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RESEARCH ARTICLE

Genomics of SOX13 gene is dynamic in Type 1 Diabetes

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ABSTRACT

Background: The SOX13 (SRY-box 13) genes belong to the high mobility group box (HMG-box) family and are primarily associated with testicular concern. This gene has an HMG-box domain that binds with DNA and plays a crucial role in growth and survival. Specifically, SOX13 is located on chromosome 1 and is an insulin-mediated gene. The presence of insulin is significant evidence of genomics variation in the SRY-box transcription factor 13, which is sensitive in type-1 diabetes (T1D). So, the SRY-box transcription factor 13 (ICA12) genes circulate in islets and the exocrine pancreas and are considered a powerful auto-antigen. Thus, beta-cell antigens trigger mechanisms of peripheral tolerance. The recognition of ICA12 as an auto-antigen is an effective marker for autoimmunity.

Aim: The study aims to in-silico analyze the SRY-box 13 gene from the family of SRY-related high mobility group box (HMG-box) genes (SOX gene family) in mammals. So, perform bioinformatics and computational pipelines and applications for experimentation and even upgradation of a particular gene and its family in two different organisms.

Results: The observation documented the total SOX13 and HMG-box domains in two mammalian genomes (i.e. Homo sapiens and Mus musculus). A computational and bioinformatics analysis demonstrated that SOX13 is an insulin-initiated gene. Also, the findings provided genomic variations of the SRY-box 13 gene response in T1D. Also, the study stated the molecular and immunologic mechanisms associated with autoimmune T1D.

Concluding Remarks: The series of data forwarded supreme future of autoimmune T1D are linked with SRY-related HMG-box 13 genes during the outgrowth of organisms. Also, the study justified that HMG-box genes reveal a significant nature during the growth in mammals. Thus, the high mobility group of ICA12 is an insulin-mediated gene that shows a preface in T1D. Also, auto-reactive CD4+ T cells and killer T cells play a fundamental role in autoimmune T1D.

Keywords: SOX13; SOX family; T1D; Gene therapy; Immunotherapy

Highlights:

- This study is associated with diabetes research and development.
- The present finding illustrated that SOX13 (ICA12) is an insulin-dependent gene.
- The SOX13 gene observed as an auto-antigen is a vital marker for autoimmunity.
- Also, auto-reactive T_h cells and T_C cells play an immunologic role in autoimmune T1D.
- Therefore, the study leads to the improvement of T1D.

Abbreviation:

WHO: World health organization
IDDM: Insulin-dependent diabetes mellitus (T1D)
NIDDM: Non-insulin-dependent diabetes mellitus (T2D)
T1D: Type 1 Diabetes
T2D: Type 2 Diabetes
CD8+ T-cell: Cytotoxic T-cell
CD4+ Cells: T helper cells
DNA: Deoxyribonucleic acid
LADA: Latent autoimmune diabetes in adults
GAD: Glutamic acid decarboxylase
SOX13: Transcription factor SOX-13
SOX: SRY-related HMG-box
NCBI: National Center for Biotechnology Information
KEGG: Kyoto Encyclopedia of Genes and Genome
SMART: Simple Modular Architecture Research Tool
EMBL: European Molecular Biology Laboratory
NJM: Neighbor-Joining Methods
BLAST: Basic Local Alignment Search Tool
HMM: Hidden Markov Model
GO: Gene Ontology
MEGA: Molecular Evolutionary Genetics Analysis
MEME: Multiple EM for Motif Elicitation
SOX5: Transcription factor SOX-5
CEP85: Centrosomal protein 85
DMRT1: Doublesex and mab-3 related transcription factor 1
PTPRN: Receptor-type tyrosine-protein phosphatase-like N
TCF7L2: Transcription factor 7-like 2
TCF7: Transcription factor 7
TCF7L1: Transcription factor 7-like 1
LEF1: Lymphoid enhancer-binding factor 1
CTNNB1: Catenin beta-1
NOTCH1: Notch homolog 1, translocation-associated
SD: Standard deviation
TF's: Transcription factors
HMG-box: High mobility group box
HSP60: Heat shock protein 60
IA-2: Islet antigen 2
IGRP: Islet-specific glucose-6-phosphatase catalytic subunit-related protein
β-cell: Beta Cell
CMV: Cytomegalovirus
GAD65: Glutamic acid decarboxylase 65
IFNG: Interferon gamma
TNF-α: Tumor necrosis factor alpha
CD28: Cluster Differentiation 28
Treg: Regulatory T cell
CD25: Cluster Differentiation 25
FOXP3: Forkhead box P3
NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells
IL12B: Subunit beta of interleukin 12
IκBα: Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha
IL-12: Interleukin 12

Introduction:

The primary challenges for computational biologists in the genomic era have been the question of how phenotypic diversity arises. The cutting-edge technology is a feature of the rapid observation of gene products such as gene fragments, homologs, paralogs, and orthologs in particular species. Novel genes may be integrated into living organisms and propose the adaptation of phenotypes. The target is not only the genes, but how, why, and what combinations of a particular gene are expressed at the cellular level is a primordial query in biology. The accessibility of complete draft genome sequences allowed the comparative study between different organisms. So, perform a genome-wide examination of the HMG box-mediated genes in two mammals. The HMG box-mediated genes govern essential functions in determining cell fate during the growth of organisms.[1-3] The SRY-related HMG-box genes regulate different components of growth (*i.e.* testis determination, neural induction and determination, lens induction, heart, lymphocyte and thymocyte development, interneuron specification and limp development, cardiac myogenesis, chondrogenesis, vascular development, tissue development, neural crest function, glial maturation, arterial walls development, pancreatic islet development, myogenesis, endoderm specification, hair follicle & vascular growth, CNS patterning and male germ cell maturation).[4] In this outlook, the study aimed to examine the susceptibility of the SOX13 gene from the SRY-related HMG-box family in two mammalian genomes. SRY-box 13 genes integrated into the enormous family of nuclear transcription factors (TFs) are testis determining factor encoded proteins with HMG-box domain bound to DNA. The SOX-13 (ICA12) transcription factor is an auto-antigen in T1D.[5-8] Autoimmunity is a critical impairment of insulin-mediated beta cells in islets. Specifically, the SRY-box 13 gene commonly produces auto-antibodies in various islet cell components. However, the key auto-antigens with antibodies observed by GAD antibodies are an enzyme that controls the biosynthesis of inhibitory neurotransmitter aminobutyric acid.[9] The GAD antibody is present in 60-70% of diabetes cohorts. Also, other auto-antigens like ICA512-tyrosine hydroxylase, insulin, and carboxypeptidase H circulate a vibration in T1D.[10] The beta-cell antigens reveal a role in type-1 diabetes (T1D) is unclear. Further, auto-antibodies are essential as predictive markers and often a detectable signature of diabetes. However, insulin is substantial evidence of the genetic variation of the nuclear SOX13 transcription factor gene defined as a protective nature in type-1 diabetes: a well-known auto-antibody target in type-1 diabetes. Characteristically, a differentiation in polymorphism situated in the pioneer region on the insulin-dependent SOX13 gene coordinated with type-1 diabetes (T1D). The quantity of repeated units of polymorphism controls the ratio of the insulin-dependent SOX13 gene in a tissue-specific manner.[11] The SOX13 is observed through auto-antigens by a screen using the blood of individuals diagnosed with type-1 diabetes.[12] Therefore, a genome-wide study of the SRY-related HMG-box of TFs is imperative to probe the molecular function and mechanisms involved with SOX13 in T1D. So, the work aimed to analyze the auto-antigen-dependent HMG-box domain of the SOX13 gene in mammals.

Results:

STRUCTURAL ANALYSIS:

The primary sequence revealed the unique formation of the nucleotides and peptides. So, the sequence composed of 1869 nucleotides and 622 peptides with 71 peptides

bound to the DNA sequence is well-known as an HMG-box domain (**Table 1**). The 3D structure illustrated that the SRY-related HMG-box domain is associated with DNA binding and protein-protein interaction. The formations of the HMG-box residue comprise triple helices in an asymmetrical array (**Fig. 1**). The HMG-box is a functional peptide domain identified in diverse mammalian genomes. The SRY-related HMG-box domain binds via the balance of DNA-dependent activities such as replication, transcription, and strand repair.

