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Expression Patterns in Psoriasis and Comorbidities: An Integrative Computational Analysis

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Abstract

Psoriatic arthritis (PsA) is a chronic type of inflammatory arthritis occurring in people who have psoriasis. Psoriasis is a long-term autoimmune ailment with characteristic patches of abnormal skin. PsA has a range of comorbidities which include cardiovascular disease, obesity and diabetes mellitus. The present study investigates genetic and molecular links between psoriatic arthritis, psoriasis and associated comorbidities. Microarray data analysis of datasets obtained from patients of these disorders was done to find the differentially expressed genes (DEGs). Common DEGs, functions and pathways present in both PsA and associated comorbidities were identified. According to network topological properties, *AKAP13* was found to be more biologically significant. This study suggests that the significant DEGs and their associated pathways may have the potential to be used as biomarkers and drug targets for PsA diagnosis and treatment, especially when a concurrent comorbidity is suspected that warrant further experimental validation.

Keywords psoriatic arthritis, comorbidity, microarray analysis, pathway analysis, topological analysis

Introduction

Rheumatism, also referred to as 'rheumatic diseases', is an encompassing term for more than 100 disorders of the connective tissues characterized by metabolic derangement, degeneration, inflammation and pain. The classification of these diseases is still widely debated in the field, with different practitioners developing their own criteria for grouping and studying the disparate rheumatic diseases.(1) The Medical Subject Headings (MeSH) subdivide rheumatic diseases into 12 categories including rheumatoid arthritis, gout, rheumatic fever etc. They also specify an additional category of rheumatic diseases- the spondyloarthropathies (SpA).

SpA include ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), enteropathic arthritis, undifferentiated spondyloarthropathy (uSpA) and juvenile-onset spondylitis. The group is mainly differentiated from other rheumatoid diseases by the involvement of the joints of the vertebral column, seronegativity for rheumatic factor (RF), high correlation with *HLA-B27* and involvement of symptoms such as enthesitis, sacroilitis and spondylitis in addition to joint inflammation.(2) While the etiology for almost all the SpAs is unclear, PsA is unique in being a sequela of psoriasis which is itself an autoimmune disorder with unclear pathophysiology. Psoriasis is a multisystem disease which is characterized by scaly, erythematous patches, papules, and plaques.(3)

The onset of PsA may be after or before psoriasis manifests or both conditions may begin simultaneously. PsA occurs in approximately 26% of patients with psoriasis, leading to prevalence in the population of 0.3% to 1%.

The evidence points to a genetic cause for psoriasis and strong *HLA-B27* driven variability in PsA susceptibility. In PsA there is a stronger association with *HLA-B* alleles than with *HLA-C* alleles, while psoriasis (particularly early onset psoriasis) is associated with *HLA-C*.(4)

Despite continuing clinical research, there is still a lack of theoretical understanding about the biomarkers and causes of PsA. Diagnosis of PsA is mainly done through radiological examination and family history. Ruling out rheumatoid arthritis in psoriasis patients is often difficult.(5) Interestingly, PsA has been shown to be associated with several comorbidities including cardiovascular disease, obesity, diabetes mellitus and depression.(6) The high epidemiological incidence of these conditions with PsA suggest a linkage at the molecular level between PsA and these diseases. The study of the genetic and molecular basis of these diseases may, therefore, aid in the elucidation of molecular targets for both diagnosis and treatment of PsA.

In the present study, a high throughput procedure for computational analysis by inclusion of high-throughput quantitative microarray gene expression data of patient samples were utilized from databases such as ArrayExpress of European Bioinformatics Institute (EBI)(7) and Gene Expression Omnibus (GEO) database of National Centre for Biotechnology Information (NCBI).(8)

Significant differentially expressed genes, functions and pathways in PsA and its associated comorbidities were identified. These may provide clues to biological processes underlying disease development and be used as biomarkers for early diagnosis of PsA. The genes and gene products may also be used as putative drug targets for novel PsA treatment.

