Translational Research Urology

Original Article

Identification of Common Hub Genes and Key Molecular Pathways between Multiple Sclerosis and Urological Disorders

Shahram Aliyari[1,2], Zahra Salehi[3], Kaveh Kavousi[2], Helia Azodian Ghajar[4], Parsa Nikoofar[5], Reza Omid[6], Parmida Dehghanpoor Farashah[7], Hassan Homayoun[8], Vahid Abedi Yarandi[7*]

[1]*Department of Bioinformatics, Kish International Campus University of Tehran, Kish, Iran*

[2]*Laboratory of Complex Biological Systems and Bioinformatics (CBB), Department of Bioinformatics, Institute of Biochemistry and Biophysics (IBB), University of Tehran, Tehran, Iran*

[3]*Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*

[4]*Department of Medical Genetics, Afzalipour Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran*

[5]*Department of Urology, Thunder Bay Regional Health Research Institute, Thunder Bay, Ontario, Canada*

[6]*Department of Radiology, Hasheminejad Hospital, Tehran University of Medical Sciences, Tehran, Iran*

[7]*Islamic Azad University of Medical Sciences, Tehran, Iran*

[8]*Department of Electrical and Computer Engineering, University of Kashan, Kashan, Iran*

HIGHLIGHTS

• Multiple sclerosis (MS) is a potentially debilitating disease of the central nervous system (CNS) with a diverse range of urologic symptoms.

• Urologic diseases are wide range of genitourinary abnormalities that can happen as the primary disease or be the consequence of another disease.

• Single-nucleotide polymorphisms (SNPs) may serve as biological markers because they can be linked to genes associated with multiple complex diseases.

ABSTRACT

Introduction
The immune system plays a vital role in affording protection for the body against a wide variety of diseases and infections. On occasion, the system malfunctions and attacks intact cells, tissues, and organs influencing any part of the body, tapering off bodily function, and leading to life-threatening. multiple sclerosis (MS) is characterized by inflammatory demyelination with a diverse range of urologic indications.

Methods
To extract the overlapped genes and single-nucleotide polymorphisms (SNPs; until November 2022) between MS and several urological disorders, we searched the DisGeNET database. Furthermore, to identify significant Gene Ontology (GO) terms and the Kyoto Encyclopedia of Genes and Genome (KEGG) pathway, the Enrichr assessment was used. Additionally, in the case of overlapped genes, the maximum level of linkage hub genes was investigated by the protein-protein interaction (PPI) network construction via cytoHubba.

Results
1362 common genes between MS and urological disease were recognized, of which 154 genes have SNPs linked with MS susceptibility. Three DisGeNET-indexed MS-associated SNPs, including rs653178, rs10936599, and rs4976646 were shared between MS and urological disorders. TNF, AKT1, IL1B, IL6, VEGFA, INS, C-C CCL5, TP53), RELA proto-oncogene, STAT3, and EGFR were detected as hub genes overrepresented in the identified pathways.

Conclusions
Of 1362 common genes, 11 key genes, and 3 SNPs were shared between MS and urology-related diseases. These identified features might serve as potential therapeutic targets in both disorders, with a probable role in the management of urological complications in MS patients.

Keywords: Single-Nucleotide Polymorphisms; Gene Expressions; Molecular Pathways; Multiple Sclerosis; Urological diseases

Introduction

Multiple sclerosis (MS), is a progressive autoimmune that incorrectly attacks a healthy brain or spinal cord of the nervous system (1). Urologic diseases are contained within a wide range of genitourinary abnormalities that can occur as the primary disease or be the consequence of another disease (2-4). Statistically, the prevalence of urologic diseases including storage or voiding symptoms or a combination of these, in MS patients varies from 32% to 96.8% (5).

Symptoms of urological disease are completely dependent on the MS phase, of which detrusor overactivity is the most commonly reported urodynamic abnormality (2). People with MS also might suffer from sexual dysfunction symptoms; although these symptoms

are rarely life-threatening, they significantly reduce the life quality of the one (4). Concerning the significant correlation between genetics and the development of various diseases, it is necessary to study the effect of genetic changes in the development of MS and disorders of the genitourinary system (6). Single-nucleotide polymorphisms (SNPs) may serve as biological markers because they can be linked to genes associated with multiple complex diseases, such as migraines, MS, Alzheimer's disease, heart diseases, schizophrenia, diabetes, and cancers (7-11). The regulatory effects of SNPs on gene expression have been identified as key functions associated with MS risk (12). Bioinformatics can process the genetic data on MS and urological disease that can be considered for the personalized management of MS patients (13, 14).

We aimed to identify common genes and SNPs involved in MS and urologic diseases using bioinformatics.

Methods

Genes associated with MS and urological disorders were downloaded independently. Afterward, the overlapped genes and the shared SNPs-associated diseases were determined and the operation of common genes in consort with hub genes were recognized.

Data Collection

A list of 31 items including MS disease subdivisions and its potentially associated urological disorders was determined (Table 1). The former includes 3, and the latter includes 28 subtypes. The selected disorders were categorized into different groups, including "multiple sclerosis," "lower urinary tract symptoms," "frequency/ overactive bladder," "benign prostatic hyperplasia," "cancers," "urolithiasis," "impotency," "infertility," "infection," "urethritis," "urinary tract infections," "polycystic kidney disease," and "urge incontinence." Subsequently, the diseases' names were searched in DisGeNET (15), one of the largest available platforms, which collects information about the genetic basis of human diseases (https://www.disgenet.org); the codes associated with those diseases were extracted.

Genetic Overlap between Selected Disorders

To investigate the genetic overlap between MS and different groups of urological disorders, genes associated with the selected diseases were extracted from DisGeNET. Since different names are attributed to a disease, we integrated the information from multiple downloaded files for each disease and removed duplicate genes. Then, a pairwise analysis was performed to identify common genes between MS and other diseases. Further, a comparison was performed between MS and 5 groups of urological disorders.

Table 1. The list of selected disorders in the present study

1	RRMS	
2	Primary progressive MS	MS
3	Secondary progressive MS	
4	LUTS	
5	Frequency/overactive bladder	
6	Benign prostatic hyperplasia	
7	Prostate cancer	
8	Kidney cancer	
9	Bladder tumor	
10	Testis tumor	Cancer
11	Penile cancer	
12	Ureter carcinoma	
13	Nocturia	
14	Hematuria	
15	Kidney stones/urolithiasis	
16	Crystallization	Urolithiasis
17	Phosphate	
18	Calculi/calculus	
19	Impotence or erectile dysfunction	Impotency
20	Premature ejaculation	
21	Infertility	Infertility
22	Azoospermia	
23	Varicocele	
24	Prostatitis	
25	Pyelocystitis	
26	Cystitis	
27	Nephritis	Infection
28	Urethritis	
29	Urinary tract infections	
30	Polycystic kidney disease	
31	Urge incontinence	

MS: Multiple sclerosis; RRMS: Relapsing-remitting multiple sclerosis; LUTS: Lower urinary tract symptoms

Shared Risk SNPs

We evaluated SNPs associated with the risk of urological disorders in MS patients. To this end, using the disgenet2r package (15, 16), the related variants reported for MS were downloaded from the database. The SNPs were selected based on a DisGeNET score >0.5, and SNPs without a specific gene name were removed from further analysis. Subsequently, 2 approaches were considered: (1) the overlapped features were determined between the SNPs-associated genes and the genes obtained from pairwise comparisons between the selected disorders, and (2) the MS-associated SNPs were checked if they were linked to other diseases, particularly urologic diseases.

