# Bioinformatic analysis of important miRNA and Gene network analysis of APC gene, a key regulator of head and neck cancer

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**Introduction:-**

Every individual in this world is cursed with getting cancer and this curse is dependent on a structure called the genome. A genome is all genetic information of an organism which consists of a nucleotide sequence of DNA (or RNA in RNA virus) A nuclear genome includes protein-coding genes and non-coding genes, the other functional regions of the genome ( Non-coding DNA), and any junk DNA. mutations to these nucleotide sequences leads to an abnormality in production of protein and leads to cancer, one such cancer is cancer that arises in the head and neck. Head and neck cancer is the most common type of cancer and is ranked seventh worldwide . These types of cancers comprise a diverse group of tumors affecting the upper aerodigestive tract (1) and comprise a heterogeneous group of cancers, most common type is squamous cell carcinoma (SCC), which arise from the epithelial lining of the oral cavity, sinonasal tract, pharynx, larynx and salivary glands etc. Most HNC are already at an advanced stage when it is diagnosed, which significantly reduces t\he survival rate, even after curative treatment. A Major risk factor includes tobacco smoking or chewing, excessive consumption of alcohol, paan masala (Gutkha), gamma and ultraviolet radiation, overexposure to sunlight, a family history of cancer and increasing age. Total incidence in the globe continues to rise with more than million cases annually and more than 10000 new cases in India every year, an increase of 20% in the last decade. However prognosis remains poor, with a 28–67% chance of survival at five years, depending upon the stage at presentation of the case.

APC is a Biallelic mutation of the *APC* gene that occurs in 45%–80% of colorectal cancers (2–4)and is observed in the earliest detectable lesions (5,6). The *APC* locus was originally identified based on its link to familial adenomatous polyposis coli (FAP), an inherited syndrome of cancer predisposition (7–9). Inherited mutations in the *APC* gene cause affected individuals to

develop hundreds to thousands of adenomatous polyps, resulting in the onset of CRC typically before the age of 40 (10)Individuals with FAP inherit a loss-of-function mutation in a single allele of *APC*, followed by an additional acquired mutation in the second allele of *APC* in the adenomas and adenocarcinomas that develop (11). Thus, the acquisition of biallelic *APC* mutations represents an early and rate-limiting step in all FAP-associated and most sporadic colorectal tumors.In studies of colorectal cancer as a whole, *APC* mutational status does not strongly correlate with outcome (12)Nevertheless, *APC* mutations exhibit an interesting pattern of differential distribution in the recognized subtypes of colorectal cancer. *APC* mutations correlate strongly with a large subset of colorectal cancers associated with intermediate prognosis.On the other hand, *APC* mutations occur infrequently within a smaller subset derived from sessile serrated adenomas and associated with microsatellite instability and good prognosis. This latter subset exhibits a relatively high proportion of activating mutations in the gene encoding β-catenin (*CTNNB1*) that are mutually exclusive of *APC* mutations(13). Interestingly, *CTNNB1 mutations* are significantly more prevalent in small adenomas than in large adenomas or adenocarcinomas, whereas *APC* mutations are well-represented across all stages of tumorigenesis. It has recently emerged that *APC* mutational status has value as a predictive marker of poor prognosis in Stage III colorectal cancer raising the possibility that *APC* mutations not only initiate colorectal cancer development, but drive clinical phenotypes relevant to progression and metastasis as well.

**Materials and Methods**

Target scan prediction Prediction of microRNA targets for APC gene in humans was carried out using Targetscan Human software program. Targetscan is a database that allows the user to filter miRNAs and its targets that are associated with deˇtermined diseases, and we filtered the results that were associated with GC. MiRTarBase is a database that predicts targets that have already been validated by molecular biology techniques. Broadly conserved, conserved and poorly conserved mRNA families were searched for the presence of 8mer, 7mer, and 6mer sites matching each miRNA seed region. Predicted regulatory targets of the TP53 gene
were identified using the program with default settings. The targets of the conserved miRNA. hsa-miR-122-5p miRNA with a miTG score of ≥0.99 were identified using the Dianalab software program. Gene network analysis of APC was carried out by STRING database online server program. Important gene interactions with a combined score of ≥0.99 were considered and listed.

