Exploring Molecular Signatures in Spondyloarthritis: A Step Towards Early Diagnosis

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Abstract. Spondyloarthritis is an acute inflammatory disorder of the musculoskeletal system often accompanied by pain, stiffness, bone and tissue damage. It majorly consists of ankylosing spondylitis, psoriatic arthritis and reactive arthritis. It follows a differential diagnosis pattern for demarcation between the spondyloarthritis subtypes and other arthritic subtypes such as rheumatoid arthritis, juvenile arthritis and osteoarthritis due to the heterogeneity causing gradual chronicity and complications. Presence of definite molecular markers can not only improve diagnosis efficiency but also aid in their prognosis and therapy. This study is an attempt to compose a refined list of such unique and common molecular signatures of the considered subtypes, by employing a reductionist approach amalgamating gene retrieval, protein-protein interaction network, functional, pathway, micro-RNA-gene and transcription factor-gene regulatory network analysis. Gene retrieval and protein-protein interaction network analysis resulted in unique and common interacting genes of arthritis subtypes. Functional annotation and pathway analysis found vital functions and pathways unique and common in arthritis subtypes. Furthermore, miRNA-gene and transcription factor-gene interaction networks retrieved unique and common miRNA's and transcription factors in arthritis subtypes. Furthermore, the study identified important signatures of arthritis subtypes that can serve as markers assisting in prognosis, early diagnosis and personalized treatment of arthritis patients requiring validation via prospective experimental studies.

Keywords: Spondyloarthritis · bioinformatics · molecular signatures · markers · early diagnosis

1 Introduction

Spondyloarthritis (SpA) or spondyloarthropathy are rheumatic diseases associated with inflammation, stiffness and pain affecting the musculoskeletal system [1] namely

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Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA) and Reactive Arthritis (ReA) [2].

AS is an inflammatory autoimmune disease involving axial spine, sacroiliac joints and peripheral joints [3]. Stiffness of spine, back pain, decreased spinal mobility and possibility of affected extra skeletal organs are primary symptoms linked to this disease. AS requires differential clinical diagnosis. Exercise, physiotherapy in addition to NSAIDs and tumor necrosis factor inhibitors (TNFIs) constitute its symptomatic treatment approaches. Uncontrolled and untreated AS could result in serious symptoms, only treatable by surgical interventions [3–5]. PsA affects axial joints, peripheral joints, nails, skin and entheses [6]. Clinical symptoms include inflammation, spondylitis and stiffness in joints [7]. Clinical factors, imaging techniques such as MRI, ultrasonography, CT and biomarkers assist in its differential diagnosis [8]. Targeted therapy is employed as a possible treatment to alleviate patient's pain and improve their health [9]. ReA, an inflammatory arthritis is usually preceded by an infection, often in the urogenital and gastrointestinal tract which acts as a potential trigger. It can affect one or more joints including axial and peripheral joints of which knee and ankle joints are frequently affected [10]. Both clinical examinations and laboratory tests play a cardinal role in its differential diagnosis [11]. Non-steroidal anti-inflammatory drugs (NSAID's), immunosuppressive drugs and glucocorticoids along with physical therapy are employed for its management [12].

Apart from SpA, there are other heterogeneous forms of arthritis majorly Rheumatoid arthritis (RA), Juvenile arthritis (JA) and Osteoarthritis (OA). The lining of the synovial joints is mainly affected in RA accompanied by bone erosion and cartilage damage with stiffness, swelling and pain in the affected joints [13, 14]. Early-stage diagnosis of RA is challenging as most symptoms resemble that of other diseases. Rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) blood tests and imaging tests aid in diagnostic analysis. Disease management is possible by pharmaceutical drugs, therapy and surgery [15]. JA is a paediatric rheumatic disease, the onset of which is observed in children of age 16 or less. It can affect both small and large joints with pain, stiffness and skin rash. A differential diagnosis is required in order to rule out other possible diseases [16]. Physical therapy and pharmaceutical drugs are methods of symptomatic treatment [17].

Though proximate classification, diagnosis and treatment of SpA is present, their differentiation and demarcation among themselves and with other arthritic subtypes is difficult due to their similarity in features during initial stages and non-standardised diagnostic tests, therapy, markers and targets leading to complications and chronicity in arthritis cases [18].

Therefore, there is a need to find precise molecular signatures for each arthritis subtype in order to impart insights into disease pathophysiology and improve its prognosis, diagnosis and treatment.