Gene Set Enrichment Analysis

Gene Ontology (GO) analyses for 3 categories, including molecular function (MF), biological process (BP), and cellular compartment (CC), and identification of Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways were performed for the overlapped genes using an Enrichr web-based tool (https://maayanlab.cloud/Enrichr) (17, 18). The GO terms and KEGG pathways with adjusted P-values less than 0.05 were considered significantly enriched. Next, the overlapped identified genes were investigated within the pathways to investigate the genes overrepresented in a set of pathways.

Constructing Protein-Protein Interaction Network to Detect Hub Genes

To synthesize the protein-protein interaction (PPI) networks of overlapped genes with confidence score >0.4, STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) database (11.5) was applied (https://string-db.org). Next, cytoHubba plugin version 0.1 using Cytoscape software version 3.8.2 (19, 20) was employed to detect candidate hub genes.

Results

Genetic Correlation between MS and Urological Disorders The selected MS and urological disorders were searched in DisGeNET, and the codes and genes in relation to them were discovered (Supplementary files S1 and S2). After omitting duplicates, genetic overlaps were distinguished amid 13 selected disorders (Tables 2 and 3 and Supplementary file S3) by the pairwise-based analysis. Number of mutual genes between MS and urological disorders were 1362 out of 1846 MS-associated genes. By filtering the genes with DisGeNET score >0.1, 250 common genes were detected between the selected diseases (Supplementary file S4). According to the results, noticeably common genes with the maximum DisGeNET rate were TNF receptor superfamily member 1A (TNFRSF1A), interleukin 7 receptor (IL7R), CD40 molecule (CD40), interleukin 2 receptor subunit alpha (IL2RA), and major histocompatibility complex, class II, DR beta 1 (HLA-DRB1).

Table 2. The overlaps of DisGeNET-indexed genes between MS and urological disorders

Diseases	Genes (n)	Common genes with MS (n)
Azoospermia	740	181
Benign prostatic hyperplasia	770	292
Bladder cancer	2619	720
Calculi and calculus	204	92
Crystallization	1	1
Cystitis	276	139
Hematuria	256	91
Impotence and erectile dysfunction	266	121
Kidney stone and urolithiasis	81	28
Kidney cancer	1177	370
LUTS	79	38
Nocturia	28	8
Overactive bladder	70	36
Phosphate	36	15
Polycystic kidney diseases	509	181
Prostate cancer	4847	1036
Prostatitis	104	61
Pyelocystitis	108	57
Testis cancer	261	70
Infertility-I	622	169
Nephritis	1359	593
Penile cancer	75	33
Premature ejaculation	17	8
Ureter cancer	13	7
Urethritis	13	5
Urinary tract infections	332	143
Urge incontinence	5	0
Varicocele	99	60

MS: Multiple sclerosis; LUTS: Lower urinary tract symptoms

Table 3. The overlap of DisGeNET-indexed genes between MS and urological disorders

Diseases groups	Genes (n)	Common genes with MS (n)
Cancer	6080	1196
Impotency	276	125
Urolithiasis	269	110
Infection	1742	675
Infertility	1052	273
All urology-related diseases	7287	1362

MS: Multiple sclerosis

Identification of Common Risk SNPs between MS and Urological Disorders

We detected 637 SNPs with a DisGeNET score above 0.5, associated with the risk of MS. Of these, 192 SNPs were recorded without a specific gene name; thus, they were removed from further analysis. Accordingly, 304 genes with one or more MS-associated SNPs remained after removing duplicates (Supplementary file S5).

To evaluate shared SNPs between MS and urological disorders, we compared 304 SNPs-associated genes with the aforementioned 1362 overlapping genes. Notably, 154 genes with ≥1 SNP were found to be shared between the studied groups (Supplementary file S5). In other words, 154 overlapped genes between MS and urological disorders have SNPs associated with MS susceptibility. Therefore, these genes and associated SNPs might be associated with urinary diseases in MS patients.

In addition, MS-associated SNPs were investigated to determine whether they link to other diseases. The correlation of those SNPs with the increased risk of disease susceptibility was reported for 191 diseases, including type 2 diabetes (insulin-dependent), Crohn's disease, and rheumatoid arthritis (Supplementary file S6). Among them, chronic kidney diseases and bladder tumors were associated with the identified SNPs (Table 4).

GO and KEGG enrichment analysis

To investigate the possible biological function of 1362 reciprocal genes, GO and KEGG pathway enrichment analyses were performed by Enrichr, and a component with adjusted P-values ≤0.01 were chosen (Supplementary file S7). In this regard, the gene expression was mainly over-represented in a cytokine-mediated signaling pathway (GO:0019221; BP), cytokine activity (GO:0005125; MF), and integral component of the plasma membrane (GO:0005887; cellular compartment [CC]). Table 5 illustrates the top 10 enriched GO terms of overlapped genes between MS and urological disorders. GO enrichment analysis results have shown consistency with

those of the KEGG pathway analysis.

For example, the results showed that overlapping genes were related to cytokine-cytokine receptor interaction, pathways in cancer, viral protein interaction with cytokine and cytokine receptor, JAK-STAT signaling pathway, tumor necrosis factor (TNF) signaling pathway, T helper 17 (Th17) cell differentiation, and IL-17 signaling pathway (Supplementary file S7).

To prioritize common candidate genes, they were classified by the number of disease-related pathways (Supplementary file S8). Then, we ranked the top 20 genes for each GO term and pathway and carried out a pairwise analysis (Table 6). With regard to the outcomes, TNF, AKT serine/threonine kinase 1 (AKT1), C-C motif chemokine ligand 5 (CCL5), and tumor protein p53 (TP53) overlapped between BP and MF terms and KEGG pathways.

Identification of Hub Genes Using the PPI Network

The PPI network of overlapped genes was constructed with 1362 nodes using STRING. The degree was calculated using the cytoHubba plugin, Cytoscape software, and the top 20 ranking genes, including TNF, IL6, AKT1, actin beta (ACTB), glyceraldehyde-3-phosphate dehydrogenase (GAPDH), IL1B, albumin (ALB), TP53, signal transducer and activator of transcription 3 (STAT3), IL10, vascular endothelial growth factor A (VEGFA), insulin (INS), epidermal growth factor receptor (EGFR), toll-like receptor 4 (TLR4), CD8a molecule (CD8A), C-X-C motif chemokine ligand 8 (CXCL8), protein tyrosine phosphatase receptor type C (PTPRC), CCL2, FN1, and fibronectin 1 (IL2) were identified as hub genes (Table 7).

