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Prediction of Single Nucleotide Polymorphisms in TNFSF4 and Confirmation of Its Relationship with AITD and SLE: Bioinformatics Approach

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Abstract: Tumor Necrosis Factor Ligand Superfamily Member4 (TNFSF4) has a huge family of physically homologous transmembrane proteins that regulate various functions in responding cells containing proliferation, differentiation, apoptosis, and inflammatory gene expression. TNFSF4 can play significant role in inflammatory diseases that its polymorphisms of the TNFSF4 gene are mostly related with Sjogren's syndrome, and systemic lupus erythematosus (SLE). The aim of this study is to investigate the genetic variations that may alter the expression, function and role of the TNFSF4 by using *in silico* methods. Single Nucleotide Polymorphisms (SNPs) on TNFSF4 are analyzed by GeneMania, SIFT, PolyPhen2, UTRscan programme, U.S. National Library of Medicine Database, ClinVar. 37 variants of TNFSF4 were found that among these 9 missense, 8 coding synonymous, 1 coding, 1 splice-3, 1 UTR-3, 11 intron, 5 UTR-5 variants. Moreover, two of them SNPs that these are rs199835957, rs372063551 were detected probably damaging by PolyPhen2 and they should be noted that vital candidates in causing diseases related to TNFSF4 and they were identified missense variants that weren't reported in ClinVar. In the future, genes of TNFSF4, TNFSFR and CD40 may be studied on polymorphisms with experimental analysis in order to contribute to science by helping to identify disease pathogenesis.

Keywords: AITD, SLE, TNFSF4, Bioinformatics, *in silico*

1. Introduction

TNFSF4 (Tumor Necrosis Factor Ligand Superfamily Member 4) is a gene which encodes cytokines and members of this family are expressed on T cells, several of which are upregulated chasing T- cell activation [1]. The precursor cell source of TNFSF is macrophages, natural killer (NK) cells and T cells that occurs a mainly cellular targets and biological effects such as inflammation and coagulation in endothelial cells, activation in neutrophils, fever in hypothalamus, catabolism in muscle and fat [1-3]. TNFSF members characteristically form homotrimers, either within the plasma membrane or after proteolytic release from the membrane, and attach to homotrimeric TNF receptor superfamily (TNFRSF) molecules, which then start an assortment of signaling pathways [4]. TNFSF4 plays significant role in many diseases as atherosclerosis [5], allergic rhinitis, asthma [6], Vogt Koyanagi Harada disease (VKH), Behcet's diseases [7] and systemic lupus erythematosus (SLE) [8] and so it can also be correlated with other autoimmune diseases. Single nucleotide polymorphisms (SNPs) studies can have huge outcomes of the increasing risk of various widespread diseases.

Some diseases strongly affect people depending on TNFSF. One of these diseases is AITDs and the other one is SLE. Autoimmune thyroid disease (AITD), mainly consists of Graves' disease (GD) and Hashimoto's thyroiditis (HT) [9]. AITD affects approximately 5% of the general population and the prevalence of antithyroid antibodies is greater in females. According to National Health and Nutrition Examination Survey (NHANES III) study, hypothyroidism was found in 4.6% of the U.S. population (0.3% clinical and 4.3% subclinical) and hyperthyroidism in 1.3% (0.5% clinical and 0.7% subclinical) making autoimmune thyroid disease related thyroid dysfunction one of the most common diseases for the population [10]. If we consider autoimmunity to the thyroid (the presence of antibodies to thyroid antigens), it is as high as 10-20% of all women [11]. AITDs is organ specific disease and also the most common AD and is affiliated with other organ-specific and non-organ specific ADs.

SLE is an autoimmune disorder that has an effect on mainly women of childbearing age. Systemic lupus erythematosus (SLE) is also a multi-organ disorder that presents itself in a thousand ways. Since these patients have self-reactive B cells that are abnormally regulated, it can cause several disorders, including multisystem organ involvement, autoantibody production, immune complex deposition and complement activation with tissue damage. In other words, SLE can mimic many diseases. Its clinical course is extremely unpredictable, which makes diagnosis and treatment a challenge for clinicians. SLE is unique among other autoimmune disorders, because as well as having an unpredictable clinical course, it can directly affect any organ [12]. It appears that the clinical course of SLE is determined by genetic material in combination with environmental factors like in AITD. The incidence of SLE is between 0.3 and 23.2 in 100,000 person-years varying between populations [13].