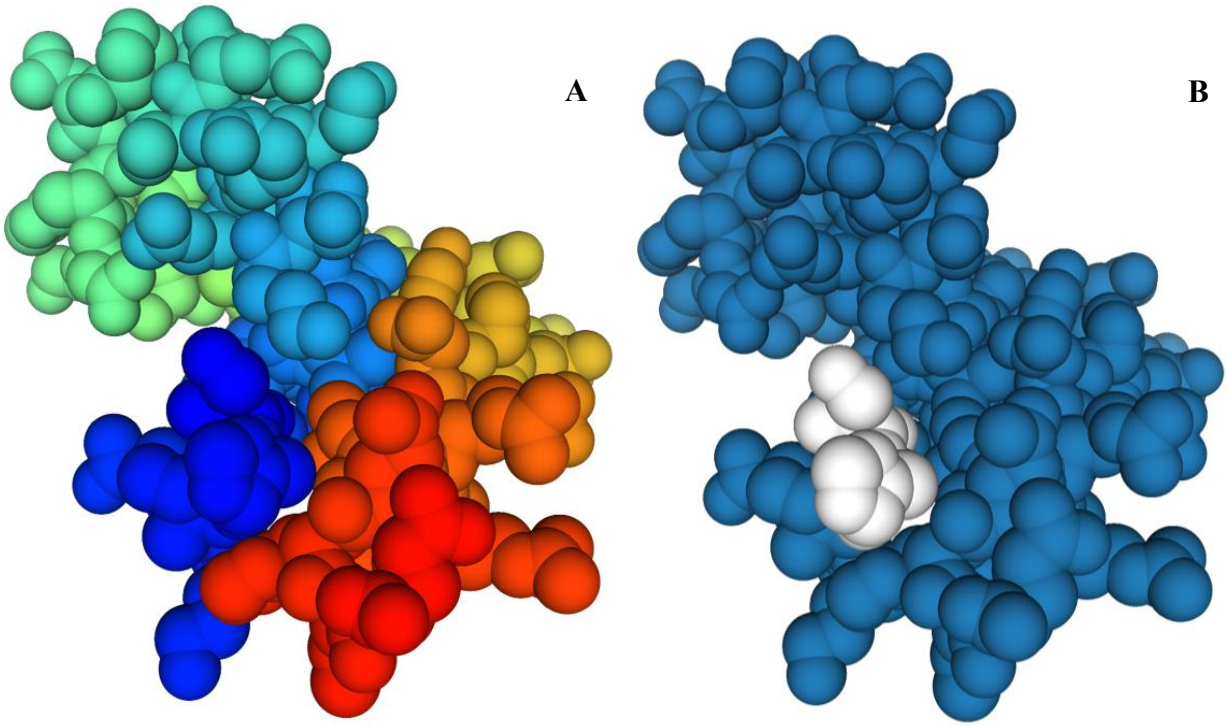

Fig. 1: Tertiary structure of SOX13 (a) and (b)

Table 1: Primary sequence of SOX13 gene (a) Nucleotide and (b) Peptide

(A) Nucleotide

>SOX13
CGCCTCGCAGCAGCGAGCCGCGAGCGCCCTTCTCCAGTCCCGGCTTGGAACTGAACTGTGTGAGCACGGGTCCTG
GAACCCGGGCCCAGAACCGGCGAGCCCAGGTCTGAGCCCAGAGCTCAGCGGTCAGCCTCGTAGGCCCTGACTCG
GAATCGAGCCGAGGCGCTGAGGTTGGAGCCGGAGAGCGTGAGAGCCGAAGAGCAGGGAGGGCGGGCCGGC
TGCGCGTCCGACGAGTCGCAGAGCAGGACCGCGGAAGGCAGGGAGACGGCCGCAAGCCCAGGGCAGAGGG
CAGAGGGCAGAGAGCGGCCTGGCTCGGCGGAGAGGGCGCCGCCCGGCCGGAACCAAGCTCGCCGCCCGGG
ACGGCGGGCCCCGTGGGGCGCGGACCCAGGGTGGCCGTGGGTCCGCAGCGACTCCCCGGCCGACGGCGGG
GGGCGTGCCCCCTCCCAGCCCAGCCTCCCCAACCCGGCCCGCCCGCCGCGTCGCGGGGGCATGTGAGCGGGA
AGCCTAGGCTGCCAGCCGCGAGGACCGCACGGAGGAGGAGCAGGAGCGCGGAGCCGCGAGCCCCGAGCCCC
GAGCCCGGCGCCTGGCTGAGTAGATGTCCATGAGGAGCCCCATCTCTGCCCAGCTGGCCCTGGATGGCGTTGGCA
CCATGGTGAACTGCACCATCAAGTCAGAGGAGAAGAAAGAGCCTTGCCACGAGGCCCCCCAGGGCTCAGCCACTG
CCGCTGAACCTCAGCCTGGAGACCCAGCCCGGGCCTCCCAGGATAGTGCTGACCCCCAAGCTCCAGCCCAGGGGA
ATTTCAGGGGCTCCTGGGACTGTAGCTCTCCAGAGGGTAATGGGTCCCCAGAACCCAAGAGACCAGGAGTGTCGG
AGGCTGCCTCTGGAAGCCAGGAGAAGCTGGACTTCAACCGAAATTTGAAAGAAGTGGTGCCAGCCATAGAGAAGCT
GTTGTCCAGTGACTGGAAGGAGAGGTTTCTAGGAAGGAACTCTATGGAAGCCAAAGATGTCAAAGGGACCCAAGA
GAGCCTAGCAGAGAAGGAGCTCCAGCTTCTGGTCATGATTCACCAGCTGTCCACCCTGCGGGACCAGCTCCTGACAG
CCCACTCGGAGCAGAAGAACATGGCTGCCATGCTGTTTGAGAAGCAGCAGCAGCAGATGGAGCTTGCCCGGCAGC
AGCAGGAGCAGATTGCAAAGCAGCAGCAGCAGCTGATTCAGCAGCAGCATAAGATCAACCTCCTTCAGCAGCAGATC
CAGCAGGTTAACATGCCTTATGTCATGATCCCAGCCTTCCCCCCAAGCCACCAACCTCTGCCTGTCACCCCTGACTCCCA
GCTGGCCTTACCCATTCAGCCCATTCCCTGCAAACCAGTGGAGTATCCGCTGCAGCTGCTGCACAGCCCCCCTGCCCC
AGTGGTGAAGAGGCCTGGGGCCATGGCCACCCACCACCCCCTGCAGGAGCCCTCCCAGCCCCTGAACCTCACAGC
CAAGCCCAAGGCCCCCGAGCTGCCCAACACCTCCAGCTCCCCAAGCCTGAAGATGAGCAGCTGTGTGCCCCGCCCC
CCCAGCCATGGAGGCCCCACGCGGGACCTGCAGTCCAGCCCCCCGAGCCTGCCTCTGGGCTTCCTTGGTGAAGG
GGACGCTGTCACCAAAGCCATCCAGGATGCTCGGCAGCTGCTGCACAGCCACAGTGGGGCCTTGGATGGCTCCCC
CAACACCCCCTTCCGTAAGGACCTCATCAGCCTGGACTCATCCCCAGCCAAGGAGCGGCTGGAGGACGGCTGTGTG
CACCCACTGGAGGAAGCCATGCTGAGCTGCGACATGGATGGCTCCCGCCACTTCCCCGAGTCCCGAAACAGCAGCC
ACATCAAGAGGCCCATGAACGCCTTCATGGTGTGGGCCAAGGATGAGCGGAGGAAGATCCTGCAAGCCTTCCCAG
ACATGCACAACTCCAGCATCAGCAAGATCCTTGGATCTCGCTGGAAGTCCATGACCAACCAGGAGAAGCAGCCCTACT
ATGAGGAACAGGCGCGGCTGAGCCGGCAGCACCTGGAGAAGTATCCTGACTACAAGTACAAGCCGCGGCCCAAG
CGCACCTGCATCGTGGAGGGCAAGCGGCTGCGCGTGGGAGAGTACAAGGCCCTGATGAGGACCCGGCGTCAG
GATGCCCGC