The hub genes were also searched among the genes determined as key genes with the highest overrepresentation in disease-associated pathways (Table 6). Based on our analysis, TNF, AKT1, IL1B, IL6, VEGFA, INS, CCL5, TP53, RELA proto-oncogene, NF-kB subunit (RELA), STAT3, and EGFR were recognized

Table 4. The DisGeNET-indexed MS-associated SNPs shared between MS and urological disorders

rs number	Variant type	Variant DPI	Variant DSI	EI	Score	Gene symbol	Disease
rs653178	Intronic	0.6	0.672	1	0.7	*ATXN2*	Chronic kidney disease
		0.6	0.672	1	0.7		Kidney failure, chronic
		0.6	0.672	1	0.7		MS
rs10936599	Synonymous	0.6	0.637	1	0.72	*MYNN*	Carcinoma of bladder
		0.6	0.637	1	0.8		MS
		0.6	0.637	1	0.72		Malignant neoplasm of the urinary bladder
rs4976646	Intronic	0.2	0.851	1	0.7	*RGS14*	Kidney failure, chronic
		0.2	0.851	1	0.7		MS

EI: Evidence Index; DSI: Disease Specificity Index; DPI: Disease Pleiotropy Index; ATXN2: Annotated for ataxin 2; MYNN: Myoneurin; RGS14: Regulator of G protein signaling 14; MS: Multiple sclerosis

Table 5. GO enrichment analysis of overlapped genes between MS and urologic diseases

Category	GO ID	GO pathways	Adjusted P-values
BP	Cytokine-mediated signaling pathway	GO:0019221	5.7E-155
	Cellular response to cytokine stimulus	GO:0071345	2E-102
	Positive regulation of cytokine production	GO:0001819	1.3E-100
	Positive regulation of intracellular signal transduction	GO:1902533	1.19E-64
	Regulation of inflammatory response	GO:0050727	1.35E-60
	Inflammatory response	GO:0006954	2.73E-58
	Regulation of apoptotic process	GO:0042981	1.67E-49
	Regulation of cell population proliferation	GO:0042127	2.36E-48
	Positive regulation of multicellular organismal process	GO:0051240	9.54E-48
	Negative regulation of apoptotic process	GO:0043066	7.72E-47
MF	Cytokine activity	GO:0005125	1.79466E-42
	Receptor ligand activity	GO:0048018	7.12754E-41
	Cytokine receptor binding	GO:0005126	1.27732E-27
	Cytokine receptor activity	GO:0004896	9.89452E-22
	Chemokine receptor binding	GO:0042379	5.62714E-19
	Chemokine activity	GO:0008009	8.9204E-18
	Chemokine receptor activity	GO:0004950	1.36392E-17
	Chemokine binding	GO:0019956	3.04336E-16
	C-C chemokine receptor activity	GO:0016493	4.33477E-16
	C-C chemokine binding	GO:0019957	1.46942E-15
CC	An integral component of the plasma membrane	GO:0005887	5.26542E-38
	Secretory granule lumen	GO:0034774	4.94988E-20
	Membrane raft	GO:0045121	1.62403E-16
	Intracellular organelle lumen	GO:0070013	1.94837E-16
	MHC protein complex	GO:0042611	2.04074E-16
	Endocytic vesicle membrane	GO:0030666	7.94631E-16
	Endoplasmic reticulum lumen	GO:0005788	4.31912E-14
	Cytoplasmic vesicle membrane	GO:0030659	4.00976E-13
	Integral component of lumenal side of endoplasmic reticulum membrane	GO:0071556	2.35025E-11
	Lumenal side of endoplasmic reticulum membrane	GO:0098553	2.35025E-11

GO: Gene Ontology; BP: Biological process; MF: Molecular function; CC: Cellular component

as the overrepresented genes in BP and MF terms and KEGG pathways (Figure 1 and Supplementary file S8).

Discussion

For the first time, this study evaluated relapsing-remitting, primary progressive, and secondary progressive subtypes

Table 6. GO enrichment analysis of overlapped genes between MS and urologic diseases

Rank	BP		MF		KEGG pathway	
	Gene symbol	Overlap	Gene symbol	Overlap	Gene symbol	Overlap
1	TNF	252/2227	TP53	25/201	MAPK1	110/201
2	TGFB1	236/2227	RELA	19/201	PIK3CB	98/201
3	AKT1	203/2227	SNCA	17/201	PIK3CD	98/201
4	IL1B	193/2227	ABL1	17/201	PIK3CA	98/201
5	SIRT1	188/2227	CCL5	15/201	PIK3R3	96/201
6	IL6	179/2227	HSP90AA1	14/201	AKT1	94/201
7	IFNG	166/2227	HMGB1	14/201	RAF1	79/201
8	VEGFA	165/2227	P2RX4	14/201	RELA	74/201
9	BMP4	163/2227	STAT1	14/201	NFKB1	74/201
10	NOTCH1	148/2227	PPARG	14/201	MAPK8	68/201
11	INS	146/2227	HIF1A	14/201	PRKCA	65/201
12	APOE	144/2227	PARK7	13/201	TNF	64/201
13	TGFB2	141/2227	ATF4	13/201	PRKCB	63/201
14	IL4	138/2227	STAT3	13/201	MAPK14	56/201
15	BMP2	136/2227	EGFR	12/201	TP53	50/201
16	CCL5	134/2227	LRRK2	12/201	IL6	48/201
17	CAV1	133/2227	MAPT	12/201	NFKBIA	48/201
18	IGF1	132/2227	BCL2	12/201	BAX	46/201
19	ADIPOQ	130/2227	EGR1	12/201	CCND1	46/201
20	THBS1	129/2227	SP1	12/201	MTOR	46/201

Table 7. The top 20 hub genes identified according to the degree method

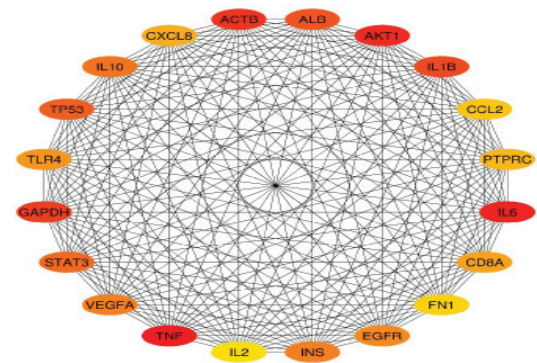| Rank	Name	Degree	Rank	Name	Degree
1	TNF	575	11	VEGFA	391
2	IL6	542	12	INS	391
3	AKT1	496	13	EGFR	365
4	ACTB	488	14	TLR4	362
5	GAPDH	484	15	CD8A	361
6	IL1B	474	16	CXCL8	359
7	ALB	461	17	PTPRC	347
8	TP53	413	18	CCL2	333
9	STAT3	408	19	FN1	331
10	IL10	398	20	IL2	326

Figure 1. The hub genes overlapped between BPs, MFs, and KEGG pathways

of MS disease and 28 urology-related diseases for common hub genes and molecular pathways using the DisGeNET database. A total of 1362 common genes were found, in which the top 11 ranking genes were identified as hub genes, including TNF, AKT1, IL1B, IL6, VEGFA, INS, CCL5, TP53, RELA, STAT3, and EGFR. There were 637 reported SNPs in MS, in which rs653178, rs10936599, and rs4976646 were shared between urological disorders. Based on the GO and KEGG pathway analysis, the most significant pathways in urologic diseases and MS comorbidity were found to be cytokine-cytokine receptor interaction, pathways in cancer, viral protein interaction with cytokine and cytokine receptor, Th17 cell differentiation, JAK-STAT, TNF, and IL-17 signaling pathways. TNF code a multifunctional pro-inflammatory cytokine that plays a crucial role in MS and is mostly released by macrophages (21).