Our study explains the relationship between AITD and SLE as *in silico*. Therefore; SNPs are shown with an explanation as deleterious or tolerant. Some specific and significant programs as SIFT, PolyPhen, SNP Mining, GeneMania, Exome Variant Server and UTRs Scan Programme are used for detection of input gene that identifies its homology. Recently, approximately 5,000,000 variants were analyzed in the coding region of human population [9]. The susceptibility SNPs for TNFSF4 gene haven't been conjecturable to date *in silico* study. *In silico* models allows scientists to experiment design and select a compound with a reasonable potential for further development of studies. Moreover; *in silico* platform can strongly lead the evolution of clinical biomarkers and preclinical assays to identify patient types and drug combinations, thus it can present information in SNPs studies to find out human complex disorders. The purpose of this study is to find out polymorphisms in TNFSF4 and to show which SNPs are linked to SLE and AITD.

2. Materials and Method

2.1. GeneMANIA Algorithm for Functionally Similar Genes

Gene Mania is a database which shows similar genes. It is used for functionally similar to input gene that is identified physical interactions, co- expression, co-localization, genetic interactions. It gives a query list by using genomics and proteomics data. This data is available at https://genemania.org [10] This data was used for TNFSF4 and its relations with other genes, thus it was predicted the function of TNFSF4 gene and gene set.

2.2. Predicting Functional, Deleterious and Tolerated SNPs Prediction

Sorting Intolerant from Tolerant Data (SIFT) is an online database that was used to search analogue sequences and select likely associated sequences which have similar function to input gene. There are some important points. According to SIFT, if the positions with standardized possibilities are lower than 0.05, these are called as deleterious but if the positions with standardized possibilities are better than or equal to 0.05, these are called as tolerated. This data is available at http://sift.jcvi.org [11].

2.3. Exome Variant Server

Exome Variant Server is procured by the The National Heart, Lung and Blood Institute (NHLBI). The purpose of this database is to find out novel genes and mechanisms accession to heart, lung and blood disorders. This database is available at http://evs.gs.washington.edu/EVS/ [12]. This database was used to determine the number of variations according to population, then the alleles were listed. EA (European African Population) allele counts and AA (African American population) allele counts was observed. As a result, the minor-allele frequency was analyzed in this data. AA, EA genotypes were calculated and evaluated.

2.4. UTRscan Programme

UTRscan is a database which is used for pattern matcher. It is used to investigate DNA, RNA, tRNA sequences that aims to get UTR motifs and these motifs are symbolical of 3'UTR and 5'UTR sequences. This is an online database that is used for collection of purposive sequence patterns placed in the 5'- or 3'-UTR sequences. The database is available at http://utrdb.ba.itb. cnr.it/ [13]. Some biological processed were analyzed by UTR scan such as determination, transcriptional regulatory pathways, and translational efficiency.