CAGAGCTACGTGATCCCCCCGCAGGCTGGCCAGGTGCAGATGAGCTCCTCAGATGTCCTGTACCCTCGGGCAGCAG
GCATGCCGCTGGCACAGCCACTGGTGGAGCACTATGTCCCTCGTAGCCTGGACCCCAACATGCCTGTGATCGTCAAC
ACCTGCAGCCTCAGAGAGGAGGGTGAGGGCACAGATGACAGGCACTCGGTGGCTGATGGCGAGATGTACCGGTA
CAGCGAGGACGAGGACTCGGAGGGCGAAGAGAAGAGCGATGGGGAGTTGGTGGTGCTCACAGACTGATCCCG
GCTGGGTGGGCCTGGCCCCTTCTCCTCTGGGGAAGACCTTGTCCCAACTCGATGGGCACAGCCAGCCAACCTAAGA
CTATGTTGGTACTTGGACTTGTTCGTGCCCCAGAGATGGGCAAAGCTGTGCACTTGCAGATACATTCATGAGGGGAGA
GGCGCCCTCCCTTCCTGAGGAGCTGTTGGCCTGGGTGGGCAGGAACTGCAGTATGGCCATGGGCTGAGCAGGCT
GAGCACCTCAGCCTTTAGGGCTTATGGCCAGGGGACACTGTATGACTCTCCTCTCCTGCAGGTGTCTATCCACCTGGG
GTATGGCATCTACCGACCTGTCTCCCTGGGGTCACATGCTTTGTTTCCATTCTTGTCCTGGCTGGACCAGCCACTGTGGG
ACCAACACCCCTCCCACACTCCCCCAGACTGCTCGTCTATCACCAGGATCGCTTTGTACTTTGTGCAAAAGGGTCTGGCT
GTCCCTTGCTGTTTTCATCTCTGCCAAGCCTATTGTGCCTCTGGCTGCTGTATGTGTGCGCGTGCACGTGTGTGTGTTTCA
TCTGTTCATTCACTGCACAAGATATTTATTGAGTGCCCACTACGTGCCAGGCACTGTTGCTGAGTTCCTGTGGGTGTGTCT
CTCGATGCCACTCCTGCTTCTCTGGGGGCCTCTTTCTGTGCTTCTCTTTGTCCCCAAATTGCTACCTCTTTGTCAGTCTGGGT
GTCTCAGGTTCTGTGTGTCCTTGTGTGCATTTCTGTCTCTCTCTGTCCTCGTCTCTCTGCAAGGCCCTCTATTTCTCTCTTTCTT
GGTGTCTGTCCTTTGCCCCCTGTGCCCTCTGGATTCTCTGGGTCTATGTAGGCCCCTGGTCTGCCCTGGGCTCATCAGC
CTTCCTGACCTCCTCCTGCCCTCCCCTTCACTCCCTCCCTGGCTCTGCCAGTCGGTTCCCACGGAGCCATTTTTAGCTCTG
ATCAGCATGGGAATGTGCCTCGGCCTCCAAGGGGCTTTGTCCTGGTGCCCCCGCCCCTGGTCCCAACCTGATCCCAC
GAGGGAGTTGGGACAGGAGGATTGATGGTGCTCCCCTTCCTGCCAGCGTCAGAGGCCCTGGAGAGGGGCTGTCC
ATGGCAGCTGGTCTTTATTCCTCCCTCATGAGCACAGGGTCGGGGGGGGTCCCCATTCTTGGAAGAGGTTGAGAAGAC
TCCTGGGCTTCAGCCTCTCCCACCCAGCCCTGCCCCTCACCTGCCTGCCCTCCCCTCCCCCACTCTATACTAGGGACTG
GATCTCAGCCTCTGATCAGTTTCACAAAGTTTGTTCCCTAAGGAAATCAAATCCCATTGTCACCTAACTCTGAAGATCTAAAT
AGCCCTTGGATCAGTATGGGAACCCCAAATCCCACAGGGCCAGATGTGGAGTCTGTGTCTGCCCCCGTCTTCTCTCCAT
CCTCAAAGCCCCCACTTCTCTCCAGGCTGTTTCTTTTTTTATGACTGTAAACATAGATAGTGCTTTATTTTGTTAATAATAAGAT
AATGATGAGTAACTTAACCAGCACATTTCTCCTGTTTACACTCGGGGGATTTTTTTGTTTTCTGATGACATAATAAAGACAGA
TCATTTCAGAAAAAAAAAAAAAAAAA

(B) Peptide

>SOX13
MSMRSPISAQLALDGVGTMVNCTIKSEEKKEPCHEAPQGSATAAEPQPGDPARASQDSAD
PQAPAQGNFRGSWDCSSPEGNGSPEPKRPGVSEAASGSQEKLDFNRNLKEVVPAIEKLLS
SDWKERFLGRNSMEAKDVKGTQESLAEKELQLLVMIHQLSTLRDQLLTAHSEQKNMAAML
FEKQQQQMELARQQQEQIAKQQQQLIQQQHKINLLQQQIQQVNMPYVMIPAFPPSHQPLP
VTPDSQLALPIQPIPCKPVEYPLQLLHSPPAPVVKRPGAMATHHPLQEPSQPLNLTAKPK
APELPNTSSSPSLKMSSCVPRPPSHGGPTRDLQSSPPSLPLGFLGEGDAVTKAIQDARQL
LHSHSGALDGSPNTPFRKDLISLDSSPAKERLEDGCVHPLEEAMLSCDMDGSRHFPESRN
SS**HIKRPMNAFMVWAKDERRKILQAFPDMHNSSISKILGSRWKSMTNQEKQPYYEEQARL**
SRQHLEKYPDYKYKPRPKRTCIVEGKRLRVGEYKALMRTRRQDARQSYVIPPQAGQVQMS
SSDVLYPRAAGMPLAQPLVEHYVPRSLDPNMPVIVNTCSLREEGEGTDDRHSVADGEMYR
YSEDEDSEGEEKSDGELVVLTD

GENOME-WIDE ANALYSIS:
The genome-wide analysis by HMMER results showed the multiple hits of 163 and 143 of SRY-related HMG-box domain in *Homo sapiens* and *Mus musculus*, respectively (**Table 2**). The standalone BLAST2 results represent 116 and 96 of the SOX13 homologs in *Homo sapiens* (Humans) and *Mus musculus* (Mice), respectively (**Table 2**). The HMMER hits enumerate from both organisms for GO annotation. So, the annotation demonstrated the number of SOX13 genes and SRY-related HMG-box domain in the SOX gene family in Humans and Mice (**Table 3**). The GO (gene ontology) analysis in Humans suggested the annotation 2291, mean level 8.247, and SD of 3.127. In Mice, annotation 2502, mean level 8.339 and SD of 3.093.

Table 2: Summary of the (a) HMG-box domain (b) SOX family and (c) Classification of the SOX family

(A) Summary of the HMG-box domain

Organism	**HMMER Hits**	**BLAST Hits**
Homo sapiens	163	116
Mus musculus	143	96
Total	**306**	**121**

(B) Summary of the SOX genes

Gene	***Homo sapiens***	***Mus musculus***
SOX-13	2	3
SOX-5	7	5
SOX-6	5	8
SOX-11	1	1

Gene	*Homo sapiens*	*Mus musculus*
SOX-14	1	2
SOX-12	1	2
SOX-17	1	6
SOX-4	1	1
SOX-18	1	1
SOX-7	2	1
SOX-15	3	1
SOX-21	1	1
SOX-1	1	1
SOX-3	1	1
SOX-2	1	1
SOX-8	1	3
SOX-10	4	1
SRY	1	1
SOX-9	1	1
SOX-30	3	1
Total	**39**	**42**

(C) Classification of the SOX family

Group	Group A	Group B	Group C
SoxA	SRY		
SoxB1	SOX1	SOX2	SOX3
SoxB2	SOX14	SOX21	
SoxC	SOX4	SOX11	SOX12
SoxD	SOX5	SOX6	SOX13
SoxE	SOX8	SOX9	SOX10
SoxF	SOX7	SOX17	SOX18
SoxG	SOX15		
SoxH	SOX30		

Table 3: Summary of the Gene Ontology annotation (a) *Homo sapiens* and (b) *Mus musculus*

(A) Homo sapiens

Gene Id	Gene	Protein
ENSP00000356172.1	SOX13	transcription factor SOX-13 isoform X1
ENSP00000478239.1	SOX13	transcription factor SOX-13 isoform X1
ENSP00000379328.2	SOX5	transcription factor SOX-5 isoform X5
ENSP00000370788.2	SOX5	transcription factor SOX-5 isoform X5
ENSP00000441973.1	SOX5	transcription factor SOX-5 isoform X5
ENSP00000439832.1	SOX5	transcription factor SOX-5 isoform X2
ENSP00000437487.1	SOX5	transcription factor SOX-5 isoform X3
ENSP00000443520.1	SOX5	transcription factor SOX-5 isoform X3
ENSP00000398273.2	SOX5	transcription factor SOX-5 isoform X5
ENSP00000432134.1	SOX6	transcription factor SOX-6 isoform X12
ENSP00000434455.1	SOX6	transcription factor SOX-6 isoform X12
ENSP00000324948.6	SOX6	transcription factor SOX-6 isoform X10
ENSP00000379644.3	SOX6	transcription factor SOX-6 isoform X10
ENSP00000433233.1	SOX6	transcription factor SOX-6 isoform X5
ENSP00000322568.3	SOX11	transcription factor SOX-11
ENSP00000347646.1	SOX12	transcription factor SOX-12
ENSP00000305343.1	SOX14	transcription factor SOX-14
ENSP00000297316.4	SOX17	transcription factor SOX-17
ENSP00000244745.1	SOX4	transcription factor SOX-4
ENSP00000341815.7	SOX18	transcription factor SOX-18
ENSP00000301921.1	SOX7	transcription factor SOX-7
ENSP00000458286.1	SOX15	protein SOX-15
ENSP00000366144.2	SOX21	transcription factor SOX-21
ENSP00000355354.2	SOX15	protein SOX-15
ENSP00000439311.2	SOX15	protein SOX-15
ENSP00000330218.1	SOX1	transcription factor SOX-1
ENSP00000359567.2	SOX3	transcription factor SOX-3
ENSP00000323588.1	SOX2	transcription factor SOX-2
ENSP00000293894.3	SOX8	transcription factor SOX-8