The TNF signaling pathway is complicated resulting in cell death, inflammation, or cell survival. Signaling

through the TNFR1 receptor tends to be pro-inflammatory and leads to death especially in diseases like MS, contrary to the TNFR2 receptor which acts as pro-homeostatic (22). Mu et al., demonstrated a significant connection between prostate cancer angiogenesis and the miR-130b/TNF-α/NF-κB/VEGFA feedback loop (23).

Other studies also have indicated the importance of TNF1 polymorphism in reflux nephropathy, impaired kidney graft survival, risk of bladder cancer, and risk of prostate cancer (24, 25). The type II transmembrane protein belonging to the TNF superfamily is called TNF superfamily member 10 (TNFSF10). Changes in the TNFSF10 signaling pathway have been detected in genitourinary cancers (26, 27).

IL-6 is an interleukin illustrating both a pro-inflammatory cytokine and an anti-inflammatory myokine (28). It has been discovered that the primary effect of IL-6 on auto-reactive effector T cells is evident in MS. For individuals with active relapsing-remitting MS (RRMS), the signaling of IL-6 has been identified as a T effector cell resistance to regulation by regulatory T cells (Tregs), resulting in disease progression (29-31).

Interference of IL-6 with synaptic plasticity mechanisms may hinder the ability to compensate for new brain lesions in RRMS patients (32, 33). According to Neurath et al., blocking the signaling of IL-6 has proven to be effective in the treatment of autoimmune and chronic inflammatory diseases such as inflammatory bowel diseases, diabetes, MS, asthma, rheumatoid arthritis, and even inflammation-associated cancers (45). Also, the major effect of IL-6 on auto-reactive effector T cells has been demonstrated in MS (34). One of the most reliable markers of chronic inflammation in prostate cancer is IL-6. Elevated serum levels of IL-6 have been found in untreated patients with metastatic or castration-resistant prostate cancer (CRPC) and are inversely correlated with tumor survival and response to chemotherapy (35).

An increase in IL-6 during bacillus Calmette-Guerin (BCG) therapy happens and is seen in nonresponders with higher-grade or persisting tumors. IL1B encodes a member of IL-1 cytokine family produced by activated macrophages as a proprotein, which is proteolytically processed to its active form by caspase 1 (CASP1/ICE). Patients with active MS display increased serum levels of IL-2 and IL-10. The clinical significance of IL-2, IL-10, and TNF-α in the prostatic secretion of patients with chronic prostatitis was investigated by He et al., (36).

In a study conducted on mice, it was found that higher levels of IL-2 and IL-10 in urine during the early stages were linked with the development of chronic urinary tract infection. Similarly, in subjects diagnosed with bacterial cystitis, a significant increase in IL-2, IL-6, and IL-8 levels in urine has been observed (37). Interleukin-1beta regulates Proliferation, Interleukin-6 and Interleukin Receptor Expression in PC-3 and DU-145 Prostatic Cancer Cells.

AKT1 is a gene encoding one of three human AKT serine-threonine protein kinases, known as protein kinase B alpha, beta, and gamma. Recently, Oktelik et al. demonstrated that AKT1 expression levels in regulatory T cells indicate the involvement of the AKT pathway in the progression of MS (38). AKT1 and AKT1 differentially regulate the susceptibility to the mouse model of MS (experimental autoimmune encephalomyelitis) by controlling thymus-derived Treg proliferation (39). According to Shen et al., it has been concluded that mitogen-activated protein kinase 4 (MAPK4) plays a crucial part in promoting the expansion in prostate cancer and its resistance to castration. This is achieved through the activation of two parallel pathways: the GATA2/AR and AKT pathways. The study suggests that MAPK4 can be a potential therapeutic target in prostate cancer, particularly in CRPC (40). Multiple investigations proved that the activation of the PI3K/AKT pathway plays a significant role in urological malignancies (41, 42).

The TP53 tumor suppressor protein is composed of various domains such as transcriptional activation, DNA binding, and oligomerization. By a PPI network analysis, Shang et al., indicated that TP53 was a candidate gene for MS (43). The role of TP53 as a regulatory protein that is often mutated in human cancers (including urological malignancies) has been reported since 1979 (44, 45). The role of TP53 in urological malignancies was suggested and confirmed by high-throughput sequencing techniques. Atala demonstrated that dysregulation of p53-RBM25-mediated circAMOTL1L biogenesis made a contribution to the progression of prostate cancer via the circAMOTL1L-miR-193a-5p-Pcdha pathway (46).

The RelA Proto-Oncogene (NF-kappa-B) is a transcription factor that is present throughout the body and plays a role in various BPs. It is kept inactive in the cytoplasm by specific inhibitors. However, patients with progressive MS have been found to have increased and ongoing activation of NF-κB in their peripheral blood cells (47). The NF-κB signaling pathway appears to be a promising therapeutic approach for prostate cancer treatment (48).

According to Degoricija et al., there was a high level of NF-κB and STAT3 activity in human urothelial carcinoma (49).

An immunohistochemical investigation suggested the possible inverse regulation of transcription factors including NF-κB and ER-β during bladder carcinogenesis (50).

The transcription factor STAT3 is responsible for regulating the expression of several genes in response to cellular stimuli. Hence, it plays a vital part in many cellular processes, including cell growth and apoptosis. Dysregulation of STAT3, a transcription factor crucial to various cellular processes, including Th17 cell

differentiation, has been concerned to MS (51, 52).

In a genome-wide association study, in a high-risk isolate for MS, Jakkula et al., revealed associated variants in the STAT3 gene (53). Several studies have highlighted the role of STAT3 in urological malignancies (54, 55). Don-Doncow et al., strongly supported the proposed idea of targeting STAT3 as a therapeutic agent in ones with metastatic CRPC (56). Eto et al., showed that STAT3 polymorphism could forecast the response to interferon-α therapy in patients with metastatic renal cell carcinoma (RCC) (57, 58).

VEGFA belongs to the PDGF/VEGF growth factor family, promoting proliferation and migration of vascular endothelial cells and playing an indispensable role in both physiological and pathological angiogenesis. Peripheral blood mononuclear cells from patients with secondary progressive MS show downregulated expression of VEGF-A (59).