3. Results

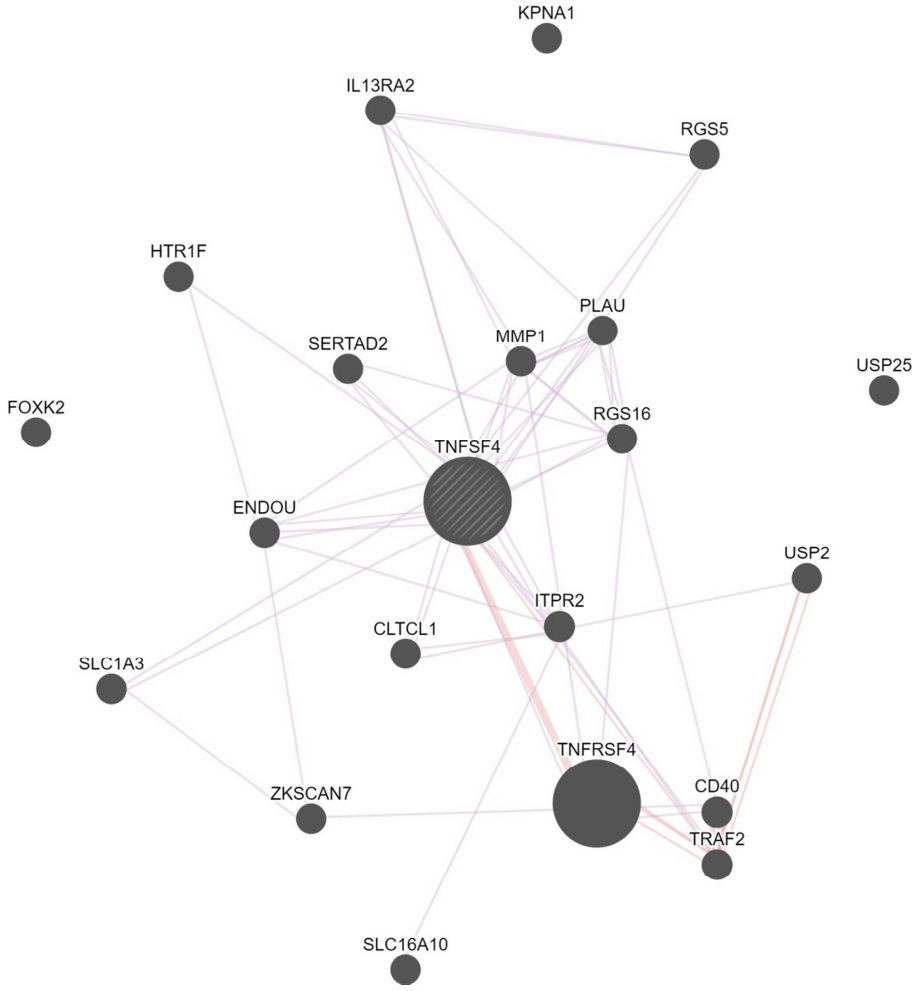

Figure 1. *The picture shows that physical interactions (pink) and co-expression (lilac) between TNFSF4 gene and its related genes.*

Table 1. *The data descriptions of genes and their co-expressions and physical interactions with TNFSF4 gene network.*

Number	Gene's Name	Explanation	Co-expression	Physical Interaction
1	HTR1F	5-hydroxytryptamine receptor 1F	YES	NO
2	FOXK2	Forkhead box K2	NO	NO
3	SLC1A3	Solute carrier family 1 member 3	YES	NO
4	ENDOU	Endonuclease poly (U) spesific	YES	NO
5	SERTAD2	SERTA domain containing 2	YES	NO
6	ITPR2	Inositol 1,4,5-triphosphate receptor type 2	YES	NO
7	TNFSFR4	Tumor necrosis factor super family receptor 4	NO	YES
8	UPS2	Ubiquitin spesific peptidase 2	NO	YES
9	RGS5	Regulator of G protein signaling 5	YES	NO
10	CD40	CD 40 molecule	YES	YES
11	TRAF2	TNF receptor associated factor 2	NO	YES
12	USP25	Ubiquitin spesific peptidase 25	NO	NO
13	PLAU	Plasminogen activator, urokinase	YES	NO
14	SLC16A10	Solute carrier family 16 member 10	NO	NO
15	KPNA1	Karyopherin subunit alpha 1	NO	NO
16	MMP1	Matrix metallopeptidase 1	YES	NO
17	IL12RA2	Interleukin 13 receptor subunit alpha 2	YES	NO
18	CLTCL1	Clathrin heavy chain like 1	YES	NO
19	ZKSAN7	Zinc finger with KRAB and SCAN domains 7	NO	NO
20	RGS16	Regulator of G-protein signaling 16	YES	NO

Table 1 shows the co-expression and physical interaction with TNFSF4 gene network. We explained twenty different genes and one of them is very significant gene which is known as CD40 molecule. Four genes (SLC16A10, KPNA1, 2KASANA, FOXK2) which have no interaction and co-expression with TNFSF4 were also found.

Table 2. *This data explains that TNFSF4 network genes' functions and its genome.*

Function	False Discovery Rate	Genes in network	Genes in genome
Regulation of production of molecular mediator of immune response	0.2680558227214164	3	44
Regulation of t cell cytokine production	0.3188879419816194	2	13
Production of molecular mediator of immune response	0.31888794198161943	3	69
Positive regulation of production of molecular mediator of immune response	0.31888794198161942	2	16
T cell cytokine production	0.31888794198161942	2	16
Regulation of immunoglobulin production	0.31888794198161942	2	16
Positive regulation of cytokine production involved in immune response	0.31888794198161942	2	13
CD40 receptor complex	0.31888794198161942	2	11
B cell activation	0.46276942084836675	3	119
Positive regulation of adaptive immune response	0.46276942084836675	2	34

A major key role of UTRs is to control mRNA stability, turnover, and translation effectiveness and in this study; UTRscan data gave 46 different genes. If various sequences for every UTR SNP are discovered to have various functional patterns, this UTR SNP is guessed to have functional meaning that this study has correlated this situation.

