Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/23829
DOI URL: http://dx.doi.org/10.21474/IJAR01/23829

RESEARCH ARTICLE

COMPUTATIONAL STUDY ON PROTEIN INTERACTIONS OF CDKN2C AND ITS IMPACT ON CANCER STUDIES

Eswari beeram

Manuscript Info

Manuscript History
Received: 10 May 2026
Final Accepted: 12 June 2026
Published: July 2026

Key words: -
CDKN2C protein; CCND1; Osteosarcoma; Multiplemyeloma; G1 phase arrest; co-expression

Abstract

CDKN2C is a tumour suppressor that suppress bone cancers like osteosarcoma and multiple myeloma by regulating cell cycle. Deletions or mutations in the gene can leads to tumour progression and worst survival however over expression leads to radiation sensitivity, G1 phase arrest and trigger apoptosis in osteosarcoma. Study on CDKN2C protein and its role in bone cancer is right now gaining evidence and few of the proteins like CDKN1C, CDKN2D, CCNL2 show primary level interactions and gene CDK4 is found be co expressed with CCND1 through prediction analysis and observed co-expression of homologs in other species through STRING database tool.

Introduction: -

Limited radiosensitivity to osteosarcoma is one of the major posing challenge and studies of Qiujian Lian etal 2024 the protein CDKN2C increases radiosensitivity by causing G1 phase cell cycle arrestand subsequent apoptosis. G1 phase arrest is mediated by deregulates the expression of phosphorylated RB protein. Deletions at chromosome 1 is identified in 7 to 4% of the multiple myeloma cancers and CDKN2C presence at 1p32.3 has been identified as one of the potential targets for deletion in multiple myeloma patients (Qiujian Lian etal 2024). One of the examples is homozygous deletion of the gene (Cox C et al.,2005).

Using high resolution mapping the deletion of the gene is identified in about 40% of the multiple myeloma cell lines (Kulkarni MS et al., 2002, Dib A et al., 2006).CDKN2C deviation in expression is known to be recorded with so many cancers but for the first time reports on its upregulation in expression in SCLC at both gene and protein level is done by Guo-Sheng Li et al.,2022 and CDKN2C expression is related to immune microenvironment and it can serve as one of the important prognostic markers in immune therapy. Immune checkpoint inhibitor related treatment is one of the promising treatments for SCLC but however its benefits is limited to few of the patients due to lack of availability in biomarkers (Esposito G et al 2020).

Corresponding Author:-Eswari beeram

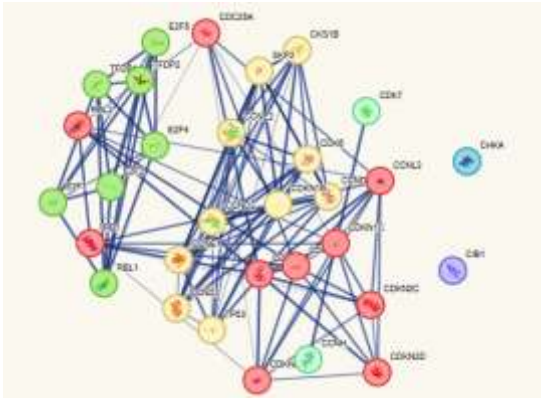


Figure:1: Study of Protein interactions of CDKN2C using STRING database by applying clusters with count of 6 using k means algorithm. Settings are customised to confidence medium score of 0.400.Optimal count of 6 is selected in silhouette analysis or elbow method to define the best model with defined simplicity and to explain the data variance.

CDKN1C, CDKN2D, CCNL2 are the few among the proteins that show primary level of interactors with CDKN2C and whereas CDKN1C, E2F4 are the second level of interactors of protein CDKN2C through proteins CCNL2.