Some recent studies have also shown that the level of VEGF gene messenger RNA (mRNA) is higher in RRMS patients than in those with secondary progressive MS (60, 61). Zeng et al., recently illustrated the association between lymphatic metastasis in prostate cancer and the co-expression of toll-like receptor 4 (TLR9) and VEGF-C (62). Some studies have also suggested the immunomodulatory roles of VEGF pathway inhibitors in RCC (63, 64). The value of preoperative plasma VEGF levels was studied in urothelial carcinoma of the bladder underwent radical cystectomy (65). Elevated plasma VEGF levels were associated with features of biologically and clinically aggressive diseases, such as worse survival outcomes in patients with urothelial carcinoma of the bladder treated with radical cystectomy (65). Angiogenesis therapy for the treatment of erectile dysfunction is considered by targeting VEGFs (66).

INS is a hormone regulating carbohydrate and lipid metabolism. Research suggests that early obesity is associated with an increased risk of developing MS, and both leptin and insulin are linked to obesity (67).

Genetic variation at the insulin locus controls some gene expression levels related to insulin, lipids, and inflammation in MS patients (67, 68). Ho et al., observed a correlation between the polymorphism of the insulin gene and obesity, leading to surge of prostate cancer risk (69). The expression of the spermatozoal insulin and cell death-inducing DNA fragmentation factor-α-like effector A gene, along with DNA fragmentation, were found to be significantly higher in the infertile MS group as compared to the fertile group. These levels were also significantly higher in both MS groups when compared to the control group (70).

People with diabetes are more prone to infections than those without diabetes. Urinary tract infection is the most common site of infection in diabetic patients (71). Statistically, up to 90% of men with diabetes experience sexual dysfunctions, such as erectile and ejaculatory dysfunction, and decreased libido, which can influence male fertility (72).

CCL5 is a chemokine gene found on the q arm of chromosome 17. The levels of chemokines CXCL8, CCL2, and CCL5 are linked to the activity of MS in patients (73). Szczuciński et al. suggested that CXCL10 and CCL5, but not CXCL11, are involved in the development of MS (74). In prostate cancer, infiltrating CD4+ T cells weaken chemotherapy sensitivity by using CCL5 signaling (75, 76). The polybromo 1 (PBRM1) mutation recruits more mast cells by upregulating CCL5 in a clear cell RCC tumor microenvironment (75).

EGFR is a transmembrane glycoprotein that is part of the protein kinase superfamily and acts as a receptor for epidermal growth factor family members. There are bidirectional relationships, metabolic activities, and functional similarities between the kidneys and CNS, suggesting that kidney tissues may significantly affect some aspects of MS. CNS impairment in these patients causes the kidney to respond to central inflammation (77). The role of EGFR in MS was investigated in a pathway and network-based analysis of genome-wide association by Baranzini SE., et al., (78).

EGFR measurement in non-muscle–invasive bladder cancer due to the prognostic activity can identify subgroups risk and predict disease recurrence and progression (79). Several studies have suggested that the invasion of urological malignancies can happen via the EGFR signaling pathway (80, 81).

The rs653178 polymorphism in the ataxin 2 (ATXN2)-SH2B adaptor protein 3 (SH2B3) locus encodes proteins that are essentially required for endocytosis and mitochondrial function and associated with peripheral arterial disease (82). Several studies have indicated the rs653178 variant in MS (83, 84). The rs653178 variant also was a candidate for chronic renal insufficiency in a cohort study (83). A member of the BTB/POZ and zinc finger domain-containing protein family involving the control of gene expression is coded by Myoneurin (MYNN). Polat et al., showed that the rs10936599 polymorphism on the MYNN gene has an impact on the development of bladder cancer in Turkish population (85). MYNN rs10936599 increases the risk of RCC, MS, depressive disorder, colorectal carcinomas, and adenomas (86-88). The regulator of G protein signaling 14 (RGS14) gene codes a member of the regulator of the G protein signaling family; rs4976646 in the RGS14 gene is related to kidney function, inflammatory bowel disease (Crohn's disease), and MS (89, 90). Due to some limitations in this study all the data analyzed in our study was retrieved from online databases. Therefore, further studies in large scale and biological experiments were required to validate our findings.

Conclusions

This study involved a comprehensive bioinformatics analysis for shared genes between MS and urologic disease. TNF, AKT1, IL1B, IL6, VEGFA, INS, CCL5, TP53, RELA, STAT3, and EGFR are key players in the development of urological disorders in MS patients. Variants rs653178, rs10936599, and rs4976646 are candidates in both MS and urological disorders. More molecular studies are needed to further investigate these polymorphisms. Our results may show more detailed understanding of the MS molecular mechanism and urology comorbidity and potential therapeutic targets for its treatment.

Authors' contributions

SH A and HH: Bioinformatics, KK: Data analysis, ZS, RO and PDF: Resources; HAGH: Writing original draft collecting data, PN and VAY: Edited the manuscript

Acknowledgments

Conflict of interest

All authors declare that there is no conflict of interest.

Funding

Ethics statement

This study was approved by ethic committee of Tehran university of Medical Sciences, Tehran, Iran ¬(IR.TUMS. MEDICINE.REC.1401.490).

Data availability

Data will be provided on request.

Abbreviations

ALB	Albumin
BCG	Bacillus Calmette-Guerin
BP	Biological process
CC	Cellular compartment
CD8A	CD8a molecule
CNS	Central nervous system
CXCL8	C-X-C motif chemokine ligand 8
EGFR	Epidermal growth factor receptor
GDA	Gene-disease association
GO	Gene Ontology
INS	Insulin
KEGG	Kyoto Encyclopedia of Genes and Genome
MF	Molecular function
MS	Multiple sclerosis
PPI	Protein-protein interaction
PTPRC	Protein tyrosine phosphatase receptor type C
RRMS	Relapsing-remitting MS
SNPs	Single-nucleotide polymorphisms
STAT3	Signal transducer and activator of transcription3
TLR4	Toll-like receptor 4
UD	Urological disorders
VDA	Variant-disease association
VEGFA	Vascular endothelial growth factor A

References

1. Doshi A, Chataway J. Multiple sclerosis, a treatable disease. Clinical medicine (London, England). 2016;16(Suppl 6):s53-s9.

2. Panicker JN, Fowler CJ. Lower urinary tract dysfunction in patients with multiple sclerosis. Handbook of clinical neurology. 2015;130:371-81.

3. De Ridder D, van Poppel H, Demonty L, D'Hooghe B, Gonsette R, Carton H, et al. Bladder cancer in patients with multiple sclerosis treated with cyclophosphamide. The Journal of urology. 1998;159(6):1881-4.

4. Nazari F, Shaygannejad V, Mohammadi Sichani M, Mansourian M, Hajhashemi V. Sexual dysfunction in women with multiple sclerosis: prevalence and impact on quality of life. BMC Urology. 2020;20(1):15.

5. Monti Bragadin M, Motta R, Messmer Uccelli M, Tacchino A, Ponzio M, Podda J, et al. Lower urinary tract dysfunction in patients with multiple sclerosis: A post-void residual analysis of 501 cases. Multiple sclerosis and related disorders. 2020;45:102378.

6. Poorolajal J, Mazdeh M, Saatchi M, Talebi Ghane E, Biderafsh A, Lotfi B, et al. Multiple Sclerosis Associated Risk Factors: A Case-Control Study. Iranian journal of public health. 2015;44(11):1498-505.