Gene Id	Gene	Protein
ENSP00000414853.1	SOX10	transcription factor SOX-10
ENSP00000372547.1	SRY	sex-determining region Y protein
ENSP00000245479.2	SOX9	transcription factor SOX-9
ENSP00000354130.2	SOX10	transcription factor SOX-10
ENSP00000380093.2	SOX10	transcription factor SOX-10
ENSP00000427984.1	SOX30	transcription factor SOX-30 isoform X1
ENSP00000309343.5	SOX30	transcription factor SOX-30 isoform X2
ENSP00000265007.6	SOX30	transcription factor SOX-30 isoform X1
ENSP00000399777.1	SOX10	transcription factor SOX-10
ENSP00000451145.1	SOX7	Transcription factor SOX-7

(B) Mus musculus

Gene Id	Gene	Protein
ENSMUSP00000122980.1	SOX13	transcription factor SOX-13 isoform X1
ENSMUSP00000092130.4	SOX13	transcription factor SOX-13 isoform X1
ENSMUSP00000119729.2	SOX13	transcription factor SOX-13 isoform X1
ENSMUSP00000107377.1	SOX5	transcription factor SOX-5 isoform X7
ENSMUSP00000107378.1	SOX5	transcription factor SOX-5 isoform X7
ENSMUSP00000133041.2	SOX5	transcription factor SOX-5 isoform X6
ENSMUSP00000076403.5	SOX5	transcription factor SOX-5 isoform X6
ENSMUSP00000047567.7	SOX5	transcription factor SOX-5 isoform X1
ENSMUSP00000145919.1	SOX6	transcription factor SOX-6 isoform X6
ENSMUSP00000126404.1	SOX6	transcription factor SOX-6 isoform X6
ENSMUSP00000129512.1	SOX6	transcription factor SOX-6 isoform X6
ENSMUSP00000102223.1	SOX6	transcription factor SOX-6 isoform X7
ENSMUSP00000145732.1	SOX6	transcription factor SOX-6 isoform X1
ENSMUSP00000145931.1	SOX6	transcription factor SOX-6 isoform X1
ENSMUSP00000072583.4	SOX6	transcription factor SOX-6 isoform X2
ENSMUSP00000129027.1	SOX6	transcription factor SOX-6 isoform X2
ENSMUSP00000078070.5	SOX11	transcription factor SOX-11
ENSMUSP00000141674.1	SOX17	transcription factor SOX-17 isoform X1
ENSMUSP00000142154.1	SOX17	transcription factor SOX-17 isoform X1
ENSMUSP00000064250.7	SOX12	transcription factor SOX-12
ENSMUSP00000138293.1	SOX12	transcription factor SOX-12
ENSMUSP00000088717.1	SRY	sex-determinating region Y protein
ENSMUSP00000091310.5	SOX14	transcription factor SOX-14
ENSMUSP00000027035.3	SOX17	transcription factor SOX-17 isoform X1
ENSMUSP00000112351.2	SOX17	transcription factor SOX-17 isoform X1
ENSMUSP00000100013.1	SOX4	transcription factor SOX-4
ENSMUSP00000062759.5	SOX18	transcription factor SOX-18
ENSMUSP00000078597.5	SOX7	transcription factor SOX-7
ENSMUSP00000127396.1	SOX21	transcription factor SOX-21
ENSMUSP00000048524.5	SOX15	protein SOX-15
ENSMUSP00000137203.1	SOX1	transcription factor SOX-1
ENSMUSP00000115237.2	SOX3	transcription factor SOX-3
ENSMUSP00000138239.1	SOX14	transcription factor SOX-14
ENSMUSP00000096755.2	SOX2	transcription factor SOX-2
ENSMUSP00000133403.1	SOX8	transcription factor SOX-8
ENSMUSP00000025003.3	SOX8	transcription factor SOX-8
ENSMUSP00000000579.2	SOX9	transcription factor SOX-9
ENSMUSP00000039466.4	SOX10	transcription factor SOX-10
ENSMUSP00000133742.1	SOX8	transcription factor SOX-8
ENSMUSP00000037519.3	SOX30	transcription factor SOX-30
ENSMUSP00000142204.1	SOX17	transcription factor SOX-17
ENSMUSP00000142116.1	SOX17	transcription factor SOX-17 isoform X1

DOMAIN, MOTIFS AND PHYLOGENY ANALYSIS:

The highest hits of the SRY-box 13 (ICA12) genes selected from both organisms for sequence alignment, a multiple sequence alignment (MSA) determines the conserved domain. The high consensus (90%) indicates the extended HMG-box domain (**Fig. 2**) and specific motifs (**Fig. 3**). The phylogenetic tree demonstrated the molecular evolutionary link of the ICA12 gene in *Homo sapiens* and *Mus musculus*. Also, a particular clade represents the multifunctional HMG-box domain-associated genes in the SOX family in both organisms' genomes (**Fig. 4**).

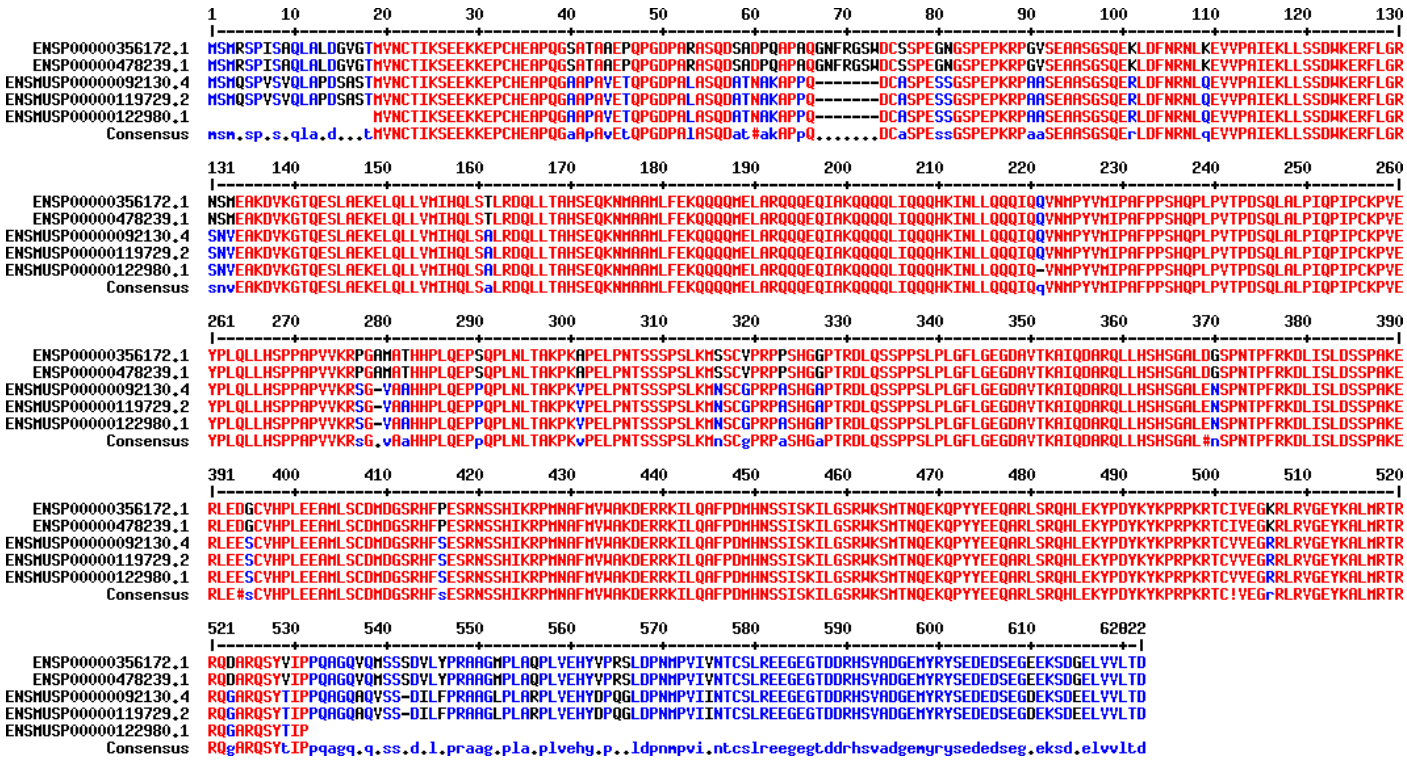

Fig. 2: Conserved domain in SOX13 gene in-between *Homo sapiens* and *Mus musculus*