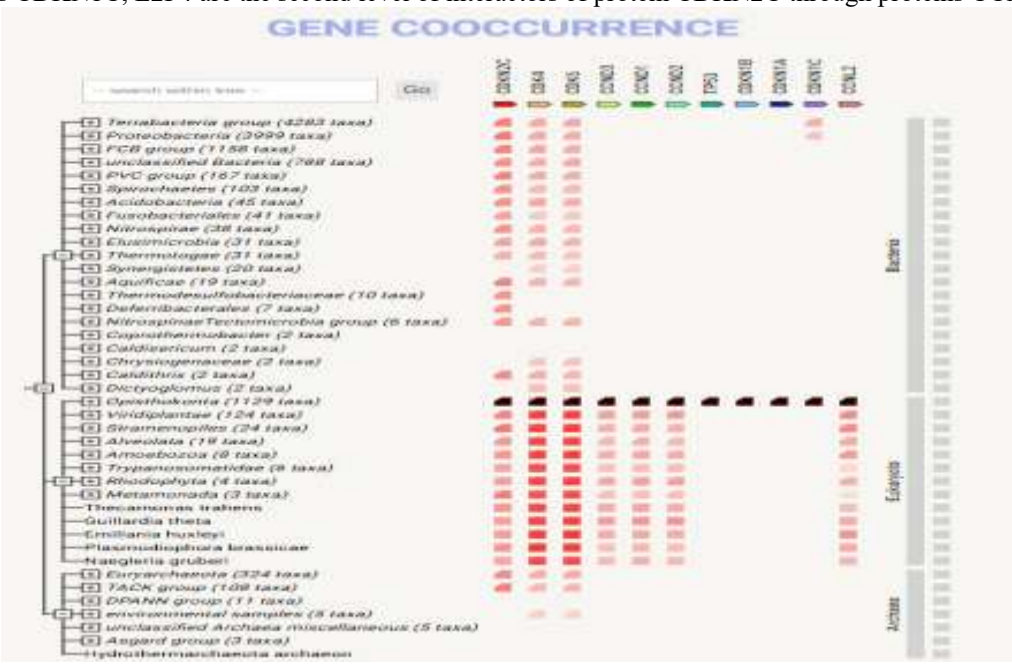


Figure:2 Study of Gene Co-occurrence ofprotein CDKN2C among different taxa

Gene occurrence has marked with CDK4 and CDK6 in Eukaryota and whereas low occurrence is seen with Archaea.The expression levels are low in Euryarchaeota a related common ancestor of Eukaryotes rather than direct ancestor of the phylum.Application of SRTING together with k means clustering simplifies the complex interaction interwork in to user friendly defined functional modules with specified groups.

k means clustering algorithm and working principle:

k means clustering algorithm is an unpredicted machine learning methodology that clusters data based on predefined number (K) of distinct non overlapping groups with feature similarity. The goal of the algorithm is to minimise the variation and to group the defined points with total similarity in to one group and also to be distinct entirely when marked with another group in a cluster. The algorithm assigns data using Euclidean distance of the data points to the nearest centroid and recalculates the mean of the assigned points to the centroid and the process repeats with initial randomly chosen centroids until the assigned cluster stabilise and indicates convergence as same group.

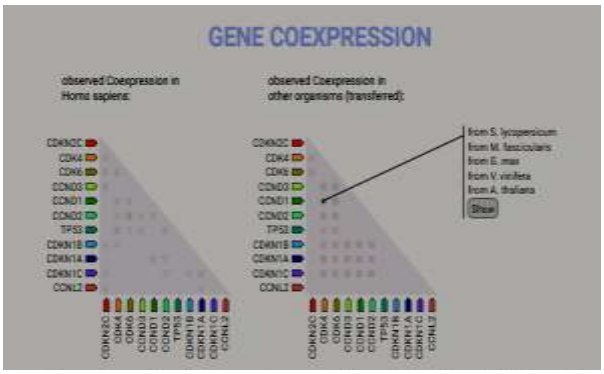


Figure: 3 Gene Co-expression studies of CDKN2C protein in homo sapiens and other related organisms. Based on Predicted association, CDK4 and CCND1 observed co-expression of homologs in other species through STRING database tool.

Relationship between RANKL & MATN3 to CDKN2C in Bone carcinogenesis:
RANKL plays an important role in osteoclastogenesis by coordinating with the precursor cells for with drawal of cell cycle and CDKN2C plays a role in cellular differentiation by regulating cell cycle in bone cells and tissue. MATN3 mutation is frequently associated with the overexpression of CDKN2C and other proliferation markers in bone.

Biological function of CDK inhibitors CDKN1C, CDKN2D, and cyclin CCNL2, E2F4 (TF):
CDKN1C is an inhibitor cyclin- CDK complexes like Cyclin E-CDK2 and Cyclin D-CDK4 and CDKN2D specifically targets cyclin dependent kinases CDK-4 &6 as an inhibitor and targets cell cycle at G1 phase similar as transcription repressor of Rb protein,E2F4there by regulating the cell proliferation and division. Cyclin CCNL2 is a non-traditional cyclin which targets transcription of genes and targets cell proliferation similar to CDKN1C,CDKN2D, and E2F4.