We incorporate a reductionist approach amalgamating gene retrieval, network, functional and pathway analysis to find unique and common genes/proteins, functions, pathways, miRNA's and transcription factors serving as molecular signatures in arthritis subtypes. The present approach reduces complexity and filters specific potential core signatures of arthritis subtypes aiding in their differentiation. We hypothesize that these

factors will serve as definite biomarkers and drug targets that will help in prognosis, early diagnosis and personalized treatment of arthritis individuals requiring substantiation via prospective experimental studies.

2 Materials and Methods

2.1 Gene Retrieval

2.1.1 Acumenta Literature LabTM

LitLab is a data-intensive resource that provides statistically mined information by deriving significant associations between gene lists and key biological and biochemical terms (http://www.acumenta.com/). It utilizes an automated data retrieval approach which is thoroughly and regularly updated. This is implemented by determining the number of abstracts that mention the gene and the terms within the term list and by ranking the terms based on their association with the genes (called as, product of frequency or PF). It then compares the LPF value of an experimental gene set to values of 1000 random gene sets so as to determine the strength of association, resulting in a score [19, 20]. It was used to retrieve literature associated genes for the terms: Psoriatic arthritis (PsA), Reactive arthritis (ReA), Rheumatoid arthritis (RA) and Juvenile arthritis (JA).

2.1.2 PubMed

A PubMed based literature search was carried out to retrieve genes for the set of arthritis types being considered in this study (i.e. Ankylosing Spondylitis (AS), PsA, ReA, RA, JA and Osteoarthritis (OA)). The search strategy implemented was: ((((“Joint Diseases”[Mesh]) AND (juvenile OR child* OR adolescence* OR infant*)) AND (arthritis)) AND ((“juvenile arthritis”) OR (“Juvenile Arthritis”))) AND (((“joint disease”) OR (“joint diseases”) OR (“Joint Diseases”))) AND (english[Filter]). The above strategy was performed for all 6 terms in the set.

2.2 Protein-Protein Interaction Network Analysis

Search Tool for the Retrieval of Interacting Genes (STRING) (version 11.0) (https://string-db.org/) was used for the evaluation of predicted protein-protein interactions corresponding to the retrieved genes of arthritis subtypes. STRING is a database that stores known protein-protein interactions in addition to predicting the interactions for input queries. The STRING database includes about 24.58 million proteins from 5090 organisms. Moreover, in order to rank annotation identifier and text matches, it employs a weighted scheme [21]. Networks were constructed for each AS, PsA, ReA, RA, JA and OA using the respective gene lists retrieved using Cytoscape [22].

2.3 Functional Annotation

The gene lists refined and curated based on interaction as per the output from STRING was used for gene ontology analysis. Gene annotation based on GO terms was accomplished by employing Gene Set Annotation (GSAn) (https://gsan.labri.fr/). It is a web-interface that produces computed synthetic annotations for input gene list by utilizing semantic similarity systems, reducing the number of GO terms while retaining an adequate level of biological data [23].

2.4 Pathway Analysis

Reactome (https://reactome.org/), an open-source repository of manually curated biological pathways written by biology subject experts and subjected to peer-review was used for pathway analysis from refined gene lists obtained from STRING [24].

2.5 Genes-miRNA Regulatory Network Analysis

The construction of gene regulating microRNA (miRNA) interaction networks was carried out by using miRNet 2.0 (https://www.mirnet.ca/). miRNet 2.0 is a web-based network visualization software for essentially target gene-miRNA and their functional analysis. The interaction tables and networks of corresponding input gene queries are created by utilizing the tool's knowledgebase [25].

2.6 Genes-TF Regulatory Network Analysis

The construction of interaction networks of transcription factors (TF)-genes was accomplished by employing Network Analyst 3.0 (https://www.networkanalyst.ca/). Network Analyst 3.0 is an interactive web-based network visualization tool for creating gene regulatory networks that can be customized in virtual reality space [26].

3 Results

3.1 Gene Retrieval

Retrieval of arthritis genes was accomplished by utilizing Acumenta Literature LabTM and Pubmed based search creating consolidated gene lists each for Ankylosing Spondylitis (AS), Psoriatic arthritis (PsA), Reactive arthritis (ReA), Rheumatoid arthritis (RA), Juvenile arthritis (JA) and Osteoarthritis (OA). The resultant gene lists comprise of 58 unique genes for AS, 440 unique genes for PsA, 75 unique genes for ReA, 98 unique genes for RA, 396 unique genes for JA and 119 unique genes for OA. The common genes between arthritis subtypes (between two or more) were 606 (Table 1 and Supplementary Material 1).