7. Jensen CJ, Stankovich J, Van der Walt A, Bahlo M, Taylor BV, van der Mei IA, et al. Multiple sclerosis susceptibility-associated SNPs do not influence disease severity measures in a cohort of Australian MS patients. PloS one. 2010;5(4):e10003.

8. Cibulka M, Brodnanova M, Grendar M, Necpal J, Benetin J, Han V, et al. Alzheimer's Disease-Associated SNP rs708727 in SLC41A1 May Increase Risk for Parkinson's Disease: Report from Enlarged Slovak Study. International journal of molecular sciences. 2022;23(3).

9. Shoily SS, Ahsan T, Fatema K, Sajib AA. Common genetic variants and pathways in diabetes and associated complications and vulnerability of populations with different ethnic origins. Scientific Reports. 2021;11(1):7504.

10. Li H, Guo J, Cheng G, Wei Y, Liu S, Qi Y, et al. Identification and Validation of SNP-Containing Genes With Prognostic Value in Gastric Cancer via Integrated Bioinformatics Analysis. Frontiers in Oncology. 2021;11.

11. Fiatal S, Ádány R. Application of Single-Nucleotide Polymorphism-Related Risk Estimates in Identification of Increased Genetic Susceptibility to Cardiovascular Diseases: A Literature Review. Frontiers in public health. 2017;5:358.

12. Gresle MM, Jordan MA, Stankovich J, Spelman T, Johnson LJ, Laverick L, et al. Multiple sclerosis risk variants regulate gene expression in innate and adaptive immune cells. Life science alliance. 2020;3(7).

13. Mooney SD, Tenenbaum JD, Altman RB. Bioinformatics. In: Shortliffe EH, Cimino JJ, editors. Biomedical Informatics: Computer Applications in Health Care and Biomedicine. London: Springer London; 2014. p. 695-719.

14. Baxevanis AD. The importance of biological databases in biological discovery. Current protocols in bioinformatics. 2011;Chapter 1:Unit 1.

15. Piñero J, Queralt-Rosinach N, Bravo A, Deu-Pons J, Bauer-Mehren A, Baron M, et al. DisGeNET: a discovery platform for the dynamical exploration of human diseases and their genes. Database. 2015;2015.

16. Piñero J, Ramírez-Anguita JM, Saüch-Pitarch J, Ronzano F, Centeno E, Sanz F, et al. The DisGeNET knowledge platform for disease genomics: 2019 update. Nucleic acids research. 2020;48(D1):D845-D55.

17. Xie Z, Bailey A, Kuleshov M, Clarke D, Evangelista J, Jenkins S, et al. 357 Wojciechowicz ML, Kropiwnicki E, Jagodnik KM: Gene set knowledge discovery with Enrichr. 358. Current protocols. 2021;1(3):e90.

18. Kuleshov MV, Jones MR, Rouillard AD, Fernandez NF, Duan Q, Wang Z, et al. Enrichr: a comprehensive gene set enrichment analysis web server 2016 update. Nucleic acids research. 2016;44(W1):W90-W7.

19. Chin C-H, Chen S-H, Wu H-H, Ho C-W, Ko M-T, Lin C-Y. cyto-

20. Hubba: identifying hub objects and sub-networks from complex interactome. BMC systems biology. 2014;8(4):1-7.

21. Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, et al. Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome research. 2003;13(11):2498-504.

21. Zahid M, Busmail A, Penumetcha SS, Ahluwalia S, Irfan R, Khan SA, et al. Tumor Necrosis Factor Alpha Blockade and Multiple Sclerosis: Exploring New Avenues. 2021;13(10).

22. Maguire AD, Bethea JR, Kerr BJJFiN. TNFalpha in MS and its animal models: Implications for chronic pain in the disease. 2021:2281.

23. Mu H, He Y, Wang S, Yang S, Wang Y, Nan C, et al. MiR-130b/TNF-α/NF-κB/VEGFA loop inhibits prostate cancer angiogenesis. 2020;22(1):111-21.

24. Yang T, Shi R, Chang L, Tang K, Chen K, Yu G, et al. Huachansu suppresses human bladder cancer cell growth through the Fas/Fasl and TNF-alpha/TNFR1 pathway in vitro and in vivo. 2015;34(1):1-10.

25. Lee EJ, Kim WJ, Moon SKJPR. Cordycepin suppresses TNF-alpha-induced invasion, migration and matrix metalloproteinase-9 expression in human bladder cancer cells. 2010;24(12):1755-61.

26. Voelkel-Johnson CJNRU. TRAIL-mediated signaling in prostate, bladder and renal cancer. 2011;8(8):417-27.

27. Deeb D, Jiang H, Gao X, Hafner MS, Wong H, Divine G, et al. Curcumin sensitizes prostate cancer cells to tumor necrosis factor–related apoptosis-inducing ligand/Apo2L by inhibiting nuclear factor-κB through suppression of IκBα phosphorylation. 2004;3(7):803-12.

28. Scheller J, Chalaris A, Schmidt-Arras D, Rose-John S. The pro-and anti-inflammatory properties of the cytokine interleukin-6. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 2011;1813(5):878-88.

29. Schuettfort VM, Pradere B, Trinh Q-D, D'Andrea D, Quhal F, Mostafaei H, et al. Impact of preoperative plasma levels of interleukin 6 and interleukin 6 soluble receptor on disease outcomes after radical cystectomy for bladder cancer. 2022;71(1):85-95.

30. Noegroho B, Siregar S, Simangunsong AIJR, Urology Ri. Correlation of visceral obesity and interleukin-6 level on LUTS due to benign prostatic enlargement. 2021;13:369.

31. Yu SH, Maynard JP, Vaghasia AM, De Marzo AM, Drake CG, Sfanos KSJTP. A role for paracrine interleukin-6 signaling in the tumor microenvironment in prostate tumor growth. 2019;79(2):215-22.

32. Shajarian M, Alsahebfosoul F, Etemadifar MJN. The Effect of IFN-β Treatment on Plasma Levels of BDNF and IL-6 in Relapsing-Remitting Multiple Sclerosis Patients. 2021;28(3):150-7.

33. Vandebergh M, Becelaere S, Dubois B, Goris A, immunology CI-WGJFi. Body Mass Index, Interleukin-6 Signaling and Multiple Sclerosis: A Mendelian Randomization Study. 2022;13.

34. Petković F, Castellano BJNRR. The role of interleukin-6 in central nervous system demyelination. 2016;11(12):1922.

35. Khatami F, Aghamir SMK, Salmaninejad A, Shivarani S, Khorrami MH. Biomarkers for Prostate Cancer Diagnosis from Genetic Perspectives. Translational Research in Urology. 2020;2(2):51-8.

36. He L, Wang Y, Long Z, Jiang CJU. Clinical significance of IL-2, IL-10, and TNF-α in prostatic secretion of patients with chronic prostatitis. 2010;75(3):654-7.

37. Peters KM, Diokno AC, Steinert BWJU. Preliminary study on urinary cytokine levels in interstitial cystitis: does intravesical bacille Calmette-Guerin treat interstitial cystitis by altering the immune profile in the bladder? 1999;54(3):450-3.