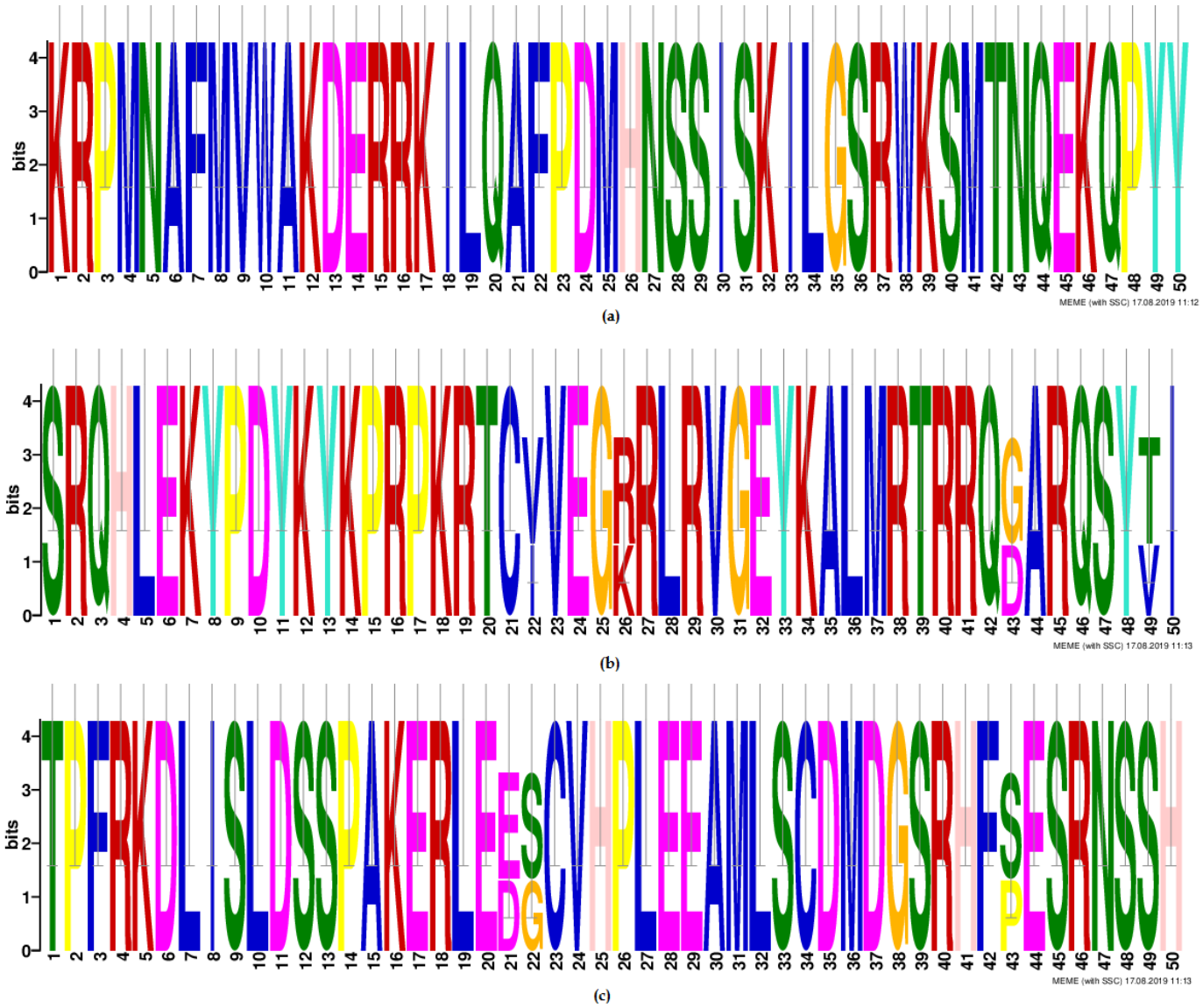

Fig. 3: Sequence motifs in SOX13 gene

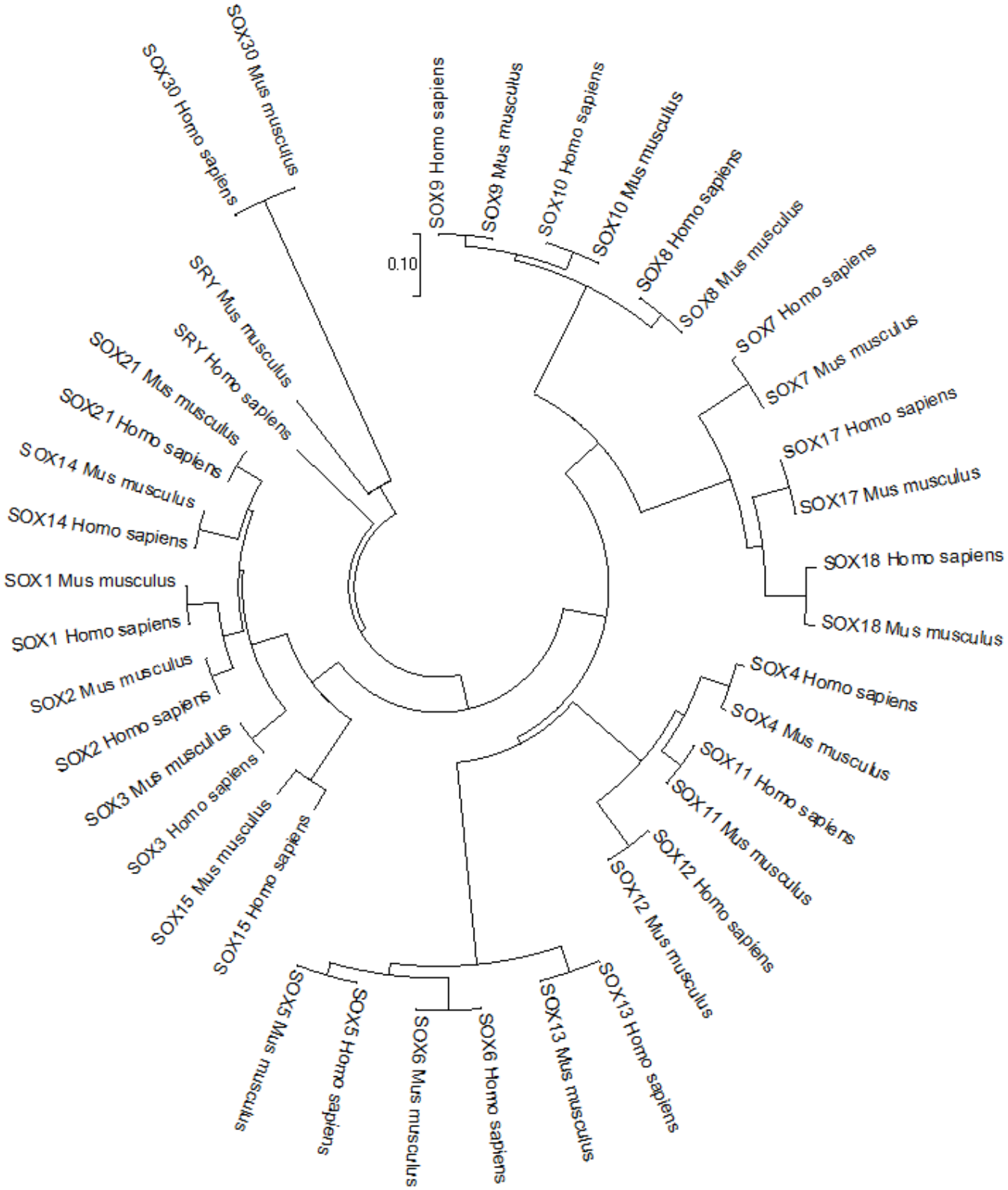

Fig. 4: The evolutionary link of SOX13 gene in the SOX family in two organisms

GENE EXPRESSION, CHROMOSOME LOCATION AND GENE REGULATORY NETWORK ANALYSIS:

The expression analysis of the five anatomical parts from the dataset shown of one measurement demonstrated the SOX13 (ICA12) gene critically expressed in the tissue, nervous system, PNS, peripheral nerve, and sural nerve in *Homo sapiens* **(Fig. 5)**. The chromosome localization study confirmed that the ICA12 gene located band 1q32.1 (start at 181,711,925 bp, end at 204,127,743 bp) (**Fig. 6**). The gene network study reveals that the SRY-box 13 (SOX13) gene interacts with other molecules, such as PTPRN, TCF7L2, TCF7, TCF7L1, LEF1, CTNNB1, NOTCH1, SOX5, CEP85, DMRT1, those molecular interactions govern the outcome of the ICA12 gene in the cells (**Fig. 7**).