Table 3. *SNP list was provided for functionally important by SIFT data.*

SNP	Protein ID	Region	Amino Acid Change	Prediction
rs17568	ENSP00000368538	CDS	E178E	Tolerated
rs10516487	ENSP00000320509	CDS	R61H	Tolerated
rs10516487	ENSP00000388817	CDS	R31H	Tolerated
rs10516487	ENSP00000421443	CDS	R46H	Tolerated
rs3733197	ENSP00000412748	CDS	A250T	Deleterious
rs3733197	ENSP00000422314	CDS	A250T	Deleterious
rs3733197	ENSP00000421443	CDS	A368T	Deleterious
rs3733197	ENSP00000320509	CDS	A383T	Deleterious
rs3733197	ENSP00000388817	CDS	A353T	Deleterious
rs3761847	ENSP00000362994	UTR_5		
rs7514229	ENSP00000281834	UTR_3		
rs7514229	ENSP00000356691	UTR_3		

rs ID	Alleles	AA Allele #	EA Genotype #	AA Genotype #	Genes	GVS Function	cDNA Change	Protein Change	PolyPhen2 (Class:Score)
rs370155078	C>G	G=0/C=4406	GG=0/GC=2/CC=4298	GG=0/GC=0/CC=2203	TNFSF4	utr-3	c.*1G>C	NA	unknown
rs373048163	G>A	A=0/G=4406	AA=0/AG=1/GG=4299	AA=0/AG=0/GG=2203	TNFSF4	coding-synonymous	c.501C>T	p.(G167=)	unknown
rs377655834	G>A	A=0/G=4406	AA=0/AG=1/GG=4299	AA=0/AG=0/GG=2203	TNFSF4	coding-synonymous	c.478C>T	p.(L160=)	unknown
rs370486904	T>C	C=0/T=4406	CC=0/CT=1/TT=4299	CC=0/CT=0/TT=2203	TNFSF4	coding-synonymous	c.384A>G	p.(Q128=)	unknown
rs146261831	C>T	T=0/C=4406	TT=0/TC=5/CC=4295	TT=0/TC=0/CC=2203	TNFSF4	missense	c.347G>A	p.(S116N)	benign:0.006
rs144164274	C>T	T=0/C=4406	TT=0/TC=1/CC=4299	TT=0/TC=0/CC=2203	TNFSF4	missense	c.247G>A	p.(D83N)	benign:0.001
rs139594528	C>T	T=1/C=4405	TT=0/TC=4/CC=4296	TT=0/TC=1/CC=2202	TNFSF4	coding-synonymous	c.246G>A	p.(E82=)	unknown
rs375172687	T>C	C=0/T=4406	CC=0/CT=1/TT=4299	CC=0/CT=0/TT=2203	TNFSF4	missense	c.241A>G	p.(K81E)	benign:0.037
unknown	R>A1	A1=0/R=4266	A1A1=0/A1R=1/RR=4126	A1A1=0/A1R=0/RR=2133	TNFSF4	coding	c.211_213del3	p.(K71del1)	unknown
rs375266956	T>C	C=0/T=4406	CC=0/CT=1/TT=4299	CC=0/CT=0/TT=2203	TNFSF4	splice-3	c.203-2A>G	NA	unknown
rs372347723	G>T	T=0/G=4406	TT=0/TG=1/GG=4299	TT=0/TG=0/GG=2203	TNFSF4	intron	c.203-4C>A	NA	unknown
rs45499993	C>A	A=0/C=4406	AA=0/AC=4/CC=4295	AA=0/AC=0/CC=2203	TNFSF4	intron	c.202+25G>T	NA	unknown
rs181674431	A>G	G=0/A=4406	GG=0/GA=3/AA=4296	GG=0/GA=0/AA=2203	TNFSF4	intron	c.202+23T>C	NA	unknown
rs374449847	G>A	A=0/G=4406	AA=0/AG=1/GG=4298	AA=0/AG=0/GG=2203	TNFSF4	intron	c.202+12C>T	NA	unknown
