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

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## 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.

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## 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.

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

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

## 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.

**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.

**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

**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 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 |

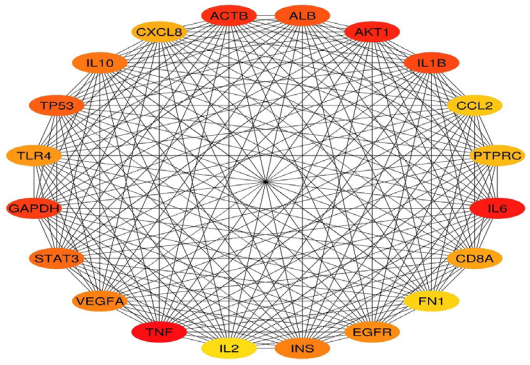


**Figure 1.** The hub genes overlapped between BPs, MFs, and KEGG pathways

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

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**Conflict of interest**

All authors declare that there is no conflict of interest.

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**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 |

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