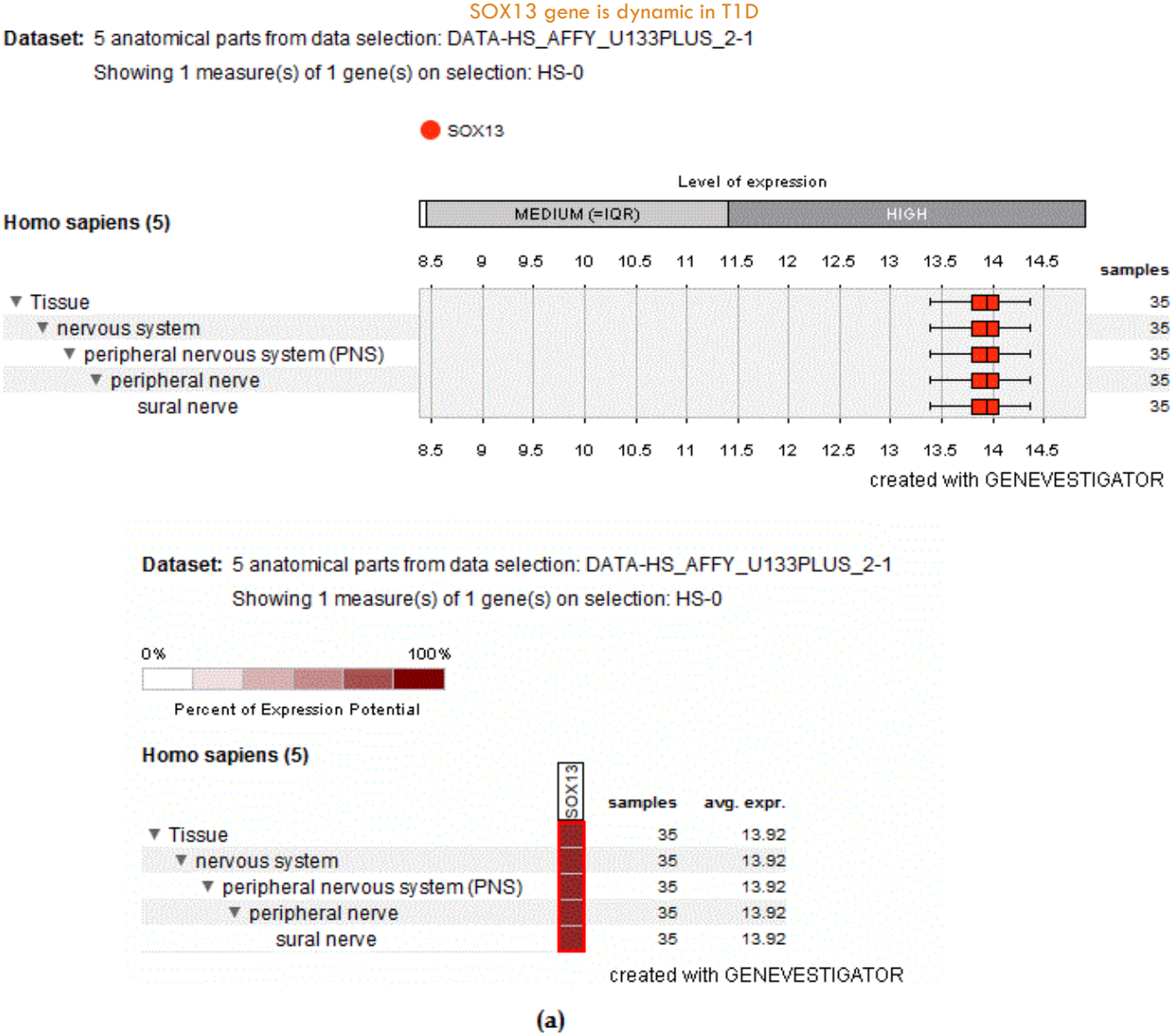

Fig. 5: SOX13 gene expression in *Homo sapiens*

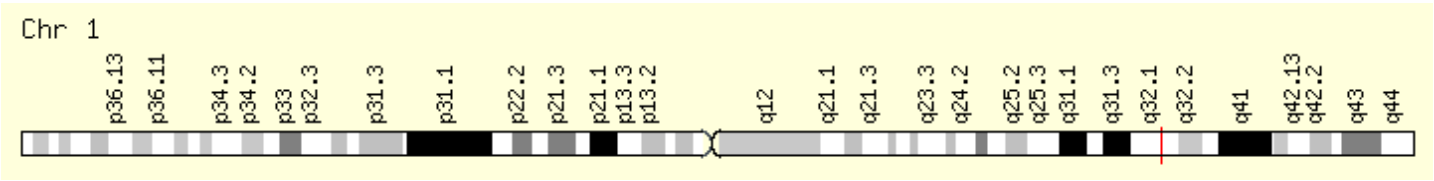

Fig. 6: Chromosome location of SOX13 gene

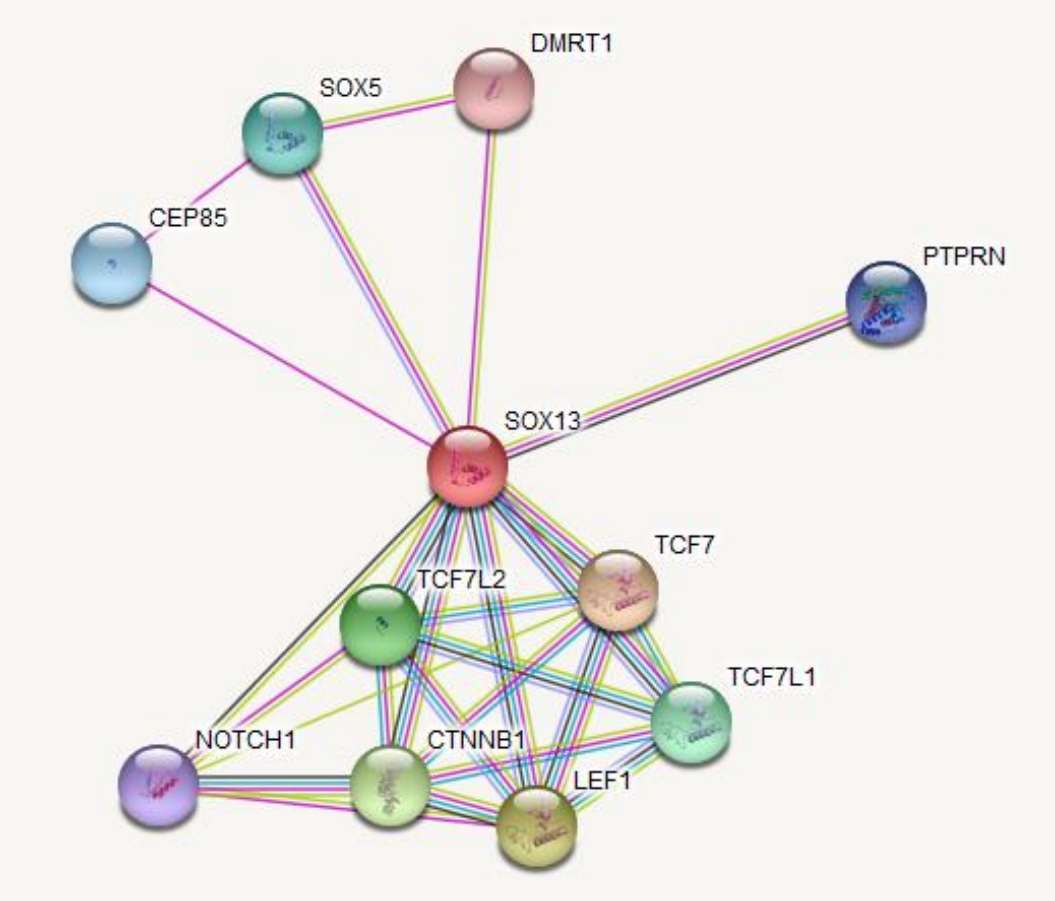

Fig. 7: The regulatory network of SOX13 gene

Discussion

Widespread data revealed that IDDM and autoimmunity are generalized by genetic diplomacy and environmental elements. Those factors attributed to autoimmune diseases included extensive variations of chemicals, pathogens, drugs, toxins, diet, stress, viral infection, organ phosphates, heavy metals, and solvents. Other factors contributing to T1D and autoimmunity are weight, puberty, increased linear growth, body mass index, and other parameters of body habits. Known studies suggested the nature of chemicals such as N-nitroso compounds, air pollutants, and persistent organic pollutants in the affected environment prevail over the thread of T1D. Those chemicals in the polluted environment reveal the gene functions and mechanisms linked with the immune system that lead to autoimmunity, and also improvement of T1D. Those factors are common for the enhancement of T1D. New findings will accelerate our understanding of IDDM. A reasonable understanding will interpret a new approach to predict the threat of T1D and validate a unique target to prevent the aggregation of the disease. The WHO classified diabetes into two categories: (a) IDDM (T1D) and (b) NIDDM (T2D) based on the clinical criteria. IDDM is a persistent chronic disease of human correlated autoimmune impairment of the beta-cells in islets. Autoimmune is a typically expended way of self-tolerance defined as a lack of immune reactivity. The feature of IDDM is knowledge of islet autoantigens by auto-reactivity (auto-reactive Th cells and cytotoxic T-cell), either humoral or cellular effectors of the immune system to islet autoantigens (insulin and GAD65). Those mechanisms suggested that Th cells (CD4+ cells) and TC unlock an immunologic role in T1D.[13,14] Auto-reactive response initiation factors are unclear. However, APCs control specific autoantigens. APCs included DCs (dendritic cells), macrophages, and B lymphocytes in the islets. The autoantigens to naive T lymphocytes by diabetes-associated HLA (human leukocyte antigen) molecules consent the pathogenic T lymphocytes and autoreactive Th cells. These pioneer Th cells generate cytokines and initiate beta-cell-specific CTLs. The initial T cells control islets and stimulate macrophages, and T lymphocytes contribute to control islet-beta cells.[15] So, the defensive IFNG (IFN-γ) and IL-10 manifest by the response of CD4+ T-cells to diabetes-associated antigens and frequencies of autoreactive CD8+ T-cells against HLA-A2-restricted antigenic epitopes. The maturity of diabetes elevated the ratio of autoreactive CD8+ T-cells in the T1D and T2D had analogous autoreactive CD4+ T-cell-derived cytokine response. Further, the HLA have triple residues recognized by (1) class I, (2) class II, and (3) class III molecules depending on the formation of genes. Primary CD8+ T-cells act with islet antigens and stipulated over-expression of class I molecule on beta-cells in T1D.[16] Also, CD4+ autoreactivity exists in diabetes and suggests mere beta-cell stress leads to the autoantigens via endocytic and phagocytic pathways. The prime response of class I molecule-mediated gene products (*i.e.* HLA-A, HLA-B, and HLA-C) rewarded peptides (endogenous) to counter cytotoxic T cells. Also, class II molecules-initiated genes like HLA-DR, HLA-DP, and HLA-DQ have restricted function and exercise peptides (exogenous) for the account of CD4+ cells. Class III molecule sustains genes encoded for immune-regulated molecules like cachexin (TNF-α), HSPs, and C3, C4, and C5 factors in the robust complement system. Theoretically, class I molecule responds as single-chain peptides that exist in intracellular antigens by killer T cells. Also, class II molecules are heterodimers and expressed mainly on antigen-presenting cells (APCs). Both are intent by alpha

and beta (α/β) chains and are subject to presenting extracellular antigens to helper T cells.[17] The dynamic link with T1D in class II molecules contributes to T1D susceptibility.[18] The precise mechanisms by preface of class II molecules pour to the break of islet beta cells are unclear, but the secure characteristics of superior peptides acquired from insulinoma-associated antigen 2 (IA-2), glutamic acid decarboxylase (GAD), proinsulin, and ZnT8 to antigen-presenting cells.[19] Insulin precursor and pre-pro-insulin are targeted auto-antigens for beta cells. Decreased levels of proinsulin influence the response of T lymphocytes in the thymuses and explore the migration of CD4+ and pro-insulin-mediated T lymphocytes to the surface and reveal the T1D. In contrast, the ratio of proinsulin in the thymus enhances the negative (-ve) selection of insulin-specific autoreactive T lymphocytes that leads to immune tolerance and controls the risk of T1D.[20] Further, the immunologic theorem coheres towards autoimmune T1D and CTLA4 molecules. The CD152 is the co-stimulatory molecule on the helper T cell's surface and binds with B7 ligands that activate CD28 molecules in T lymphocyte co-stimulation,[21-23]. CTLA4 reveals a signal to control T lymphocyte activation by the abundance of Treg. The CTLA4 interacts with a cluster of differentiation 3 (CD3) receptors to initiate the phosphorylation of molecules and directed enhancement of T lymphocytes after binding to HLA molecules via APCs.