rs372834430	T>C	C=1/T=4405	CC=0/CT=0/TT=4299	CC=0/CT=1/TT=2202	TNFSF4	coding-synonymous	c.195A>G	p.(Q65=)	unknown
rs374158518	G>C	C=0/G=4406	CC=0/CG=1/GG=4298	CC=0/CG=0/GG=2203	TNFSF4	missense	c.193C>G	p.(Q65E)	benign:0.009
rs149786415	T>C	C=0/T=4406	CC=0/CT=1/TT=4298	CC=0/CT=0/TT=2203	TNFSF4	coding-synonymous	c.192A>G	p.(V64=)	unknown
rs141837753	G>A	A=22/G=4384	AA=0/AG=0/GG=4299	AA=0/AG=22/GG=2181	TNFSF4	coding-synonymous	c.186C>T	p.(I62=)	unknown
rs368338886	C>T	T=1/C=4405	TT=0/TC=0/CC=4300	TT=0/TC=1/CC=2202	TNFSF4	missense	c.173G>A	p.(R58Q)	benign:0.294
rs147675528	C>T	T=0/C=4406	TT=0/TC=1/CC=4299	TT=0/TC=0/CC=2203	TNFSF4	missense	c.164G>A	p.(R55Q)	benign:0.001
rs372063551	G>A	A=0/G=4406	AA=0/AG=1/GG=4299	AA=0/AG=0/GG=2203	TNFSF4	missense	c.163C>T	p.(R55W)	probably-damaging:0.963
rs374926869	T>C	C=1/T=4403	CC=0/CT=0/TT=4299	CC=0/CT=1/TT=2201	TNFSF4	intron	c.154-24A>G	NA	unknown
rs10489270	G>A	A=28/G=1356	AA=21/AG=342/GG=1228	AA=0/AG=28/GG=664	TNFSF4	intron	c.154-56C>T	NA	unknown
rs369211002	A>G	G=0/A=1752	GG=0/GA=1/AA=1990	GG=0/GA=0/AA=876	TNFSF4	intron	c.153+1763T>C	NA	unknown
rs115864391	A>G	G=4/A=1748	GG=0/GA=0/AA=1991	GG=0/GA=4/AA=872	TNFSF4	intron	c.153+1741T>C	NA	unknown
rs377661313	A>G	G=0/A=1752	GG=0/GA=1/AA=1990	GG=0/GA=0/AA=876	TNFSF4	intron	c.153+1736T>C	NA	unknown
rs56217303	C>T	T=2/C=1750	TT=0/TC=20/CC=1971	TT=0/TC=2/CC=874	TNFSF4	intron	c.153+1729G>A	NA	unknown
rs373510628	C>G	G=5/C=1747	GG=0/GC=0/CC=1991	GG=0/GC=5/CC=871	TNFSF4	intron	c.153+1683G>C	NA	unknown
rs148349364	A>C	C=2/A=4404	CC=0/CA=0/AA=4300	CC=0/CA=2/AA=2201	TNFSF4	coding-synonymous	c.144T>G	p.(S48=)	unknown
rs199835957	C>T	T=0/C=4406	TT=0/TC=2/CC=4298	TT=0/TC=0/CC=2203	TNFSF4	missense	c.79G>A	p.(V27M)	probably-damaging:0.999
rs371334974	C>T	T=0/C=4406	TT=0/TC=1/CC=4299	TT=0/TC=0/CC=2203	TNFSF4	missense	c.43G>A	p.(A15T)	benign:0.063
rs370473906	G>A	A=1/G=4405	AA=0/AG=0/GG=4300	AA=0/AG=1/GG=2202	TNFSF4	utr-5	c.-20C>T	NA	unknown
rs113957847	G>A	A=7/G=4399	AA=0/AG=0/GG=4300	AA=0/AG=7/GG=2196	TNFSF4	utr-5	c.-44C>T	NA	unknown
rs368426337	A>G	G=0/A=4406	GG=0/GA=1/AA=4299	GG=0/GA=0/AA=2203	TNFSF4	utr-5	c.-45T>C	NA	unknown
rs369775833	C>T	T=0/C=4406	TT=0/TC=1/CC=4299	TT=0/TC=0/CC=2203	TNFSF4	utr-5	c.-47G>A	NA	unknown
rs145777208	G>A	A=0/G=2654	AA=0/AG=1/GG=2308	AA=0/AG=0/GG=1327	TNFSF4	utr-5	c.-52C>T	NA	unknown