Study of transcripts for the gene RANKL using AUGUSTUS tool using FASTA sequence collected from NCBI database:

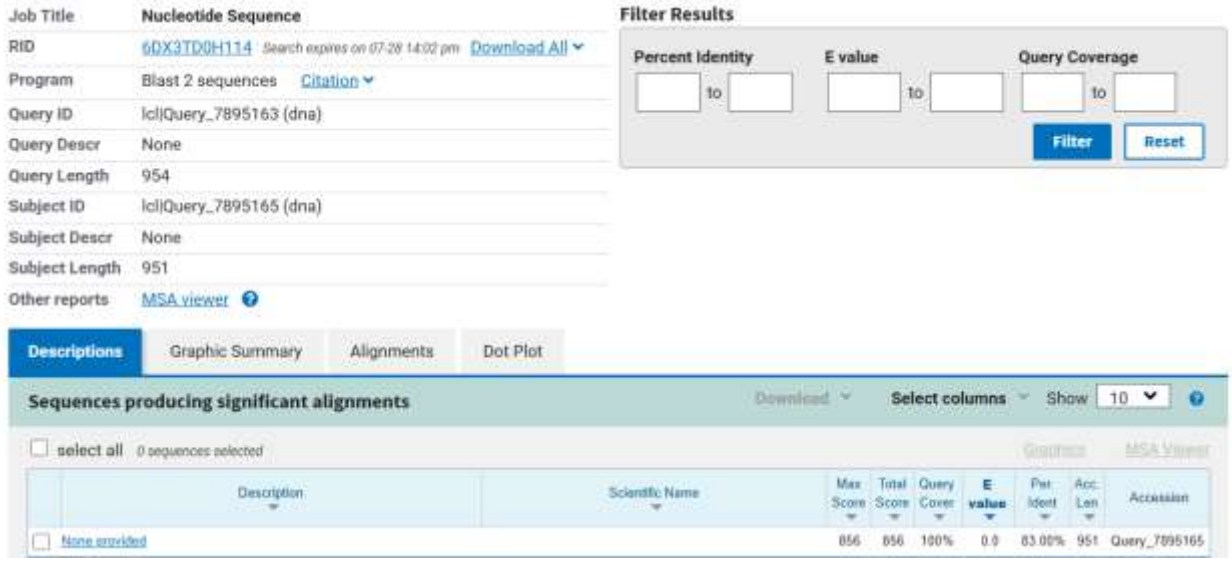
AUGUSTUS is a popular open-source software tool used for eukaryotic gene prediction, and utilizes a Generalized Hidden Markov Model (GHMM) to predict gene structures based on sequence alone or incorporates evidence from RNA-SeqESTs, and protein alignments through performing ab initio prediction. It is available both as via web interface (WebAUGUSTUS) or local installation through Git hub.

RANKL: Comparison of RANKL transcripts and protein sequence between Homo sapiens (GenBank: AF019047.1) andmus musculus {(GenBank: AF019048.1) curated from NCBI database using mRNA sequence as the genome input}selecting options both strands and only complete genes with alternative transcripts as few instead of many or none.

