***,IGF1,ITGA4,IL6,TNF,LAMA2
hsa05164	Influenza A	0.015	NFKB1,EIF2S1,**CDK4**,**IL1B**,CXCL10,SOCS3,TPSAB1,CASP8,IFNA8,**TLR7**,TRAF3,IL6,TNF,PIK3R1,CASP1,**CCL5**
hsa05120	Epithelial cell signaling in Helicobacter pylori infection	0.0163	MAPK13,CSK,NFKB1,**EGFR**,ATP6V0D2,CXCR1,CXCL1,LYN,**CCL5**
hsa05322	Systemic lupus erythematosus	0.0194	SNRPD3,C6,FCGR2A,C7,CD28,CD86,FCGR1A,C1QC,C1QA,TNF,LOC102723407
hsa05414	Dilated cardiomyopathy	0.0194	**TGFB1***,ITGAV,ITGA9,CACNA1C,ITGB7,ADRB1,IGF1,ITGA4,TNF,LAMA2,LOC102723407
hsa04917	Prolactin signaling pathway	0.0205	MAPK13,NFKB1,**CCND2**,SOCS3,FOXO3,SOS1,**ESR1**,PIK3R1,PRLR
hsa04020	Calcium signaling pathway	0.026	CACNA1C,ERBB3,**EGFR**,SPHK1,**EDNRA**,OXTR,TRDN,ADRB1,PLCE1,PHKA1,HRH1,CXCR4,TBXA2R,AGTR1,P2RX6,BDKRB2,LOC102723407

ID	Pathway	FDR	Matching genes accord to list extracted from the systematic review
hsa05206	MicroRNAs in cancer	0.026	NFKB1,**THBS1**,**CCND2**,**NOTCH3**,**TIMP3**,ERBB3,**EGFR**,**FGFR3**,**CCNG1**,**PTGS2**,**PIM1**,SPRY2,SOS1,**CD44**,PIK3R1
hsa05132	Salmonella infection	0.0274	MAPK13,PFN1,NFKB1,CYTH4,CSE1L,**IL1B**,RHOB,LY96,ARHGEF26,CASP8,CD14,IL6,TNF,PTPRC,PIK3CG,**NAIP**,CASP1,MAP2K6
hsa05150	Staphylococcus aureus infection	0.0275	FCGR2A,KRT17,FPR3,FCGR1A,C1QC,C1QA,ITGB2,CFD,**FPR1**,LOC102723407
hsa00350	Tyrosine metabolism	0.0282	ADH1A,PNMT,ADH1B,AOC3,AOX1,IL4I1
hsa04210	Apoptosis	0.0285	CTSZ,NFKB1,**CTSC**,CTSD,GADD45G,EIF2S1,CASP10,CTSB,CASP8,TUBAL3,TNF,PIK3R1,TUBA1A
hsa05235	PD-L1 expression and PD-1 checkpoint pathway in cancer	0.0285	MAPK13,NFKB1,**EGFR**,CD28,CD247,PIK3R1,CD3G,**HIF1A**,MAP2K6,LCK
hsa05332	Graft-versus-host disease	0.0306	**IL1B**,CD28,CD86,IL6,TNF,KLRC1
hsa04218	Cellular senescence	0.033	MAPK13,**TGFB1***,**SERPINE1**,NFKB1,GADD45G,**CDK4**,**CCND2**,**RBL2**,**FOXO1**,FOXO3,CDK1,IL6,PIK3R1,MAP2K6
hsa04623	Cytosolic DNA-sensing pathway	0.033	NFKB1,**IL1B**,CXCL10,IFNA8,IL6,CASP1,**CCL5**,CCL4
hsa01521	EGFR tyrosine kinase inhibitor resistance	0.0363	ERBB3,**EGFR**,**FGFR3**,FOXO3,IGF1,SOS1,IL6,TGFA,PIK3R1
hsa04750	Inflammatory mediator regulation of TRP channels	0.0376	MAPK13,PTGER2,**IL1B**,PTGER4,PLA2G4A,IGF1,HRH1,PIK3R1,BDKRB2,MAP2K6
hsa04080	Neuroactive ligand-receptor interaction	0.0445	PTGER2,SSTR1,PTGER4,P2RY14,**EDNRA**,**TAC1**,OXTR,VIPR1,LEPR,FPR3,ADRB1,CNR1,AGTR2,LPAR1,HRH1,NPY,TBXA2R,AGTR1,P2RX6,BDKRB2,ADCYAP1,**FPR1**,PRLR,MAS1
hsa04014	Ras signaling pathway	0.0459	NFKB1,FGF7,PLA1A,**EGFR**,NTRK2,**CSF1R**,ANGPT2,**FGFR3**,RASAL3,PLA2G4A,PLCE1,PLA2G5,IGF1,SOS1,RASGRP3,TGFA,PIK3R1,FGF1
hsa04670	Leukocyte transendothelial migration	0.0459	CLDN11,MAPK13,CYBA,**CXCL12**,ITGA4,ITGB2,CLDN5,CXCR4,ITK,PIK3R1,VAV1
hsa04926	Relaxin signaling pathway	0.0459	MAPK13,**TGFB1***,NFKB1,**EGFR**,COL1A2,COL4A5,COL4A2,COL4A1,COL4A3,COL4A4,SOS1,PIK3R1
hsa05161	Hepatitis B	0.0459	MAPK13,**TGFB1***,NFKB1,CASP10,STAT4,CASP8,IFNA8,TRAF3,SOS1,IL6,TNF,PIK3R1,JAK3,MAP2K6
hsa05223	Non-small cell lung cancer	0.0483	GADD45G,**CDK4**,**EGFR**,FOXO3,SOS1,TGFA,PIK3R1,JAK3