Materials and Methods

Gene expression dataset selection

Datasets for the following diseases were searched in European Bioinformatics Institute (EBI) ArrayExpress: psoriatic arthritis, cardiovascular disease, type 1 diabetes, type 2 diabetes, obesity and psoriasis.

The criteria for filtering and selecting the datasets were (i) datasets with patient-derived samples (disease vs. control), (ii) patient cohorts not undergoing any sort of treatment, (iii) datasets which were published in journals, and (iv) datasets with microarray

assays.

Microarray data pre-processing and statistical analysis

Command-based Bioconductor R suite was used for carrying out data normalization and statistical analysis of the selected datasets. Robust multi-array average (RMA) and employment of linear models for gene expression evaluation employing moderated t-statistics with log-odds by empirical Bayes shrinkage were utilized to find logFC, p.Value, adj.p.Val, Ave Expr, t- and B-value of every individual gene of the selected datasets.(9-10)

Identification and comparison of differentially expressed genes

The differentially expressed genes (DEGs) were screened on the basis of 1.5 fold variation and p values. The cutoff criteria for identifying upregulated and downregulated genes was 1.5 fold change (log2 ratio) of more than 0.58 for upregulated genes, and less than 0.58 for downregulated genes. Only DEGs with a p-value of less than 0.05 were considered significant. Since p-value related to the probability that chance could have generated the variation observed, a lesser p-value indicates higher significance of results.

Gene ontologies and pathway analysis

The Gene Ontology (GO) Consortium was used to identify the cellular and molecular pathways of the common significant differentially expressed genes. The GO Consortium is a curated online database containing the cellular, molecular, and biochemical functions of various genes built as a tool for the unification of biology.(11-12) The GO data was obtained from GeneCards (www.genecards.org).

GeneCards is an integrated online resource created by automatically data-mining gene information from disparate biological databases, and has web-based 'cards' for each individual gene.(13)

Network and topological analysis

Search tool for the retrieval of interacting genes (STRING) (http://string-db.org/) which is a curated database consisting of protein and gene interaction data was for protein–protein interactions (PPIs) (14) of the target human DEGs. Cytoscape was used for evaluation of the topological properties consisting of nodes, edges, closeness centrality, clustering coefficient, eccentricity, betweenness centrality, stress, degree, neighbourhood connectivity, number of directed edges, radiality and topological coefficient.(15)

Results

Gene expression dataset selection

1 psoriatic arthritis (PsA) dataset, 4 cardiovascular disease (CVD) datasets, 7 diabetes mellitus datasets, 3 obesity datasets and 10 psoriasis datasets were found using the given selection criteria (Table 1). To avoid irregularities and increase robustness of analysis, datasets with patient vs control samples, microarray data and no treatment samples were used.

Microarray data pre-processing and statistical analysis

Background correction and removal of local artefacts and noises from the RAW Affymetrix intensity values was done using Robust multi-array average (RMA). The values were log2 transformed and a linear mathematical model. Moderated t-statistics and log-odds of the differential expression by the empirical Bayes shrinkage resulted in the generation of statistical values.

Identification and comparison of differentially expressed genes

Cutoff values of [$p < 0.05$ and $FC \geq 1.5$ ($|\log2\ FC| > 0.58$) were used to identify significant differentially expressed genes (DEGs). The DEGs thus obtained from various comorbidities related to PsA were compared with the DEGs in PsA and common DEGs were identified (Table 2).

Gene ontologies and pathway analysis

The GO enrichment terms for significant common DEGs were compared to find common biological processes from GeneCards. The GO pathways for the common DEGs were identified (Table 3).

Network and topological analysis

The protein-protein interaction among significant common DEGs were found from STRING database (Figure 1). The topological characteristics were found using Cytoscape tool (Table 4).