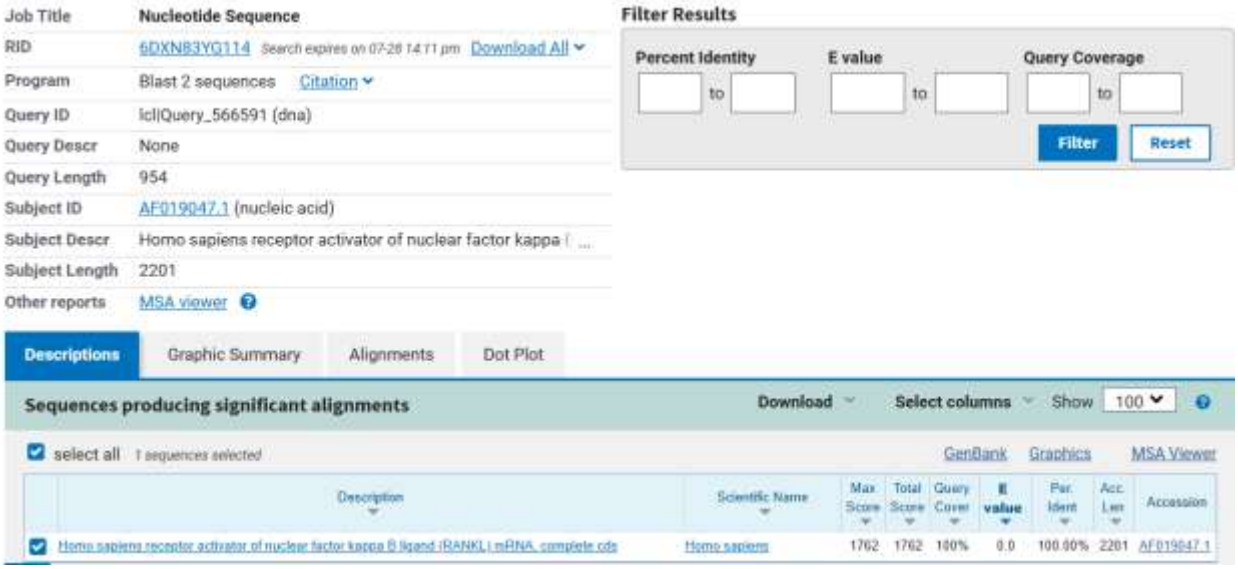
Homo sapiens:
ATGCGCCGCGCCAGCAGAGACTACACCAAGTACCTGCGTGGCTCGGAGGAGATGGGCGGCGGCCCCGGAGCCCCG
CACGAGGGCCCCCTGCACGCCCCGCCGCCGCCTGCGCCGCACCAGCCCCCCGCCGCCTCCCGCTCCATGTTCGTGG
CCCTCCTGGGGCTGGGGCTGGGCCAGGTTGTCTGCAGCGTCGCCCTGTTCTTCTATTTCAGAGCGCAGATGGATCCT
AATAGAATATCAGAAGATGGCACTCACTGCATTTATAGAATTTTGAGACTCCATGAAAATGCAGATTTTCAAGACA
CAACTCTGGAGAGTCAAGATACAAAATTAATACCTGATTCATGTAGGAGAATTAAACAGGCCTTTCAAGGAGCTG
TGCAAAAGGAATTACAACATATCGTTGGATCACAGCACATCAGAGCAGAGAAAGCGATGGTGGATGGCTCATGGT
TAGATCTGGCCAAGAGGAGCAAGCTTGAAGCTCAGCCTTTTGCTCATCTCACTATTAATGCCACCGACATCCCATC
TGGTTCCCATAAAGTGAGTCTGTCCTCTTGGTACCATGATCGGGGTTGGGCCAAGATCTCCAACATGACTTTTAGC
AATGGAAAACTAATAGTTAATCAGGATGGCTTTTATTACCTGTATGCCAACATTTGCTTTCGACATCATGAAACTTC
AGGAGACCTAGCTACAGAGTATCTTCAACTAATGGTGTACGTCACTAAAACCAGCATCAAAATCCCAAGTTCTCAT
ACCCTGATGAAAGGAGGAAGCACCAAGTATTGGTCAGGGAATTCTGAATTCCATTTTTATTCCATAAACGTTGGTG
GATTTTTTAAGTTACGGTCTGGAGAGGAAATCAGCATCGAGGTCTCCAACCCCTCCTTACTGGATCCGGATCAGGA
TGCAACATACTTTGGGGCTTTTAAAGTTCGAGATATAGATTGA

mus musculus:

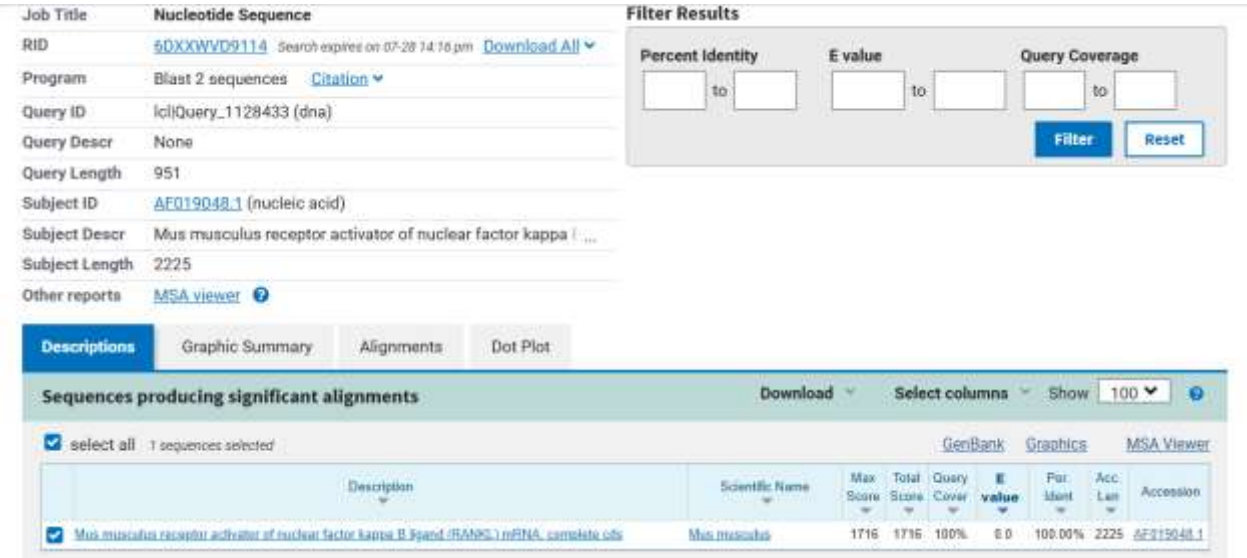
ATGCGCCGGGCCAGCCGAGACTACGGCAAGTACCTGCGCAGCTCGGAGGAGATGGGCAGCGGCCCCGGCGTCCCA
CACGAGGGTCCGCTGCACCCCGCGCCTTCTGCACCGGCTCCGGCGCCGCCACCCGCCGCCTCCCGCTCCATGTTCC
TGGCCCTCCTGGGGCTGGGACTGGGCCAGGTGGTCTGCAGCATCGCTCTGTTCCTGTACTTTCGAGCGCAGATGGA
TCCTAACAGAATATCAGAAGACAGCACTCACTGCTTTTATAGAATCCTGAGACTCCATGAAAACGCAGATTTGCAG
GACTCGACTCTGGAGAGTGAAGACACACTACCTGACTCCTGCAGGAGGATGAAACAAGCCTTTCAGGGGGCCGTG
CAGAAGGAACTGCAACACATTGTGGGGCCACAGCGCTTCTCAGGAGCTCCAGCTATGATGGAAGGCTCATGGTTG
GATGTGGCCCAGCGAGGCAAGCCTGAGGCCCAGCCATTTGCACACCTCACCATCAATGCTGCCAGCATCCCATCG
GGTTCCCATAAAGTCACTCTGTCCTCTTGGTACCACGATCGAGGCTGGGCCAAGATCTCTAACATGACGTTAAGCA
ACGGAAAACTAAGGGTTAACCAAGATGGCTTCTATTACCTGTACGCCAACATTTGCTTTCGGCATCATGAAACATC
GGGAAGCGTACCTACAGACTATCTTCAGCTGATGGTGTATGTCGTTAAAACCAGCATCAAAATCCCAAGTTCTCAT
AACCTGATGAAAGGAGGGAGCACGAAAAACTGGTCGGGCAATTCTGAATTCCACTTTTATTCCATAAATGTTGGG
GGATTTTTCAAGCTCCGAGCTGGTGAAGAAATTAGCATTCAGGTGTCCAACCCTTCCCTGCTGGATCCGGATCAAG
ATGCGACGTACTTTGGGGCTTTCAAAGTTCAGGACATAGACTGA