Table 1. Unique and common genes of arthritis subtypes via literature mining

Arthritis subtypes	No. of genes using Acumenta Literature Lab™	No. of genes using Pubmed	Unique genes	Common genes
Ankylosing Spondylitis	N/A	101	58	606
Psoriatic arthritis	784	233	440	
Reactive arthritis	343	19	75	
Rheumatoid arthritis	250	154	98	
Juvenile arthritis	886	81	396	
Osteoarthritis	N/A	141	119	

3.2 Protein-Protein Interaction Network Analysis

Network analysis was performed using the mined unique and common genes of arthritis subtypes via Search Tool for the Retrieval of Interacting Genes (STRING) database creating protein-protein interaction networks corresponding to the mined genes. The number of interacting genes/proteins in the core network unique for AS, PsA, ReA, RA, JA and OA are 19, 368, 19, 28, 315 and 63 respectively. The number of interacting genes/proteins in the core network common in arthritis subtypes are 544 (Supplementary Material 2). The interacting networks were retrieved from Cytoscape and are depicted in Fig. 1 (green nodes represent proteins corresponding to mined genes and black edges represent interaction between the proteins).

3.3 Functional Annotation

Functional annotation was carried out utilizing the interacting genes of arthritis subtypes using Gene Set Annotation (GSAn). The analysis retrieves significant functions unique in AS, PsA, ReA, RA, JA and OA and common in arthritis subtypes (Supplementary Material 3). Figure 2 depicts the top unique functions of arthritis subtypes based on number of genes involved in particular function.

3.4 Pathway Analysis

The interacting genes of arthritis subtypes were utilized for pathway analysis using Reactome pathway database. Significant pathways unique in AS, PsA, ReA, RA, JA and OA and common in arthritis subtypes are retrieved (Supplementary Material 4). Figure 3 depicts the top unique pathways of arthritis subtypes based on number of genes involved in particular pathway.

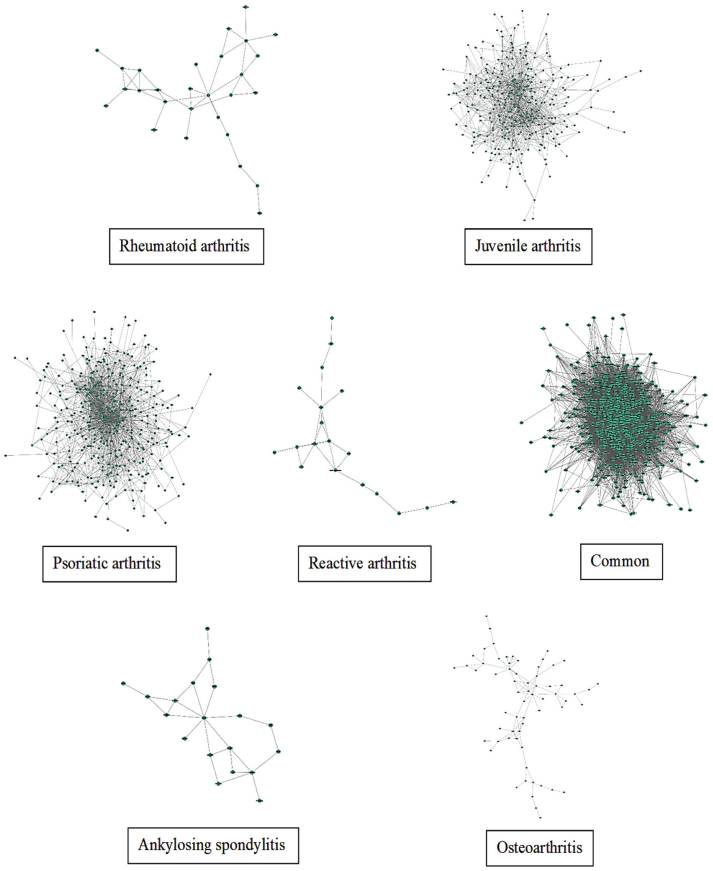

Fig. 1. Interacting networks of unique and common genes of arthritis subtypes via STRING and Cytoscape