[17] Further, IL2RA encodes the alpha chain associated with T1D. IL2RA response is observed in memory T lymphocytes, naive T lymphocytes, and activated monocytes.[24] CD25 is key for binding with IL-2 and is manifested as a preface in the growth of regulatory T-cells (Treg). TAC (IL-2R) antigen is controlled by the activity of effector T cells and regulatory cells (Treg) via the response of FOXP3. So, CD25 (P55) may significantly lead to the therapy of autoimmunity. The response of IL2RA on the surface of the Treg is good for regulating T-cell proliferation by response to immunogenic stimulus.[17,25,26]. Nevertheless, lymphoid tyrosine phosphatase (PTPN22) is a protein tyrosine phosphatase associated with T1D.[27] Lymphoid tyrosine phosphatase (LYP) mainly responds in T cells and is revealed by kinases in the TCR signalling. Lymphoid tyrosine phosphatase interacts with C-terminal Src tyrosine kinase (CSK) by T lymphocyte activation.[28] Further, the small ubiquitin-like modifier 4 (SUMO4) is a major factor in T1D.[50] The reciprocate of methionine to valine (M55V) in IDDM5 reveals an etiological variant linked with T1D. This phenomenon created a potential decrease in sumoylation capacity, higher NF-κB, and release of IL12B.[29] Limited evidence suggests that IDDM5 (SUMO4) sumoylates IκBα and regulates NF-κB transcriptional dynamism.[30] The NF-κB reveals a core regulatory nature in the immune system involved in autoimmune diabetes. [31] Besides, polymorphisms in the classical STAT protein family are linked with T1D.[32] STAT4 from the STAT protein family is found in peripheral blood monocyte cells (PBMCs), dendritic cells (DCs), and macrophages (MΦ) at places of inflammation[33]. STAT4 directly interacts with the IL12RB (CD212) and promotes active roles in IL-12 signalling[34]. IL-12 is an immunoregulatory cytokine in the phenomenon of killer T cells and Th1 cells, supporting the nature of proinflammatory cytokines. However, the TGF-beta, NF-κB, p38 MAPK, toll-like receptor, and interleukin 6 are also linked with autoimmune and inflammation related to T1D[35]. So, the immunologic theorem indicated that the CD4+ T-cell auto-reactivity is linked to T1D/T2D and represents a combined mechanism of beta-cell activity. Therefore, autoreactive CD8+ T-cells appear to T1D and are subject to the accelerated beta-cell mass. Hence, estimating CD8+ autoreactivity in T1D reveals illness conditions and possibly a response to immunotherapy.[36] Many years of investigation illustrated insulin or pro-insulin as the initial auto-antigen. The normal functions of insulin in islet-beta cells make a healthy candidate. We keep in mind that the prime auto-antigen in T1D is unclear. The T1D-associated auto-antigens propose immunologic mechanisms involved with islet beta cells controlled by the immune process. So, the auto-antigens are robust and control of antigen tolerance is associated with immunotherapy for symptom and prognostic markers of T1D. The characteristic of autoimmune T1D is known by the phenomenon of auto-reactive T lymphocytes and auto-antibodies. Antibodies target self-antigens and promote the production of auto-antibodies, which is a characteristic of autoimmunity. However, the autoimmunity does not correspond to autoimmune disorders. Autoimmunity can appear as a complex framework in the immune process and maintain immune homeostasis.[37-39] However, the quantitative and qualitative variations reveal that natural antibodies and auto-antibodies prevail as pathogenetic autoimmunity. Thus, the observation of auto-antibodies is a condition to consider as an autoimmune nature. Besides, autoimmunity is not allowed as a pathogenetic role in NIDDM (T2D). Etiologically unclear, but environmental factors can contribute to obesity and poor physical activity. Characteristics of NIDDM can support antibodies to self-antigens in the formation of complex antigens. Also, non-insulin-dependent diabetes mellitus refers to LADA or hypothetically slow-onset autoimmune diabetes. So, the dynamism of autoimmune is linked with lymphocyte infiltration of islets and circulating serum antibodies.[40,41] Also, the markers of autoimmune include auto-antibodies to insulin (IAAs), GAD65, and tyrosine phosphatases (IA2 and IA-2BETA). However, the notable finding in this work is that the beta-cell antigen-dependent genes reveal a major role in T1D. Beta-cell antigens enhance peripheral tolerance mechanisms and act proficiently in diagnosing autoimmune diabetes. The antigen-dependent SOX13 (ICA12) gene homologs of the SOX family play a sole function in T1D. SOX13 gene is not membrane-bound like GAD65 and IA-2 but binds to chromatin. [24, 42, 44-46] However, the examination of the insulin-dependent SOX13 gene is essential for antigens to get a better understanding of T1D. So, identified beta-cell auto-antigens are necessary for the control of diabetes. The ubiquity of SOX13 observed as an auto-antigen is a molecular signature for autoimmunity. Many studies worldwide demonstrated that auto-antigens are etiopathogenesis of T1D.[47-52] Therefore, the observation supported the mammalian testis-determining factors described by the unique classes of genes that encode the SOX family. The properties of those genes play an extensive role during the growth of the organism.