BLAST search of RANKL with the sequences above from Homosapiens and mus musculus generated through AUGUSTUS



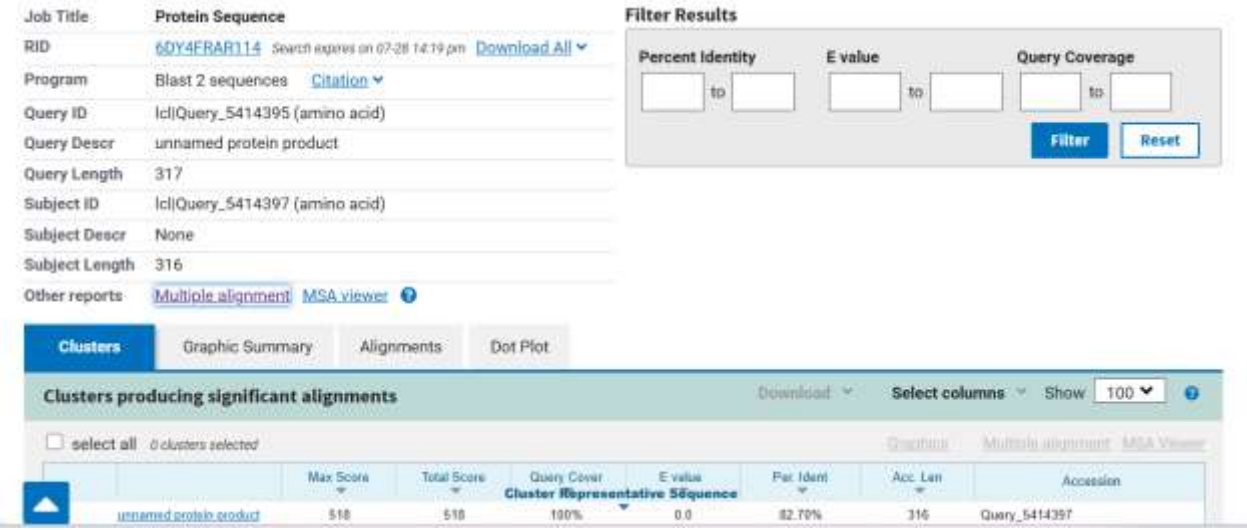
BLAST search of RANKL with the sequence above from Homosapiens generated through AUGUSTUS and with NCBI sequence with accession id AF019047.1.



BLAST search of RANKL with the sequence above from mus musculus generated through AUGUSTUS and with NCBI sequence with accession id AF019048.1.