Figure 2. *This data shows SNPs of TNFSF genes that identifies splice or nonsense or frameshift (pink), missense (red), coding synonymous (green), coding (blue), utr (orange), coding complex (yellow) by NHLBI Exome Sequencing Project.*

Our results showed the polymorphism changes of African American and European African population (Figure 2). We have determined 8 coding-synomymous, 9 missense, 1 coding, 1 splice-3, 1 utr-3, 5 utr-5 and 11 intron variation in CD40 molecule. Two of them could be damaging mutation for humans.

4. Discussion

Most recently, studies showed that polymorphisms and expressions of TNF superfamily cytokines, receptors, indicating proteins and genetic variations are related to autoimmune, autoinflammatory and inflammatory diseases. However, this situation has continued to be explored [14]. Some polymorphisms have exposed direct results on gene expression and infrequently downstream phenotype for illness-related variants positioned TNFSF4.

In this study, the CD40 was found very close to TNFSF4. Because; CD40 belongs to the TNF receptor family that its ligand, CD40L (CD154), is a trimeric membrane protein that is homologous to TNF and it is expressed on B cells. One of the major indicators for activation is IFN-γ from Th1 type CD4 T cells in the macrophage and the other indicator is CD40L on the T cell that combined CD40 on the macrophage cell surface. Consequently, the macrophage expresses much more CD40 and TNF receptors on its surface that helps raise the level of activation.

According to the results, GeneMania shows that CD40 gene has physical interaction and co-expression with TNFSF4 and TNFSF gene. TNFSFR are belong to structurally homologous transmembrane proteins which attach TNFSF proteins and produce signals that organize proliferation, differentiation, apoptosis, and inflammatory gene expression thus it can cause autoimmune diseases. HTR1F, FOXK2, SLC1A3, ENDOU, SERTAD2, ITPR2, RGS5, PLAU, MMP1, IL12RA2, CLTCL1, RGS16 genes have co-expression with TNFSF4 that explains synchronical recognition, clustering and investigation of thousands of genes with analogous patterns across many forms [15]. TRAP2, MMP1, IL12RA2 genes have been studied with SLE [16, 17], autoimmune diseases [14, 18] and thyroid [19] diseases but there aren't any studies on SLE, autoimmune diseases, and thyroid diseases with other genes. The TNFSF4-associated genes' functions and its appearance in the genome were grouped that defines as if it is greater than or equal to the probability that this is a false positive.

SIFT data was shown that rs3733197 had deleterious and rs10516487, rs17568 had tolerated amino acid changes, thus this situation is also very important because of its effects on protein's functionality. According to Figure 2, there were discovered 37 variants in European American and African American population. 9 missense, 8 coding synonymous, 1 coding, 1 splice-3,1 utr-3, 11 intron, 5 utr-5 variants were analyzed that two of them SNPs that these are rs199835957, rs372063551 were shown probably damaging by PolyPhen2 and 13 unknown SNPs was described as *in silico*. There was no information about 37 variants and there haven't been reported in ClinVar before, so there haven't shown any clinical link with diseases. Our findings demonstrated that harmful (damaging) SNPs in the TNFSF4 gene can be the cause or causes of problems and they can be significant candidate for various types of human diseases related to TNFSF4.

In the future, genes of TNFSF4, TNFSFR and CD40 may be studied on polymorphisms with experimental analysis in order to contribute to identify disease pathogenesis. Therefore, our study is promising for the development of more effective drug design.

5. Conclusion

TNFSF4 is a gene that encodes cytokines and members of this family are expressed on T cells, several of which are upregulated chasing T- cell activation. Therefore, TNFSF4 can play significant role in inflammatory diseases that its polymorphisms of the TNFSF4 gene are mostly related with Sjogren's syndrome, and systemic lupus erythematosus (SLE). In this study, genetic variations that may alter the expression, function and role of TNFSF4 were investigated by using bioinformatics tools. Our findings demonstrated that harmful (damaging) SNPs in the TNFSF4 gene can be responsible of abnormalities and they can be significant candidate to be the cause of various types of human diseases related to TNFSF4.

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