Higher the topological and clustering coefficients, stress, closeness centrality and betweenness centrality, more are the neighbors of the node and shortest paths passing via the nodes. The extent of the information to other reachable nodes is higher and the strength of the control the node exerts over the interactions of other nodes is also higher. *AKAP13* is found to be more significant and important interactor in the network as indicated by the results.

Discussion

Computational analysis of genes and their phenotypes has developed into a valuable tool for disease research, drug development and biomarker research in recent years.

The pathogenesis of disease like arthritis and psoriasis, which do not have transparent causes or etiological agents, may be elucidated by studying genetic expression patterns and whole-genome association studies in patients and controls, revealing 'genetic signatures' of the disease in question. In such diseases, the dearth of accurate diagnostic technology precludes the need for study of putative biomarkers of disease. Further, the spondyloarthropathies are treated with non-steroidal anti-inflammatory drugs (NSAIDs) which only provide symptomatic relief for pain associated with joint inflammation and do not treat the underlying cause of the disease. Therefore, the identification of potential drug targets by finding genes linked to the disorder holds great value for the development of targeted treatments.

Numerous studies have constructed and utilized computational pipelines for the selection of promising genetic candidates in a variety of diseases.(39-42) Most of these operate by integrating publicly available disease datasets to identify differentially expressed genes (DEGs) using different statistical techniques.

DEGs are the genes which have are significantly over or under-expressed in patients as compared to healthy people. These genes are found through transcriptomic analysis of whole blood, organ biopsy, or particular cells obtained from both patients and matched controls. These may be key genes to the pathogenesis of disease, providing (1) a starting point for studying the disease mechanism, (2) biomarkers for accurate diagnosis, and (3) targets for novel drugs.

Table 1. Selected microarray gene expression datasets

Dataset accession#	No. of Assays	No. of upregulated DEGs	No. of downregulated DEGs	Disease	Reference
Cardiovascular disease vs. control					
E-GEOD-703	19	20	179	Pulmonary arterial hypertension	[16]
E-GEOD-24752	6	42	102	Essential hypertension	[17]
E-GEOD-69601	6	141	34	Idiopathic portal hypertension	[18]
E-GEOD-76701	8	121	107	Ischemic heart failure	[19]
Diabetes mellitus vs. control					
E-GEOD-9006	234	16	40	Type 1 diabetes	[20]
E-GEOD-9006	234	78	62	Type 2 diabetes	[20]
E-GEOD-21340	20	33	55	Type 2 diabetes	[21]
E-GEOD-25724	13	66	178	Type 2 diabetes	[22]
E-GEOD-29221	24	182	41	Type 2 diabetes	[23]
E-GEOD-33440	22	64	84	Type 1 diabetes	[24]
E-GEOD-55098	22	91	10	Type 1 diabetes	[25]
Obesity vs. control					
E-GEOD-9624	11	94	116	Obesity	[26]
E-GEOD-18897	80	14	25	Obesity	[27]
E-GEOD-48964	6	39	61	Obesity	[28]
Psoriasis vs. control					
E-GEOD-2737	7	108	139	Psoriasis	[29]
E-GEOD-9710	16	70	182	Psoriasis	[30]
E-GEOD-13355	180	18	230	Psoriasis	[31]
E-GEOD-14905	82	22	225	Psoriasis	[32]
E-GEOD-20264	7	87	150	Psoriasis	[33]
E-GEOD-41664	157	27	217	Psoriasis	[34]
E-GEOD-50790	8	72	164	Psoriasis	[35]
E-GEOD-61281	104	44	40	Psoriasis	[36]
E-GEOD-75343	45	115	130	Psoriasis	[37]
E-GEOD-80047	50	54	187	Psoriasis	[38]
Psoriatic arthritis vs. control					
E-GEOD-61281	104	58	28	Psoriatic arthritis	[36]