Amino acid sequence:
Homo sapiens:
MRRASRDYTKYLRGSEEMGGGPGAPHEGPLHAPPPPAPHQPPAASRSMFVALLGLGLGQVVCSVALFFYF
RAQMDPNRISEDGTHCIYRILRLHENADFQDTTLESQDTKLIPDSCRRIKQAFQGAVQKELQHIVGSQHIRAE
KAMVDGSWLDLAKRSKLEAQPFAHLTINATDIPSGSHKVSLSSWYHDRGWAKISNMTFSNGKLIVNQDGF
YYLYANICFRHHETSGDLATEYLQLMVYVTKTSIKIPSSHTLMKGGSTKYWSGNSEFHFYSINVGGFFKLRS
GEEISIEVSNPSLLDPDQDATYFGAFKVRDID

Mus Musculus:
MRRASRDYGKYLRSSEEMGSGPGVPHEGPLHPAPSAPAPAPPPAASRSMFLALLGLGLGQVVCSIALFLYF
RAQMDPNRISEDSTHCFYRILRLHENADLQDSTLESEDTLPDSCRRMKQAFQGAVQKELQHIVGPQRFSGA
PAMMEGSWLDVAQRGKPEAQPFAHLTINAASIPSGSHKVTLSSWYHDRGWAKISNMTLSNGKLRVNQDG
FYYLYANICFRHHETSGSVPTDYLQLMVYVVKTSIKIPSSHNLMKGGSTKNWSGNSEFHFYSINVGGFFKLR
AGEEISIQVSNPSLLDPDQDATYFGAFKVQDID



BLAST similarity of protein sequence RANKL from Homosapiens and musmusculus generated through AUGUSTUS tool.

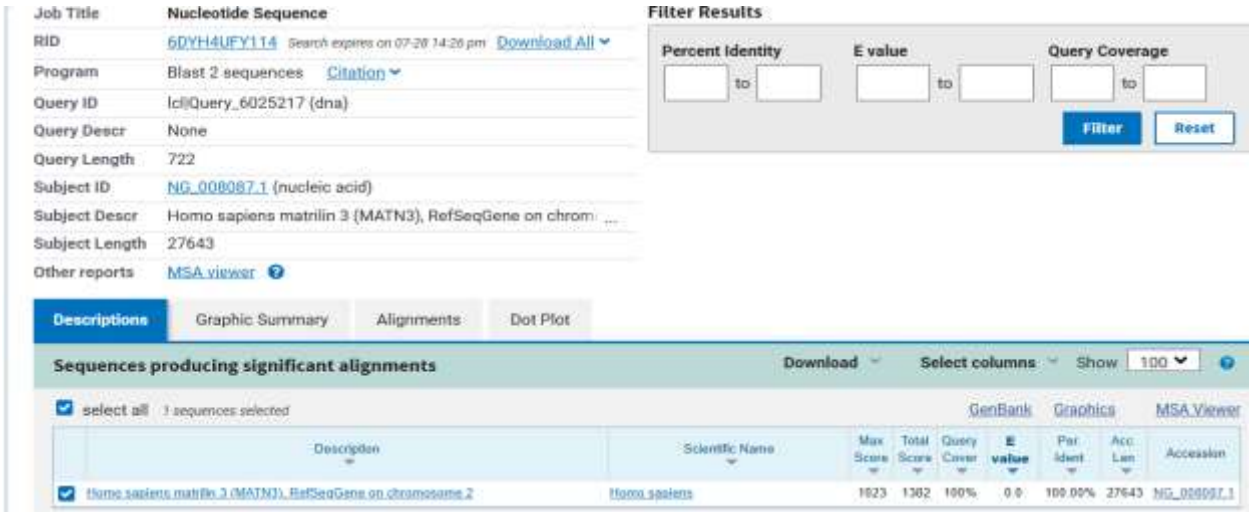
Study of Transcripts in protein Matrilin 3 in Homo sapiens present on chromosome 2 using AUGUSTUS online tool:NCBI Reference Sequence: NG_008087.1:

Nucleotide Transcripts:

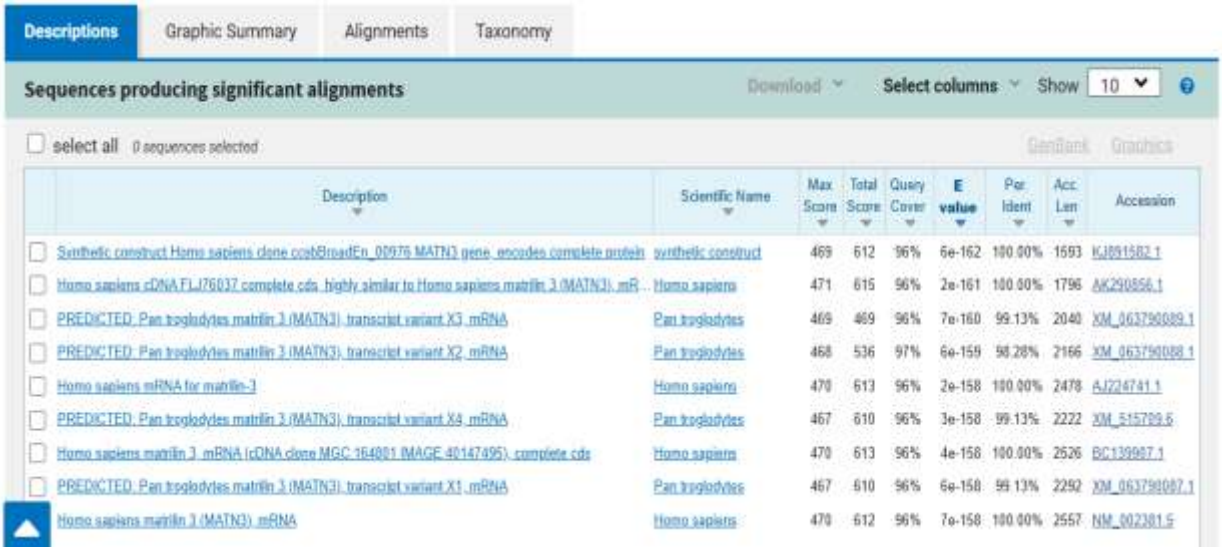
GTGTTTGCAAGAGCAGACCCTTGGACCTGGTGTTTATCATTGATAGTTCTCGTAGCGTACGGCCCCTGG
AATTCACCAAAGTGAAAACTTTTGTCTCCCGGATAATCGACACTCTGGACATTGGGCCAGCCGACACG
CGGGTGGCAGTGGTGAACTATGCTAGCACTGTGAAGATCGAGTTCCAACTCCAGGCCTACACAGATAA
GCAGTCCCTGAAGCAGGCCGTGGGTCGAATCACACCCTTGTCAACAGGCACCATGTCAGGCCTAGCCA
TCCAGACAGCAATGGACGAAGCCTTCACAGTGGAGGCAGGGGCTCGAGAGCCCTCTTCTAACATCCCT
AAGGTGGCCATCATTGTTACAGATGGGAGGCCCCAGGACCAGGTGAATGAGGTGGCGGCTCGGGCCC
AAGCATCTGGTATTGAGCTCTATGCTGTGGGCGTGGACCGGGCAGACATGGCGTCCCTCAAGATGATG
GCCAGTGAGCCCCTAGAGGAGCATGTTTTCTACGTGGAGACCTATGGGGTCATTGAGAAACTTTCCTC
TAGATTCCAGGAAACCTTCTGTGCGCTGGACCCCTGTGTGCTTGGAACACACCAGTGCCAGCACGTCT
GCATCAGTGATGGGGAAGGCAAGCACCACTGTGAGTGTAGCCAAGGATACACCTTGAATGCCGACAA
GAAAACGTGTTCAGGTGAGGCCTGTGTAGGGGGCCGTGACTGA

Protein sequence:

VCKSRPLDLVFIIDSSRSVRPLEFTKVKTFVSRIIDTLDIGPADTRVAVVNYASTVKIEFQLQAYTDKQSLKQ
AVGRITPLSTGTMSGLAIQTAMDEAFTVEAGAREPSSNIPKVAIIVTDGRPQDQVNEVAARAQASGIELYAV
GVDRADMASLKMMASEPLEEHVFYVETYGVIEKLSSRFQETFCALDPCVLGTHQCQHVCISDGEGKHHCE
CSQGYTLNADKKTCSGEACVGGRD.



BLAST similarity with Transcripts generated in protein Matrilin 3 in Homo sapiens present on chromosome 2 using AUGUSTUS online tool using NCBI Reference Sequence: NG_008087.1



BLAST protein sequence similarity with Transcripts generated usingusing AUGUSTUS online tool with protein Matrilin 3 in Homo sapiens present on chromosome 2: NCBI Reference Sequence: NG_008087.1.