3.5 Genes-miRNA Regulatory Network Analysis

The interacting genes of arthritis subtypes were used for generating microRNA (miRNA)-gene networks via miRNet 2.0. miRNA-gene interactions unique in AS, PsA, ReA, RA, JA and OA and common miRNA's in arthritis subtypes are obtained (Supplementary Material 5). The nodes and edges obtained for AS are 460 (miRNA: 461 and genes: 15) and 642 respectively; for PsA are 2284 (miRNA: 2080 and genes: 204) and 11347 respectively; for ReA are 301 (miRNA: 287 and genes: 14) and 388 respectively; for RA are 476 (miRNA: 461 and genes: 15) and 638 respectively; for JA are 2120 (miRNA: 2120 and genes: 154) and 9488 respectively and for OA are 1243 (miRNA: 1206 and genes: 37) and 3240 respectively. The miRNA-gene interaction networks are represented in Fig. 4 (pink nodes represent gene, blue nodes represent miRNAs and black edges represent interaction between genes and miRNAs).

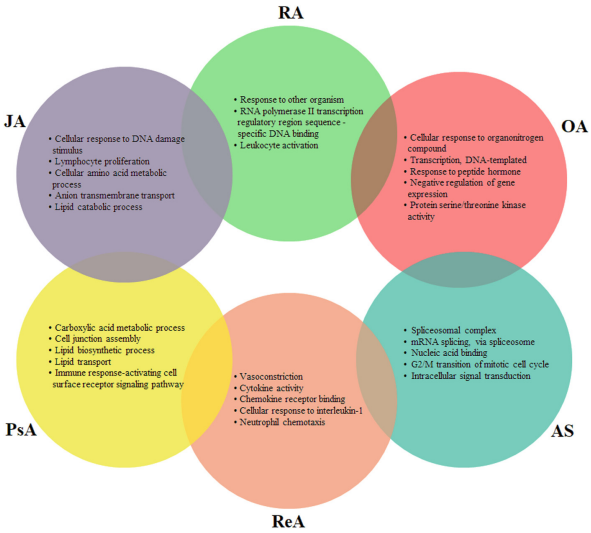

Fig. 2. Depiction of top unique functions in arthritis subtypes * AS: Ankylosing Spondylitis; PsA: Psoriatic arthritis; ReA: Reactive arthritis; RA: Rheumatoid arthritis; JA: Juvenile arthritis; OA: Osteoarthritis

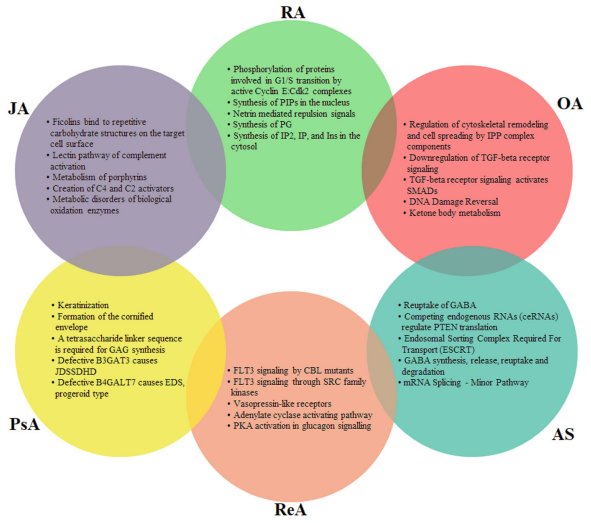

Fig. 3. Depiction of top unique pathways in arthritis subtypes * AS: Ankylosing Spondylitis; PsA: Psoriatic arthritis; ReA: Reactive arthritis; RA: Rheumatoid arthritis; JA: Juvenile arthritis; OA: Osteoarthritis

3.6 Genes-TF Regulatory Network Analysis

The transcription factor (TF)-gene networks for AS, PsA, ReA, RA, JA and OA were created via Network Analyst 3.0 using interacting genes of arthritis subtypes. TF-gene