**miRDB prediction**

Target mRNAs were predicted using miRDB online server program. miRNA targets with a target score of more than 95 were considered for further analysis. The target details and the predicted genes for the miRNA hsa- miR-3922-5p were carried out.(14–17)

**Gene network analysis**

Gene network analysis of APC was carried out by STRING database online server program.This software was used in order to determine the various links that APC has with other genes. This database allows the

user to filter out the desired gene links for the user's benefits.

MiRDB prediction for APC gene. Gene 324 is predicted to be targeted by 184 miRNAs in miRDB. Selected target score for the following data from MiRDB is >95

**Results:-**

| Target Rank | Target Score | miRNA Name | MiRNA sequence | Important genes |
|---|---|---|---|---|
| 1 | 99 | hsa-miR-3120-3p | 5' - **cacagcaaguguagacaggca** - 3' | **PXYLP1, SCAF4, TGIF2, APBB2. , ETV5** |
| 2 | 99 | hsa-miR-561-3p | 5' - **caaaguuuaagauccuugaagu** - 3' | **ARIH1, MED14, ACTR2, ACVR2A, C16orf72** |
| 3 | 99 | hsa-miR-6853-3p | 5' - **uguucauuggaacccugcgcag** - 3' | **GRIK2, APC, CA13, DIP2C, PARP12** |
| 4 | 98 | hsa-miR-5696 | 5' - **cucauuuaaguagucugaugcc** - 3' | **AHCTF1, DNAJB14, TENT5A, APIP, RNFT1** |
| 5 | 97 | hsa-miR-6504-3p | 5' - **cauuacagcacagccauucu** - 3' | **MS12, SCAMP1, ARIH1, CDC73, ATAD2B** |
| 6 | 97 | hsa-miR-3942-5p | 5' - **aagcaauacuguuaccugaaau** - 3' | **SLBP, CXCL16, BHMT, CDK6, RB1** |
| 7 | 97 | hsa-miR-582-5p | 5' - **uuacaguuguucaaccaguuacu** - 3' | **GABPB1, PRDM12, ABTB2, TNKS2, BCL11B** |
| 8 | 97 | hsa-miR-10399-5p | 5' - **aauuacagauugucucagaga** - 3' | **MS12, ARIH1, CDC73, ATAD2B, TBC1D19** |
| 9 | 97 | hsa-miR-4703-5p | 5' - **uagcaauacaguacaaauauagu** - 3' | **BHMT, SLBP, CXCL16, OTOGL, TRIM43B** |
| 10 | 96 | hsa-miR-153-3p | 5' - **uugcauagucacaaaagugauc** - 3' | **UNC5C, KCNQ4, SERTAD2, KLF5, HEY2** |

| | | | | |
|---|---|---|---|---|
| 11 | 95 | hsa-miR-4282 | 5' - **uaaaauuugcauccagga** - 3' | **TMOD2, C21orf91, ZDHHC21, RPS6KA6, RBM27** |
| 12 | 95 | hsa-miR-30e-3p | 5' - **cuuucagucggauguuuacagc** - 3' | **CDC73, ZEB2, NUFIP2, PCLO, LRRTM2** |

MiRNA (hsa-miR-3120-3p)with a target score of 99 is further detailed.