Discussion:-

Study of CDKN2C protein interactions and coexpression networks help to identify critical therapeutic targets like CDK4 and CCND1 inorder to overcome the cell cycle dysregulation caused by deletions in CDKN2C gene. CDKN2C gene encodes p18-INK4c protein, a cyclin-dependent kinase inhibitor which prevents cell cycle progression through molecular gating mechanisms at G1/S phase. Deletion of the following gene CDKN2C leads to uncontrolled cell proliferation in certain lymphomas, melanomas, and neuroblastomas.Cells that lack CDKN2C cause a shift towards positive regulators of cell cycle CDK4/6 and CCND1 (Cyclin D1) to trigger the cell division. However, Coexpression and protein- protein interaction network study through databases offers advantage of finding the possible possibilities on how loss of CDKN2C shifts to or upregulates the CDK4-CCND1 axis. These predictions may help in finding the suitable biomarkers that makes the tumor vulnerable to the drugs (Cavalu S et al., 2024). Targeting the cancer cells that show high expression of CDK4/6 through CDK4/6 inhibitors (such as palbociclib, ribociclib, or abemaciclib) restores the cell cycle block and may serve as promising candidates for the treatment of various mixed lymphomas or adenomas (Safaroghli-Azar A et al., (2026); Hussein SA et al., (2025)).

Conclusion:-

By this study we can conclude study of CDKN2C protein interactions and coexpression analysis can help in prediction of biomarkers like CDK4, CCND1 for targeting the cell cycle progression in cells with deletions of CDKN2C gene.

References: -

1. Qiujian Lian, Haonan Zhao, Bingxuan Wang, Ping Ling, Jingyan Li, Peijun Dai, Junyong Ge, Xu Su, Zhiwei Wang, Suchi Qiao (2024). Enhancing radiosensitivity in osteosarcoma via CDKN2C overexpression: A mechanism involving G1 phase arrest mediated by inhibition of CDK4 expression and Thr172 phosphorylation, Biochemical and Biophysical Research Communications, Vol. 735,150840,https://doi.org/10.1016/j.bbrc.2024.150840.
2. Cox C, Bignell G, Greenman C, et al. (2005). A survey of homozygous deletions in human cancer genomes. Proc Natl Acad Sci U S A; 102; 4542–7.https://doi.org/10.1073/pnas.0408593102
3. Kulkarni MS, Daggett JL, Bender TP, Kuehl WM, Bergsagel PL, Williams ME (2002) . Frequent inactivation of the cyclin-dependent kinase inhibitor p18 by homozygous deletion in multiple myeloma cell lines: ectopic p18 expression inhibits growth and induces apoptosis. Leukemia; 16;127–34.https://doi.org/10.1038/sj.leu.2402328
4. Dib A, Peterson TR, Raducha-Grace L, et al. (2006). Paradoxical expression of INK4c in proliferative multiple myeloma tumors: bi-allelic deletion vs increased expression. Cell Div;1: 23.https://doi.org/10.1186/1747-1028-1-23

5. Li GS, Chen G, Liu J, Tang D, Zheng JH, Luo J, Jin MH, Lu HS, Bao CX, Tian J, Deng WS, Fu JW, Feng Y, Zeng NY, Zhou HF, Kong JL. Clinical significance of cyclin-dependent kinase inhibitor 2C expression in cancers: from small cell lung carcinoma to pan-cancers. BMC Pulm Med. 2022 Jun 24;22(1):246. https://doi.org/10.1186/s12890-022-02036-5 PMID: 35751045; PMCID: PMC9233395.
6. Esposito G, Palumbo G, Carillio G, Manzo A, Montanino A, Sforza V, Costanzo R, Sandomenico C, La Manna C, Martucci N, et al. (2020) Immunotherapy in small cell lung cancer. Cancers (Basel);12(9):2522. https://doi.org/10.3390/cancers12092522. [DOI] [PMC free article] [PubMed] [Google Scholar].
7. Cavalu S, Abdelhamid AM, Saber S, Elmorsy EA, Hamad RS, Abdel-Reheim MA, Yahya G, Salama MM. Cell cycle machinery in oncology: A comprehensive review of therapeutic targets. FASEB J. 2024 Jun 15;38(11): e23734. doi: 10.1096/fj.202400769R. PMID: 38847486.
8. Safaroghli-Azar A, Mekonnen LB, Lenjisa J, Milne R, Wang S. Cell-cycle targeted cancer therapy: clinical advances, biological gaps, and the emergence of selective CDK4 inhibitors. J Hematol Oncol. 2026 Apr 6;19(1):31. doi: 10.1186/s13045-026-01794-7. PMID: 41943159; PMCID: PMC13188447.
9. Hussein SA, Saadawy AH, Badr E, Abdollah MRA, Wael N, Allam RM, Al-Abd AM, Roncero Sanchez AM, Tolba MF. The landscape of cyclin-dependent kinase 4/6 inhibitors in solid malignancies: emphasis on immunotherapy combinatorial strategies. Med Oncol. 2025 Aug 26;42(10):447. doi: 10.1007/s12032-025-02996-8. PMID: 40856900; PMCID: PMC12380978.