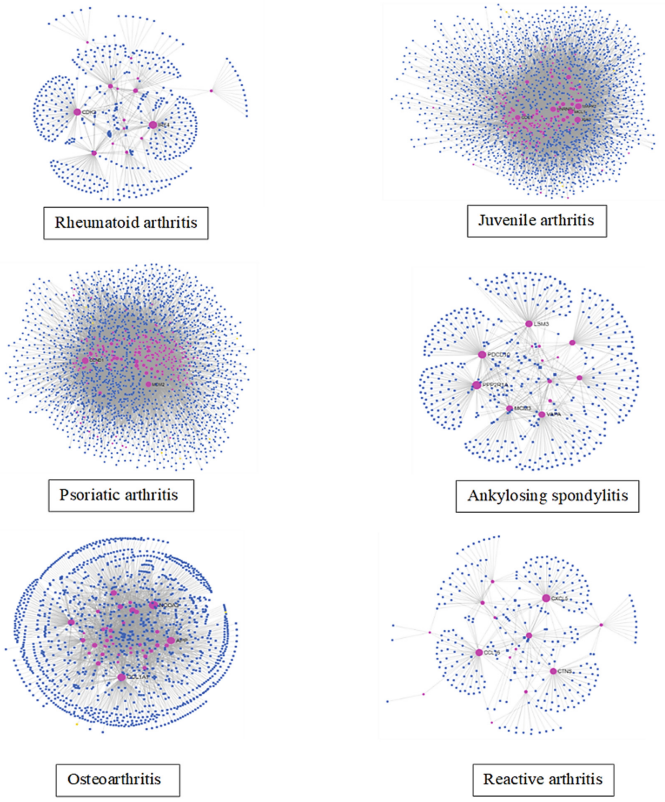

Fig. 4. Regulatory networks of genes-miRNA in arthritis subtypes

interactions unique in AS, PsA, ReA, RA, JA and OA and common TF's in arthritis subtypes are obtained (Supplementary Material 6). The nodes and edges obtained for AS are 214 and 421 respectively; for PsA are 477 and 3739 respectively; for ReA are 142 and 174 respectively; for RA are 151 and 210 respectively; for JA are 443 and 3565 respectively and for OA are 293 and 1010 respectively as represented in Fig. 5 (pink nodes represent gene, blue nodes represent TFs and black edges represent interaction between genes and TFs).

3.7 Identification of Important Molecular Signatures in Arthritis Subtypes

The important unique molecular signatures were selected on the basis of those target genes having corresponding functions, pathways, miRNA's and TF's in arthritis subtypes.

Vital signatures for AS include 3 genes namely MCM3, VAPA and LSM3 with corresponding 5 functions, 4 pathways, 207 miRNA's and 118 TF's. PsA includes 70 genes with corresponding 51 functions, 156 pathways, 1265 miRNA's and 291 TF's. ReA includes 2 genes namely FLT3LG and AVP with corresponding 2 functions, 14 pathways, 11 miRNA's and 89 TF's. RA includes 1 gene namely PLD4with corresponding 1 function, 1 pathway, 11 miRNA's and 2 TF's. JA includes 56 genes with corresponding

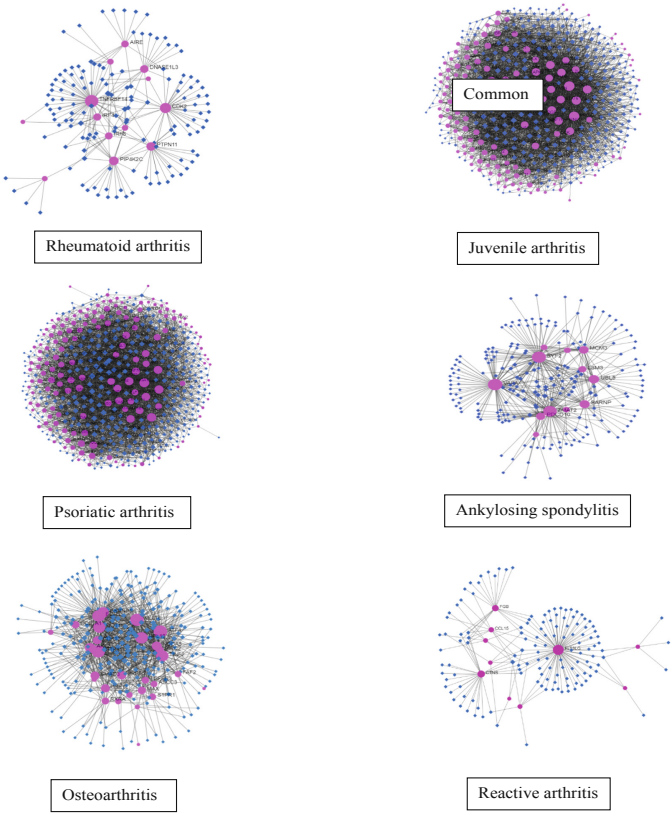

Fig. 5. Regulatory networks of genes-TF in arthritis subtypes

35 functions, 131 pathways, 1393 miRNA's and 274 TF's. OA includes 9 genes with corresponding 5 functions, 31 pathways, 544 miRNA's and 174 TF's (Supplementary Material 7).