Table 2. Common significant differentially expressed genes between datasets

Upregulated genes	No of datasets	Dataset ID	Disease
ZEB2	2	GSE696901, GSE61281	PsA, CVD
SNX29	2	GSE696901, GSE61281	PsA, CVD
TGFBR3	2	GSE55098, GSE61281	PsA, Type 1 Diabetes
AKAP13	3	GSE25724, GSE80047, GSE61281	PsA, Type 2 Diabetes, Psoriasis
PRKCZ	2	GSE25724, GSE61281	PsA, Type 2 Diabetes
KMT2A	2	GSE20264, GSE61281	PsA, Psoriasis
SYNCRIP	2	GSE50790, GSE61281	PsA, Psoriasis
NPAT	2	GSE75343, GSE61281	PsA, Psoriasis
Downregulated genes	No of datasets	Dataset ID	Disease
COPS2	3	GSE25724, GSE80047 GSE61281	PsA, Type 2 Diabetes, Psoriasis
CLEC4D	2	GSE18897, GSE61281	PsA, Obesity
CSTA	2	GSE23737, GSE61281	PsA, Psoriasis
SAR1B	2	GSE41664, GSE61281	PsA, Psoriasis

Table 3. Common significant pathways of differentially expressed genes

#Pathway ID	Pathway description	Represented DEGs
GO:0006351	transcription, DNA-templated	*ZEB2, KMT2A, NPAT*
GO:0006355	regulation of transcription, DNA-templated	*ZEB2, KMT2A, NPAT, COPS2*
GO:0006366	transcription from RNA polymerase II promoter	*ZEB2, KMT2A, COPS2*
GO:0006357	regulation of transcription from RNA polymerase II promoter	*ZEB2, KMT2A, COPS2*
GO:0007179	transforming growth factor beta receptor signaling pathway	*TIGFBR3, PRKCZ*
GO:0016477	cell migration	*TIGFBR3, PRKCZ*
GO:0007165	signal transduction	Intracellular: *TIGFBR3, PRKCZ, AKAP13* Unspecified: *COPS2*
GO:0060216	definitive hemopoiesis	*TGFBR3, KMT2A*
GO:0006468	protein phosphorylation	*AKAP13, PRKCZ*
GO:0051899	membrane depolarization	*PRKCZ, KMT2A*
GO:0008283	cell proliferation	Positive: *PRKCZ, TGFBR3* (cardiac muscle cell) Negative: *KM2A, TGFBR3* (epithelial) Unspecified: *COPS2, ZEB2* (forebrain)
GO:0002223	stimulatory C-type lectin receptor signaling pathway	*CLEC4D, ZEB2*
GO:0016192	vesicle mediated transport	*SAR1B, PRKCZ*

Table 4. Topological analysis of significant differentially expressed genes

Name	Betweenness Centrality	Closeness Centrality	Clustering Coefficient	Stress	Topological Coefficient
SAR1B	0.33	0.43	0	10	0.5
PRKCZ	0	0.31	0	0	0
SNX29	0	0.4	0	0	0
AKAP13	0.73	0.6	0	22	0.33
ZEB2	0	0.33	0	0	0
TGFBR3	0.33	0.46	0	10	0.5
KMT2A	0.53	0.54	0	16	0.5
CLEC4D	0	1	0	0	0
CSTA	0	1	0	0	0
SYNCRIP	0	1	0	0	0
COPS2	0	1	0	0	0

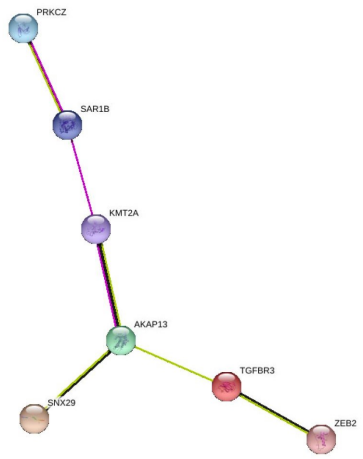

Figure 1. Protein interaction network between different differentially expressed genes

The detection of DEGs may be done by employing statistical methods such as the t-test, B-test, SAM (significance analysis of microarrays) and fold-change rule. In general, these models set a threshold based on gene data distribution and genes above or below this threshold are considered to be differentially expressed.