38. Oktelik FB, Yilmaz V, Turkoglu R, Akbayir E, Tuzun E, Deniz G, et al. Expression of Akt1 and p-Akt1 in peripheral T cell subsets of multiple sclerosis patients. 2021;121(6):1777-82.

39. Ouyang S, Zeng Q, Tang N, Guo H, Tang R, Yin W, et al. Akt-1 and Akt-2 differentially regulate the development of experimental autoimmune encephalomyelitis by controlling proliferation of thymus-derived regulatory T cells. 2019;202(5):1441-52.

40. Shen T, Wang W, Zhou W, Coleman I, Cai Q, Dong B, et al. MAPK4 promotes prostate cancer by concerted activation of androgen receptor and AKT. 2021;131(4).

41. El Ahanidi H, El Azzouzi M, Arrouchi H, Alaoui CH, Tetou M,

Bensaid M, et al. AKT1 and PIK3CA activating mutations in Moroccan bladder cancer patients´ biopsies and matched urine. 2022;41.

42. Khatami F, Hasanzad M. Circulating Tumor Cells as a Novel Prostate Cancer Diagnostic Tool. Translational Research in Urology. 2020;2(3):93-5.

43. Shang Z, Sun W, Zhang M, Xu L, Jia X, Zhang R, et al. Identification of key genes associated with multiple sclerosis based on gene expression data from peripheral blood mononuclear cells. PeerJ. 2020;8:e8357.

44. Zigeuner R, Ratschek M, Rehak P, Schips L, Langner CJU. Value of p53 as a prognostic marker in histologic subtypes of renal cell carcinoma: a systematic analysis of primary and metastatic tumor tissue. 2004;63(4):651-5.

45. Rioux-Leclercq N, Turlin B, Bansard J-Y, Patard J-J, Manunta A, Moulinoux J-P, et al. Value of immunohistochemical Ki-67 and p53 determinations as predictive factors of outcome in renal cell carcinoma. 2000;55(4):501-5.

46. Atala AJTJoU. Re: dysregulation of p53-RBM25-mediated circAMOTL1L biogenesis contributes to prostate Cancer progression through the circAMOTL1L-miR-193a-5p-Pcdha pathway. 2020;203(2):256-7.

47. Yan J, Winterford CM, Catts VS, Pat BK, Pender MP, McCombe PA, et al. Increased constitutive activation of NF-κB p65 (RelA) in peripheral blood cells of patients with progressive multiple sclerosis. 2018;320:111-6.

48. Jain G, Cronauer MV, Schrader M, Möller P, Marienfeld RBJW-jou. NF-κB signaling in prostate cancer: a promising therapeutic target? 2012;30(3):303-10.

49. Degoricija M, Šitum M, Korać J, Miljković A, Matić K, Paradžik M, et al. High NF-κB and STAT3 activity in human urothelial carcinoma: a pilot study. 2014;32(6):1469-75.

50. Kontos S, Kominea A, Melachrinou M, Balampani E, Sotiropoulou-Bonikou GJIjou. Inverse expression of estrogen receptor-β and nuclear factor-κB in urinary bladder carcinogenesis. 2010;17(9):801-9.

51. Hosseini A, Babaloo Z, Gharibi T, Shomali N, Marofi F, Hashemi V, et al. Epigenetic mechanisms shape the underlining expression regulatory mechanisms of the STAT3 in multiple sclerosis disease. 2020;13(1):1-6.

52. Yu Z, Zhang Y, Tang Z, Song J, Gao X, Sun T, et al. Intracavernosal adeno-associated virus-mediated S100A1 gene transfer enhances erectile function in diabetic rats by promoting cavernous angiogenesis via VEGF-A/VEGFR2 signaling. 2019;16(9):1344-54.

53. Jakkula E, Leppä V, Sulonen A-M, Varilo T, Kallio S, Kemppinen A, et al. Genome-wide association study in a high-risk isolate for multiple sclerosis reveals associated variants in STAT3 gene. 2010;86(2):285-91.

54. Golus M, Bugajski P, Chorbińska J, Krajewski W, Lemiński A, Saczko J, et al. STAT3 and Its Pathways' Dysregulation—Underestimated Role in Urological Tumors. 2022;11(19):3024.

55. Qing Z, Yuan W, Wang J, Song W, Luo J, Wu X, et al. Verapamil inhibited the development of ureteral stricture by blocking CaMK II-mediated STAT3 and Smad3/JunD pathways. 2022;54(11):2855-66.

56. Don-Doncow N, Marginean F, Coleman I, Nelson PS, Ehrnström R, Krzyzanowska A, et al. Expression of STAT3 in prostate cancer metastases. 2017;71(3):313-6.

57. Eto M, Kamba T, Miyake H, Fujisawa M, Kamai T, Uemura H, et al. STAT3 polymorphism can predict the response to interferon-α therapy in patients with metastatic renal cell carcinoma. 2013;63(4):745-52.

58. Aghamir SMK, Nasir Shirazi M, Khatami F. A Systematic Review of Circulating Tumor Cells in Renal Cell Carcinoma. Translational Research in Urology. 2021;3(1):10-8.

59. Iacobaeus E, Amoudruz P, Ström M, Khademi M, Brundin L, Hillert J, et al. The expression of VEGF-A is down regulated in peripheral blood mononuclear cells of patients with secondary progressive multiple sclerosis. 2011;6(5):e19138.

60. Saravani M, Rokni M, Mehrbani M, Amirkhosravi A, Faramarz S, Fatemi I, et al. The evaluation of VEGF and HIF-1α gene polymorphisms and multiple sclerosis susceptibility. 2019;21(12):e3132.

61. Carbone ML, Lacal PM, Messinese S, De Giglio L, Pozzilli C, Persechino S, et al. Multiple sclerosis treatment and melanoma development. 2020;21(8):2950.

62. Zeng X-Z, Huang Z-S, Fang H-P, Wu J-Y, Huang Q-X, Zhuang C-B, et al. Coexpression of TLR9 and VEGF-C is associated with lymphatic metastasis in prostate cancer. 2022;24(4):380.

63. Hirsch L, Flippot R, Escudier B, Albiges LJD. Immunomodulatory roles of VEGF pathway inhibitors in renal cell carcinoma. 2020;80(12):1169-81.

64. Pan X-w, Xu D, Chen W, Chen J-x, Ye J-q, Gan S-s, et al. USP39 Promotes Malignant Proliferation and Angiogenesis of Renal Cell Carcinoma by Inhibiting VEGF-A Alternative Splicing. 2020.

65. Mori K, Schuettfort VM, Katayama S, Laukhtina E, Pradere B, Quhal F, et al. The value of preoperative plasma VEGF levels in urothelial carcinoma of the bladder treated with radical cystectomy. 2022;8(4):972-9.

66. Lysiak JJ, Kavoussi PK, Ellati RT, Steers WD, Annex BHJTJoSM. Angiogenesis therapy for the treatment of erectile dysfunction. 2010;7(7):2554-63.