**Mature miRNA:**
miRNA Name: hsa-miR-3120-3p.
miRNA Sequence:
5' - cacagcaaguguagacaggca - 3' (length = 21).

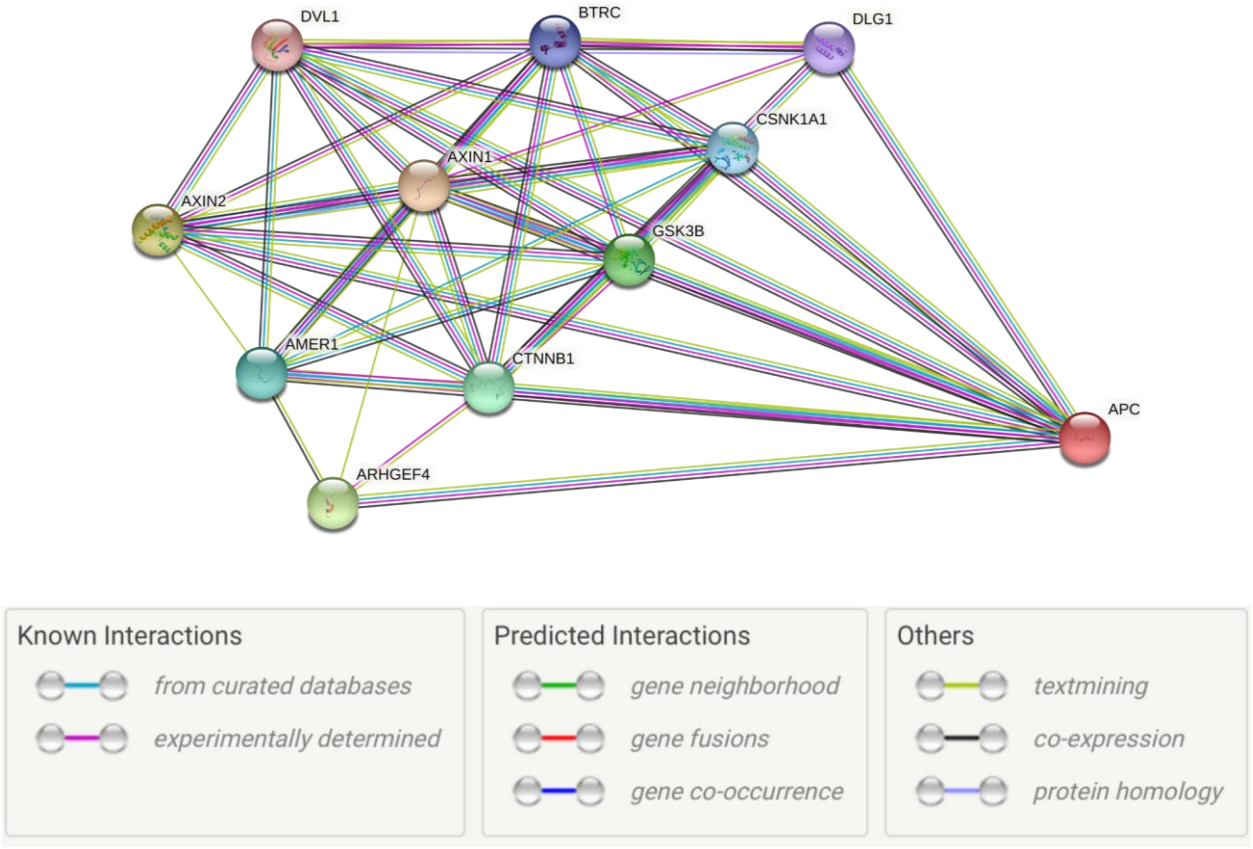
**Precursor miRNA:**
Precursor Name: hsa-mir-3120.
Genomic Location Chr1:172138808-172138888 (+).
Precursor Sequence

```
        a          ug c     a    ugag
gucaugug cugccugucug  c ugcugu cagg   c
||||||||| ||||||||||  | |||||| ||||   g
caguacac gacggacagau  g acgaca gucu   g
        a          gu a     c    ugua
```

There are 1253 predicted targets for hsa-miR-3120-3p in miRDB out of which the selected target score for selected miRNA is >=98

| Target Rank | Target Score | miRNA Name |
|---|---|---|
| 1 | 100 | hsa-miR-3120-3p |
| 2 | 99 | hsa-miR-3120-3p |
| 3 | 99 | hsa-miR-3120-3p |
| 4 | 99 | hsa-miR-3120-3p |
| 5 | 99 | hsa-miR-3120-3p |
| 6 | 99 | hsa-miR-3120-3p |
| 7 | 99 | hsa-miR-3120-3p |
| 8 | 99 | hsa-miR-3120-3p |
| 9 | 99 | hsa-miR-3120-3p |
| 10 | 98 | hsa-miR-3120-3p |
| 11 | 98 | hsa-miR-3120-3p |
| 12 | 98 | hsa-miR-3120-3p |
| 13 | 98 | hsa-miR-3120-3p |

| | | |
|---|---|---|
| 14 | 98 | hsa-miR-3120-3p |
| 15 | 98 | hsa-miR-3120-3p |




ROB01, APBB2, PXYLP1,ARIH1, GRIK2 were some of the genes found to have interactions of miRNA associated with APC gene.