A key limitation which limits comparison of different datasets is the non-interoperability of the statistical analyses- studies have found that when tested with the same dataset, different statistical models output different lists of DEGs.(43-44)

To overcome this limitation, in this study Linear Models of Microarray Analysis (limma) was implemented through Bioconductor R on the raw unprocessed data from 26 different datasets to cross-compare the differentially expressed genes in these datasets. Limma incorporates log2fold changes, moderated t-statistic and B-statistic. The moderated t-statistic in limma is an improvement on the simple t-test as it moderates the standard error across genes using a Bayesian model, thus increasing the degrees of freedom and increasing reliability.[9] Using Bioconductor R to implement limma in the selected datasets, we selected DEGs with log2FC greater than 0.58 or lesser than -0.58, which were also statistically significant with p value less than 0.05.

The DEGs found in maximum number of datasets were A-kinase anchoring protein 13 (*AKAP13*) which was upregulated in 1 dataset each from psoriatic arthritis, psoriasis, and type 2 diabetes; and COP9 signalosome complex subunit 2 (*COPS2*) which was downregulated in one dataset each from psoriatic arthritis, type 2 diabetes, and psoriasis. Other upregulated DEGs were transforming growth factor beta receptor III (*TGFBR3*), zinc finger E-box-binding homeobox 2 (*ZEB2*), sorting nexin 29 (*SNX29*), protein kinase C zeta (*PRKCZ*), histone-lysine N-methyltransferase 2A (*KMT2A*), synaptotagmin binding cytoplasmic RNA interacting protein (*SYNCRIP*) and nuclear protein of the ATM locus (*NPAT*).

The other downregulated genes included C-type lectin domain family 4 member D (*CLEC4D*), cystatin A (*CSTA*) and SAR1 gene homolog B (*SAR1B*).

The DEGs were further analysed for possible connections to particular biological processes and pathways using GO enrichment analysis.

The most common biological processes shared by the DEGs across datasets were cell proliferation, signal transduction, and regulation of DNA transcription. Cell proliferation is an established characteristic of the molecular pathology of psoriatic arthritis, as the disease exacerbates through a vicious cycle of inflammation and cell proliferation. The most effective TNF alpha drugs against psoriatic arthritis also act on inhibiting cell production and maturation in myeloid dendritic cells which cause inflammation.(45) Signal transduction and DNA transcription regulation may act as putative targets for future psoriatic arthritis therapies. Other well-represented biological pathways include protein phosphorylation, vesicle-mediated transport, and cell migration. *AKAP13* was found to be more biologically significant as compared to other DEGs according to the network topological properties.

Conclusion

In conclusion, the present study provides insight into the genetic signatures of psoriatic arthritis (PsA) and its associated comorbidities. The number of common differentially expressed genes (DEGs) found also gives credence to the idea of a few common genetic risk factors or triggers for both PsA and associated disorders. The results suggest novel biomarkers and drug targets of PsA, as well as for checking whether a particular disorder is linked with the presence of PsA in the patient or not. As many of the comorbidities may manifest before visible symptoms of PsA appear, these candidate genes provide a valuable way of finding PsA much before than was originally possible.

Overall, our findings implicate significant DEGs outlined above, with their associated biological pathways, in the pathogenesis of both PsA and further comorbidities including psoriasis, cardiovascular disease, type 2 diabetes, and obesity. The DEGs and the associated processes may be used as probable biomarkers and drug targets in PsA in the near future. However, this primary study with *in-silico* analysis needs to be bolstered by larger experimental and epidemiological studies to produce truly actionable findings.

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Conflicts of interest

Authors declare no financial and non-financial conflicts of interest.

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