67. Biström M, Hultdin J, Andersen O, Alonso-Magdalena L, Jons D, Gunnarsson M, et al. Leptin levels are associated with multiple sclerosis risk. 2021;27(1):19-27.

68. Sawcer S, Franklin RJ, Ban MJTLN. Multiple sclerosis genetics. 2014;13(7):700-9.

69. Ho G, Melman A, Liu S, Li M, Yu H, Negassa A, et al. Polymorphism of the insulin gene is associated with increased prostate cancer risk. 2003;88(2):263-9.

70. Elsamanoudy AZ, Abdalla HA, Hassanien M, Gaballah MAJD, syndrome m. Spermatozoal cell death-inducing DNA fragmentation factor-α-like effector A (CIDEA) gene expression and DNA fragmentation in infertile men with metabolic syndrome and normal seminogram. 2016;8(1):1-10.

71. Gotoh D, Cao N, Alexandre EC, Saito T, Morizawa Y, Hori S, et al. Effects of low-dose insulin or a soluble guanylate cyclase activator on lower urinary tract dysfunction in streptozotocin-induced diabetic rats. 2021;286:120001.

72. Asafu-Adjei DA, Gittens PR. Diabetes and Male Infertility. Male Infertility: Springer; 2020. p. 865-71.

73. Bartosik-Psujek H, Stelmasiak ZJEjon. The levels of chemokines CXCL8, CCL2 and CCL5 in multiple sclerosis patients are linked to the activity of the disease. 2005;12(1):49-54.

74. Szczuciński A, Losy JJN. CCL5, CXCL10 and CXCL11 chemokines in patients with active and stable relapsing-remitting multiple sclerosis. 2011;18(1):67-72.

75. Jin S, Xiang P, Liu J, Yang Y, Hu S, Sheng J, et al. Activation of cGMP/PKG/p65 signaling associated with PDE5-Is downregulates CCL5 secretion by CD8+ T cells in benign prostatic hyperplasia. 2019;79(8):909-19.

76. Ma J, Shayiti F, Ma J, Wei M, Hua T, Zhang R, et al. Tumor-associated macrophage-derived CCL5 promotes chemotherapy resistance and metastasis in prostatic cancer. 2021;45(10):2054-62.

77. Rostami S, Emami-Aleagha M-S, Ghasemi-Kasman M, Allameh AJCJoIM. Cross-talks between the kidneys and the central nervous system in multiple sclerosis. 2018;9(3):206.

78. Baranzini SE, Galwey NW, Wang J, Khankhanian P, Lindberg R, Pelletier D, et al. Pathway and network-based analysis of genome-wide association studies in multiple sclerosis. 2009;18(11):2078-90.

79. Di Maida F, Mari A, Gesolfo CS, Cangemi A, Allegro R, Sforza S, et al. Epidermal growth factor receptor (EGFR) cell expression during adjuvant treatment after transurethral resection for non-muscle-invasive bladder cancer: a new potential tool to identify patients at higher risk of disease progression. 2019;17(4):e751-e8.

80. Zhou Z, Zhang Z, Chen H, Bao W, Kuang X, Zhou P, et al. SBSN drives bladder cancer metastasis via EGFR/SRC/STAT3 signalling. 2022:1-12.

81. Yang N, Gao J, Hou R, Xu X, Yang N, Huang SJOM, et al. Grape Seed Proanthocyanidins Inhibit Migration and Invasion of Bladder Cancer Cells by Reversing EMT through Suppression of TGF-β Signaling Pathway. 2021;2021.

82. Kullo IJ, Shameer K, Jouni H, Lesnick TG, Pathak J, Chute CG, et

al. The ATXN2-SH2B3 locus is associated with peripheral arterial disease: an electronic medical record-based genome-wide association study. 2014;5:166.

83. Niu P-P, Song B, Wang X, Xu Y-MJFiG. Serum Uric Acid Level and Multiple Sclerosis: A Mendelian Randomization Study. 2020;11:254.

84. Harroud A, Richards JB, Baranzini SEJN-NN. Mendelian randomization study shows no causal effects of serum urate levels on the risk of MS. 2021;8(1).

85. Polat F, Yilmaz M, Diler SBJUJ. The association of MYNN and TERC gene polymorphisms and bladder cancer in a Turkish population. 2019;16(1):50-5.

86. Shepard CJ, Cline SG, Hinds D, Jahanbakhsh S, Prokop JW-JPG. Breakdown of multiple sclerosis genetics to identify an integrated disease network and potential variant mechanisms. 2019;51(11):562-77.

87. Machiela MJ, Hofmann JN, Carreras-Torres R, Brown KM, Johansson M, Wang Z, et al. Genetic variants related to longer telomere length are associated with increased risk of renal cell carcinoma. 2017;72(5):747-54.

88. Erkal B, Akçeşme B, Çoban A, Korkut ŞVJMS, Disorders R. A Comprehensive in Silico Analysis of Multiple Sclerosis Related Non-Synonymous SNPs and Their Potential Effects on Protein Structure and Function. 2022:104253.

89. Wuttke M, Li Y, Li M, Sieber KB, Feitosa MF, Gorski M, et al. A catalog of genetic loci associated with kidney function from analyses of a million individuals. 2019;51(6):957-72.

90. De Lange KM, Moutsianas L, Lee JC, Lamb CA, Luo Y, Kennedy NA, et al. Genome-wide association study implicates immune activation of multiple integrin genes in inflammatory bowel disease. 2017;49(2):256-61.

Author (s) biosketches

Aliyari SH, MD, Department of Bioinformatics, Kish International Campus University of Tehran, Kish, Iran, and Laboratory of Complex Biological Systems and Bioinformatics (CBB), Department of Bioinformatics, Institute of Biochemistry and Biophysics (IBB), University of Tehran, Tehran, Iran.

Email: aliyari.shahram@gmail.com

Salehi Z, MD, Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

Email: zahra.salehi6463@yahoo.com

Kavousi K, MD, Laboratory of Complex Biological Systems and Bioinformatics (CBB), Department of Bioinformatics, Institute of Biochemistry and Biophysics (IBB), University of Tehran, Tehran, Iran.

Email: kkavousi@ut.ac.ir

Azodian Ghajar H, MSc, Department of Medical Genetics, Afzalipour Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran.

Email: Helia.azodian.ghajar@gmail.com

Nikoofar P, MD, Department of Urology, Thunder Bay Regional Health Research Institute, Thunder Bay, Ontario, Canada.

Email: parsa.nikoofar@gmail.com

Omid O, MD, Department of Radiology, Hasheminejad Hospital, Tehran University of Medical Sciences, Tehran, Iran.

Email: shadravanmehdi1380@gmail.com

Dehghanpoor Farashah P, MD, Islamic Azad University of Medical Sciences, Tehran, Iran.

Email: parmida.farashah@yahoo.com

Homayoun H, Assistant professor, Department of Electrical and Computer Engineering, University of Kashan, Kashan, Iran.

Email: hassan.homayoun@hotmail.com

Abedi Yarandi V, MD, Islamic Azad University of Medical Sciences, Tehran, Iran.

Email: drvahidabedi@gmail.com