Molecular Mimicry

Viral illness is the analytical factor influencing the risk of T1D. So, the characteristics of viruses associated with T1D. Those viruses include rotavirus, mumps virus, coxsackie A virus, coxsackie B virus, Poliovirus, Echovirus, CMV and other viruses.[53-56] It is unclear whether viruses act as an accelerator in the dynamic immune process initiated by different factors or whether viruses only attack the entire immune process. Generally, the molecular mechanism describing the viral illness observed during the threat of IDDM is molecular complexity. The molecular blueprint of T1D depends on the structural similarity of peptide sequence (conformational structure) between auto-antigen and pathogen[57]. The virus shares a uniform epitope on the islet cell component that processes similar auto-antigens and activates T lymphocytes (T-cells) to encourage a cross-reactive autoimmune response[58]. However, the functional study revealed that the T cells with viral peptides assume the islet auto-antigen is vital to prove the preface of the molecular complexity and improvement of T1D. The major characteristics of IDDM are the knowledge of beta-cell-initiated proteins as auto-antigens by auto-reactive CD4+ and CD8+ T cells and auto-antibodies. These auto-antigens include pro and pre-insulin, GAD65, IA-2, ZnT8, ICAs, Imogen 38, PDX1, CHGA, IGRP, HSP60, and ICA69.[59-60] So, the autoreactive T lymphocytes are sensitive to beta cell autoantigens like GAD, IA-2, and ZnT8. IGRP and Imogen 38 revealed β-cell autoantigens by the function of pancreatic islet autoreactive Th cells. The complementary DNA subtraction forwards the analytical response of β-cell-initiated proteins. So, the β-cell loss is caused by lymphocytic infiltration of the islet via dendritic cells, macrophages, and T lymphocytes. Empirical studies proposed that Th cells and CTLs reveal a characteristic towards pathogenesis and autoimmune diabetes (T1D).[61-65]

However, the factors initiating auto-reactive responses are unclear. Yet, the specific finding forwarded the auto-antigens recruited by APCs. Also, the APCs include DCs, macrophages, and B lymphocytes in the pancreatic islet cells. In contrast, the auto-antigens to naive T cells by diabetes-associated HLA molecules lead to the priming and activation of pathogenic T lymphocytes and the pre-activation of auto-reactive CD4+ T cells. These activated Th cells produce cytokines and beta-cell-specific cytotoxic T lymphocytes.[15,66] So, auto-antibodies play a unique role in auto-antigen processing by HLA molecules. Numerous studies observed that the HLA alleles are linked with auto-antibodies.[67] The loop between HLA and auto-antibodies still needs further examination to interpret the two significant pathogenic mechanisms. Therefore, it is hard to pinpoint which immunological mechanisms initiate viral illness and autoimmunity.

Methods:

DATABASE AND PRIMARY SEQUENCE:

The objective (query) sequence is retrieved from various specific databases such as Universal Protein Resource (UniProt) (Morgat A et al. 2019), National Center for Biotechnology Information (NCBI). Eric W Sayers et al. 2019, GenBank. EW Sayers et al. 2020, European Molecular Biology Laboratory (EMBL). W Baker et al. 2000, Kyoto Encyclopedia of Genes and Genomes (KEGG). Hiroyuki Ogata et al. 1999 and DNA Data Bank of Japan (DDBJ). T Okido et al. 2022. Web-based application of Simple Modular Architecture Research Tool (SMART). J Schultz et al. 1998 performs the examinations of the particular peptide residues in objective sequence (query or suspected sequence). The SWISS-MODEL database retrieves for prediction of amino acids (peptides) structure. The above database is a bioinformatics web server for comparative modelling of the structure of protein molecules. This database generates a 3D structure utilized in different effective research applications. The Swiss model is a regularly revised database of remodelling of organism proteome for biological research.T Schwede et al. 2003. Pfam performs for particular protein family information. Also, the PROCHECK web base tool performs for stereochemical quality of amino acids (peptide) structure.Laskowski R A et al. 1993

GENOME SEQUENCE

The organism's genome sequences are downloaded from various specialized databases:

1. Ensembl Genomes.Kevin L Howe et al. 2020
2. NCBI.Eric W Sayers et al. 2019

ORGANISMS

1. Homo sapiens: Genome assembly: GRCh38.p13 (GCA_000001405.28)
2. Mus musculus: Genome assembly: GRCm39 (GCA_000001635.9)

STANDALONE TOOLS

The HMM ER software packages execute through MSA methods for the objective domain as a profile search (parameters: 1.0e-3). The above mathematical and statistical algorithms are assembled by an MSA of the query sequence residue for profile search. SR Eddy. 2020 The above-implemented probabilistic model is well-known as a precise HMM.A Degirmenci. 2014. The standalone basic local alignment search tool 2 (BLAST2) executes for homolog genes in both organisms. Zhang J et al. 1997

GENE ONTOLOGY ANNOTATION

Gene ontology annotation is a method of the functional analysis of the genes in the genome across species for biological variance. So, the Omics box initializes using parameters 1.0e-3 for GO (gene ontology) annotation. Omics box is a computational and bioinformatics application for high-throughput GO annotation of particular sequences in organisms.A Conesa et al. 2005 The functional property of genes rectified via gene ontology annotation is a popular tool for practical work. Ashburner et al. 2000

DOMAIN

Sequence domain analysis is a core component for the upgradation of conserved residue in two different organisms' genomes. So, MSA methods are performed using a web-based application of MultAlin for analysis of the conserved region in sequences between both organisms. The MSA method calculates the specific pair of the homologous sequences and steak them up. Then observe the identical, differences, and similarities in sequences. The highest hits sequences are applied for MSA to upgrade the sustain domain. M Chatzou et al. 2016 and C Mitchell. 1993

MOTIFS

The motif-based sequence analysis tools retrieve for resolution of sequence-specific motifs. MEME suite is a bioinformatics and computational web-based tool to analyze and validate particular motifs in the sequence. Timothy L et al. 2015

PHYLOGENY

An analysis of phylogeny in genomes is necessary to explore the molecular Darwinism link between genes in both organisms. Therefore, MEGAX practice for constructing an evolutionary tree using *Neighbor-Joining Methods*. N Saitou et al. 1987 and Sudhir Kumar et al. 2018

GENE EXPRESSION

The gene expression analysis is elicited by the genevestigator application. The genevestigator is a high-performance research engine for expression analysis of an organism's gene contents. The genevestigator initializes to identify and validate specific targets. Tomas Hruz et al. 2008

CHROMOSOMAL LOCATION

The chromosomal location is retrieved through a gene card web-based application. The gene card is a database of an organism's genes that provides knowledge on all recognized and predicted genes. The above database is updated and available for biomedical research. M Safran et al. 2010

GENE REGULATORY NETWORK

The gene regulatory matrix reveals a molecular interaction in the cellular process to dominate the volume of mRNA or proteins. Some proteins act to activate genes as the TFs bind to the promoter area and initiate the response of different proteins known as regulatory cascades. STRING database retrieves for prediction of protein-protein interaction. STRING database includes various resources like experimental data and computational prediction of nucleic acids and proteins. T Schlitt et al. 2003, D Szklarczyk et al. 2017

Declaration:

CONSENT FOR PUBLICATION:

The work furnished in this paper is original and communicated by the correspondent addressed in the manuscript. The author disclosed that the documents are not concerned elsewhere and have not been received for evaluation by other journals.

ETHICAL APPROVAL:

The study contains an in-silico analysis of the mammalian genome examination and upgradation of the particular gene in different organisms.

AVAILABILITY OF DATA AND MATERIALS:

The data and materials are available on reasonable request.

COMPETING OF INTERESTS:

The author declared that the work has no conflict of interest.

FUNDING:

The author did not avail of financial assistance from any source in undertaking the present study.

AUTHOR CONTRIBUTIONS:

This research paper contains a single author. SC proposed the idea, experimented, analyzed data and prepared the manuscript.

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