**Figure1:** The following image represents the gene network analysis of APC gene. Which helps us in understanding the various links that APC have towards other genes.

**Link between APC and other genes**

Adenomatous polyposis coli protein; Tumor suppressor. Promotes rapid degradation of CTNNB1 and participates in Wnt signaling as a negative regulator. APC activity is correlated with its phosphorylation state. Activates the GEF activity of SPATA13 and ARHGEF4. Plays a role in hepatocyte growth factor (HGF)-induced cell migration. Required for MMP9 up-regulation via the JNK signaling pathway in colorectal tumor cells. Acts as a mediator of ERBB2-dependent stabilization of microtubules at the cell cortex.

**DLH 1**

Disks large homolog 1; Essential multidomain scaffolding protein required for normal development (By similarity). Recruits channels, receptors and signaling molecules to discrete plasma membrane domains in polarized cells. May play a role in adherens junction assembly, signal transduction, cell proliferation, synaptogenesis and lymphocyte activation. Regulates the excitability of cardiac

myocytes by modulating the functional expression of Kv4 channels. Functional regulator of Kv1.5 channel; Belongs to the MAGUK family.

**CTNNB1**

Catenin beta-1; Key downstream component of the canonical Wnt signaling pathway. In the absence of Wnt, forms a complex with AXIN1, AXIN2, APC, CSNK1A1 and GSK3B that promotes phosphorylation on N-terminal Ser and Thr residues and ubiquitination of CTNNB1 via BTRC and its subsequent degradation by the proteasome. In the presence of Wnt ligand, CTNNB1 is not ubiquitinated and accumulates in the nucleus, where it acts as a coactivator for transcription factors of the TCF/LEF family, leading to activate Wnt responsive genes.

**CSNK1A1**

Casein kinase I isoform alpha; Casein kinases are operationally defined by their preferential utilization of acidic proteins such as caseins as substrates. It can phosphorylate a large number of proteins. Participates in Wnt signaling. Phosphorylates CTNNB1 at 'Ser-45'. May phosphorylate PER1 and PER2. May play a role in segregating chromosomes during mitosis. May play a role in keratin cytoskeleton disassembly and thereby, it may regulate epithelial cell migration.

**ARHGEF4**

Rho guanine nucleotide exchange factor 4; Acts as guanine nucleotide exchange factor (GEF) for RHOA, RAC1 and CDC42 GTPases. Binding of APC may activate RAC1 GEF activity. The APC-ARHGEF4 complex seems to be involved in cell migration as well as in E-cadherin-mediated cell-cell adhesion. Required for MMP9 up-regulation via the JNK signaling pathway in colorectal tumor cells. Involved in tumor angiogenesis and may play a role in intestinal adenoma formation and tumor progression.

**GSK3B**

Glycogen synthase kinase-3 beta; Constitutively active protein kinase that acts as a negative regulator in the hormonal control of glucose homeostasis, Wnt signaling and regulation of transcription factors and microtubules, by phosphorylating and inactivating glycogen synthase (GYS1 or GYS2), EIF2B, CTNNB1/beta-catenin, APC, AXIN1, DPYSL2/CRMP2, JUN, NFATC1/NFATC, MAPT/TAU and MACF1. Requires primed phosphorylation of the majority of its substrates.