4 Discussion

Even though a vast amount of data pertaining to spondyloarthritis and its various subtypes is present, the heterogeneity of the disease is an impediment to its early and accurate diagnosis. Therefore, differential diagnosis among themselves and with other arthritis subtypes and symptomatic treatment is indispensable in clinical settings leading to gradual chronicity [27]. The identification of unique molecular signatures, considered as vital indicators of disease susceptibility, have the potential to improve the current diagnostic and therapeutic process. Earlier research studies have focused on investigating molecular signatures in a particular disease sub-type [28–30].

The current study is distinctive, wherein an in-silico reductionist approach has been utilized to determine both unique and common genes of spondyloarthritis and

other arthritis subtypes Ankylosing Spondylitis (AS), Psoriatic arthritis (PsA), Reactive arthritis (ReA), Rheumatoid arthritis (RA), Juvenile arthritis (JA) and Osteoarthritis (OA).

Thorough mining was performed to retrieve unique and common gene lists of arthritic subtypes, serving as primary data for the study which were then subjected to network analysis and construction. Previous studies have shown that COL1A1, COL3A1, COL11A1 genes may play an important role in the progression of OA [31]. Moreover, PRKCH has been identified as a coding risk gene variant in RA. Other risk genes that have been reported in studies to be associated with RA include CDK2, CDK4, IRF4, PADI4, P2RY10, and ARAP1 [32, 33]. ESR1, GSTM1, GSTP1, GZMH, MTR, MTRR genes have been tested for JA association. WISP3 is one of the genes independently confirmed for association with arthritis subtype [34]. The gene lists formulated in our study include all the above-mentioned genes respectively, imparting credibility to the work along with their interaction with a repertory of interacting genes unique and common in arthritis subtypes.

Further, functional annotation and pathway analysis was employed on the interacting genes retrieving significant functions and pathways associated with arthritis subtypes. Polymorphisms of RUNX genes have been found to be linked to increase risk of immune-related inflammatory diseases [35–38]. In this study, two pathways involving RUNX1 and RUNX3 have been identified (namely, RUNX3 Regulates Immune Response and Cell Migration, RUNX1 regulates transcription of genes involved in differentiation of keratinocytes) as common pathways in the considered subtypes. Apart from these a plethora of unique and common fundamental functions and pathways have been found for arthritis subtypes.

miRNA (micro-RNA)-gene and TF (transcription factor)-gene regulatory interaction networks from interacting genes of arthritis subtypes were obtained. The identified miRNA hsa-mir-146a-5p, hsa-mir-155-3p associated with RA have been identified in previous studies as well [39]. The miRNAs hsa-mir-17-5p, hsa-mir-126-3p, hsa-mir-199a-3p that were found to be associated with PsA as per the results of this study have also been observed in a study by Pelosi, 2018 [40]. Our results retrieve plenitude of unique and common miRNA's and TF's for arthritis subtypes.

Furthermore, the important unique molecular signatures for arthritis subtypes (genes, functions, pathways, miRNA's and TF's) as obtained in results Sect. 3.7 can be utilized as significant molecular signatures for demarcation of spondyloarthropathies among themselves and with other arthritis subtypes aiding in improvisation of pathophysiology, early diagnosis and targeted therapy in arthritis requiring prospective substantiation via experimental analysis.

In future, analysis regarding the in-depth prognosis of disease, pathogenicity, personalized treatment possibilities, consideration of impact of ethnicity due to difference in susceptibility genes in different populations, consideration of gender and sensitivity analysis for this study can be carried out. The important unique molecular signatures were selected on the basis of those target genes having corresponding functions, pathways, miRNA's and TF's in arthritis subtypes.

5 Conclusion

The current study presents a reductionist computational approach for the identification of important molecular signatures (genes, functions, pathways, miRNA's and TF's) unique and common in spondyloarthritis and other arthritis subtypes namely Ankylosing Spondylitis (AS), Psoriatic arthritis (PsA), Reactive arthritis (ReA), Rheumatoid arthritis (RA), Juvenile arthritis (JA) and Osteoarthritis (OA). These might have potential to be employed as possible markers for early diagnosis and treatment of arthritic subtypes in near future to researchers and clinicians that warrants validation via prospective experimental studies.

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