**AXIN1**

Axin-1; Component of the beta-catenin destruction complex required for regulating CTNNB1 levels through phosphorylation and ubiquitination, and modulating Wnt-signaling. Controls dorsoventral patterning via two opposing effects; down-regulates CTNNB1 to inhibit the Wnt signaling pathway and ventralized embryos, but also dorsalizes embryos by activating a Wnt-independent JNK signaling pathway. In Wnt signaling, probably facilitates the phosphorylation of CTNNB1 and APC by GSK3B. Likely to function as a tumor suppressor gene.

**AXIN2**

Axin-2; Inhibitor of the Wnt signaling pathway. Down-regulates beta-catenin. Probably facilitate the phosphorylation of beta- catenin and APC by GSK3B.

**Discussion:**

Various gene links have been identified from our study in relation to the APC gene . The most common cancer associated with APC was observed to be colorectal cancer however since genetic information gets transferred over each multiplication. There is a possibility that APC will be associated with head and neck cancers as well. It has been shown that the location of germline mutations in the *APC* gene is the most striking source of variability affecting the number of polyps that will develop in the colon of FAP patients (18). Other researchers has also found a correlation between the severity of the disease in FAP patients who donated their affected embryos for our FAP-hESC lines and the 3D structure of their derived colon organoids and the location of their germline APC mutations(19). It was previously suggested that a stable truncated APC protein may act in a dominant negative fashion to inactivate APC transcribed from the WT allele. Homodimerization of APC at the amino-terminus implies a possible dominant negative mode of action for mutant APC in heterozygous cells, in which shorter proteins can functionally inactivate the full-length WT protein(19–21) The first 170 amino acids are sufficient for APC homodimerization in-vitro, an association which requires the 45 amino acids only. FAP3 carries a heterozygous frameshift mutation that is predicted to be in amino acid 60, presumably resulting in lack of function of the mutated allele (‘first hit’), but the normal allele expresses the APC since the ‘second hit’ didn’t occur yet. Consequently, in the absence of a gain-of-function effect, the patient presents only mild disease, and the corresponding complexed organoids derived in vitro are similar to those of WT hESCs expressing the two normal alleles of the APC. Therefore, we hypothesis that while the APC germline mutations in FAP1 and FAP2 may result in a truncated protein that can cause a dominant-negative effect on the normal allele, the germline mutated protein translated in FAP3 is likely too short to interfere with the normal APC protein.

In recent years, gene expression, as well as other molecular profiling, has been used as biological tools for diagnosis of cancer (22) These molecular approaches also have the potential to explore molecular mechanisms of the disease and to pave the road to targeted cancer fighting drugs and advanced treatments (23). APC is one the most important elements of the Wnt-signaling pathway; its activation is a general characteristic of solid tumors such as bladder, prostate, and renal tumors. Epigenetic down regulation of Wnt pathway inhibitors may contribute to aberrant activation of the Wnt signaling pathway (24). Hypermethylation of APC promoter can silence gene expression by interfering with the binding of transcription factors to the promoter

In a previous study OCD cases reported herein showed pathogenic mutations in *CTNNB1* and *APC* genes and strong β-catenin accumulation in the cytoplasm and in the nuclei, consistent with Wnt-signaling activation. The molecular profile of OCD may help in its diagnosis, as well as in the identification of potential molecular targets for therapy in the future.

In previous research Loss of heterozygosity at APC and MCC genes was investigated in 57 and 40 unrelated primary oral leukoplakia (a precancerous lesion) and squamous cell carcinomas (SCC), respectively, by polymerase chain reaction

(25-34). In these samples, most of the leukoplakia patients had a tobacco smoking habit whereas the majority of cancer patients had tobacco chewing habit. LOH at APC gene was observed in 4 of 16 (25%) and 1 of 29 (3%) informative tumor and leukoplakia DNAs from tobacco chewers, respectively. LOH at MCC gene was not detected either in tumor or in leukoplakia DNAs. This infrequent LOH at APC gene of pre-cancer and cancer tissues suggests that it may not be an early event in oral carcinogenesis in these patients.

**Conclusion:**

In conclusion the Functional gene - miRNA interaction may contribute to growth of APC.These findings indicate miRNAs act together to promote tumour progression.This could help develop miRNA targeted therapy and study tumorigenesis process of head and neck cancer.

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