



Research Article

An integrated approach for the study of APOBEC3B associated genes and its impact on hypoxic and immune signaling pathways in ovarian cancer

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Abstract: APOBEC3B is suspected to be an enzymatic source of mutation in a small number of human cancers; it has also been associated with bone leiomyosarcoma and human T-cell leukemia virus type 1. The key processes regulated or effected by APOBEC3B include gene expression, mRNA editing, particularly C → U Conversion, and deoxycytidine deaminase activity. The main goal of this work was to do an organized investigation of the genes associated with APOBEC3B and their functional significance in human ovarian cancer. Datasets for this project were obtained from openly available sources including TCGA and GEO. Depending on the requirements for collecting the values, several bioinformatics approaches have been applied at various levels. Additionally, the changed genes were prepared for the examination of pathway enrichment after the differentially expressed genes had been obtained. We identified numerous significant pathways that are directly related to ovarian cancer that are altered as a result of altered gene expression patterns and mutational alterations. APOBEC3B and some of these genes are related. The cell cycle, p53 signaling, immunological signaling pathways, progesterone-mediated oocyte maturation, apoptosis, and critical metabolic pathways are among the most severely damaged processes. In terms of these pathways components (genes), we conclude that TP53, TTN, MUC16, CSMD3, USH2A, BRCA1, HMCN1, CCDC26, PCAT2, PVT1, MYC, CCAT1, PCAT1, MECOM, AHNAK, PAK1, SKAP1, DNM2, SORL1, RRM1/2, CDK2, SMC4, CCNB2, CDC20, MELK, and ATAD2 appear to be highly significant based on gene expression, mutational, CNAs, SVs, network analysis.

Keywords: APOBEC3B; ovarian cancer; expression and mutation analysis; hypoxic genes; network-approach

1. Introduction

Genomic instability is thought to play a role in the development of major human diseases, such as cancer[1-5]. Rapid cancer growth causes clonal selection in tumour cells, which furthers the development of drug resistance and unfavourable clinical outcomes. Mutations are categorised as driver and passenger mutations and may be caused by a variety of events, both internal and external, and are thought to be among the potential genomic instability factors. They have a big impact on clinical outcomes, drug resistance, and the growth of cancer. Higher levels of anomalies are also revealed by the pattern of gene expression, as well as their immediate functional impact[2, 6-12].

Technology breakthroughs paired with major advances in interdisciplinary methodologies have allowed for the direct characterization of critical functional mutations, genes, and pathways associated in a range of complex human diseases, including cancer. It has long been understood that chemical exposure and radiation damage are the main contributors to carcinogenic mutagenesis[13-19]. 11 polynucleotide cytosine deaminase family enzymes, including APOBEC1, AID, APOBEC2, APOBEC3 proteins (also known as A3A, A3B, A3C, A3D, A3F, A3G, and A3H), and APOBEC4 are encoded in the human genomes. These enzymes are crucial in the intrinsic DNA mutation process. There are no reports of either APOBEC2 or APOBEC4 mutational activity. A tissue-specific expression of APOBEC1 and AID, which have effects on tumours of those tissues, hepatocytes and B cells, respectively, has been established.

In 2002, these enzymes were recognised individually as DNA mutators and antiviral agents. APOBEC3B is expected to be the member of the 11 family members that is overexpressed in ovarian cancer cohorts and is thought to be most frequently linked to ovarian cancer mutations. Ovarian cancer is one of the most common cancers in women worldwide[20-27].

The APOBEC3B mutation is one of several potential causes of ovarian cancer, along with DNA alterations or mutations, variations in gene expression patterns, and epigenetic changes. It is acknowledged to have a significant role in the disease's potential clinical effects on patients. The clusters of closely spaced, single-strand-specific DNA alterations that are the hypermutation hallmark of ovarian cancer are brought on by an increase in the mutation burden brought on by APOBEC3B. The genomic alterations induced by APOBEC3B in the human genome are supported by a wealth of evidence, and the patterns of mutation have undergone rigorous analysis. The elements regulating their expression have also been discovered, in a manner similar to how Linda and her colleagues discovered the molecular bases of its function. There are claims that p53 and NF- κ B independently control APOBEC3B expression. Previous research has shown that some genes and proteins control or stifle the synthesis of certain enzymes. Analyses of APOBEC3B-related networks and target genes can help identify therapy targets for cancers with APOBEC3B mutations (for mutations). The correlations between APOBEC3B hyper-expression, APOBEC3B interaction networks, and the survival curves of patients with mutations or overexpression of these related genes have not received much attention in the literature. In the many different forms of human malignancies, notably ovarian cancer, a complete investigation of APOBEC3B-induced mutations and the accompanying interaction networks is required. Numerous investigations of genomic alterations in various cancer types have been carried out using TCGA data[3, 20-23, 25, 27-30].

However, none of them have specifically focused on and explored the genetic aberrations of APOBEC3B and its related interaction networks across the various ovarian cancer subtypes. In order to assess the relationship and impact of APOBEC3B in ovarian cancer, including the network-level understanding of these enzymes and their related molecular parts, our potential focus has been on the combined analysis of gene expression datasets and mutational datasets. Previous works have specifically discussed APOBEC3B's function. Furthermore, depending on changes in their expression or mutation, we have focused on determining the clinical importance of those co-expressed APOBEC3B genes. The clinical importance of all the genes that are specifically changed in ovarian cancer is the subject of our second objective. According to our research, a large number of genes in the human network database interact with APOBEC3B, and these genes are crucial players in essential pathways, notably those that are related to ovarian cancer. Gene mutations or inconsistent gene expression both affect these pathways. The same conclusion is reached when looking at clinically significant genes and genes that have experienced mutations.

2. Methods

We gathered the datasets for expression and mutational profiles in this work from two publically accessible ovarian cancer databases (GEO and TCGA). The majority of comparison studies have been conducted between normal and tumour sample sets. The details of the mutational datasets are as follows: datasets were OC (from the TCGA database) (Liu et al., 2018; Pereira et al., 2016). Most of this work has utilised MATLAB for data processing, normalisation, analysis, and figure plotting. Similar to that, most computational analysis—from normalisation to statistical analysis—has been done using MATLAB[22, 31-39].

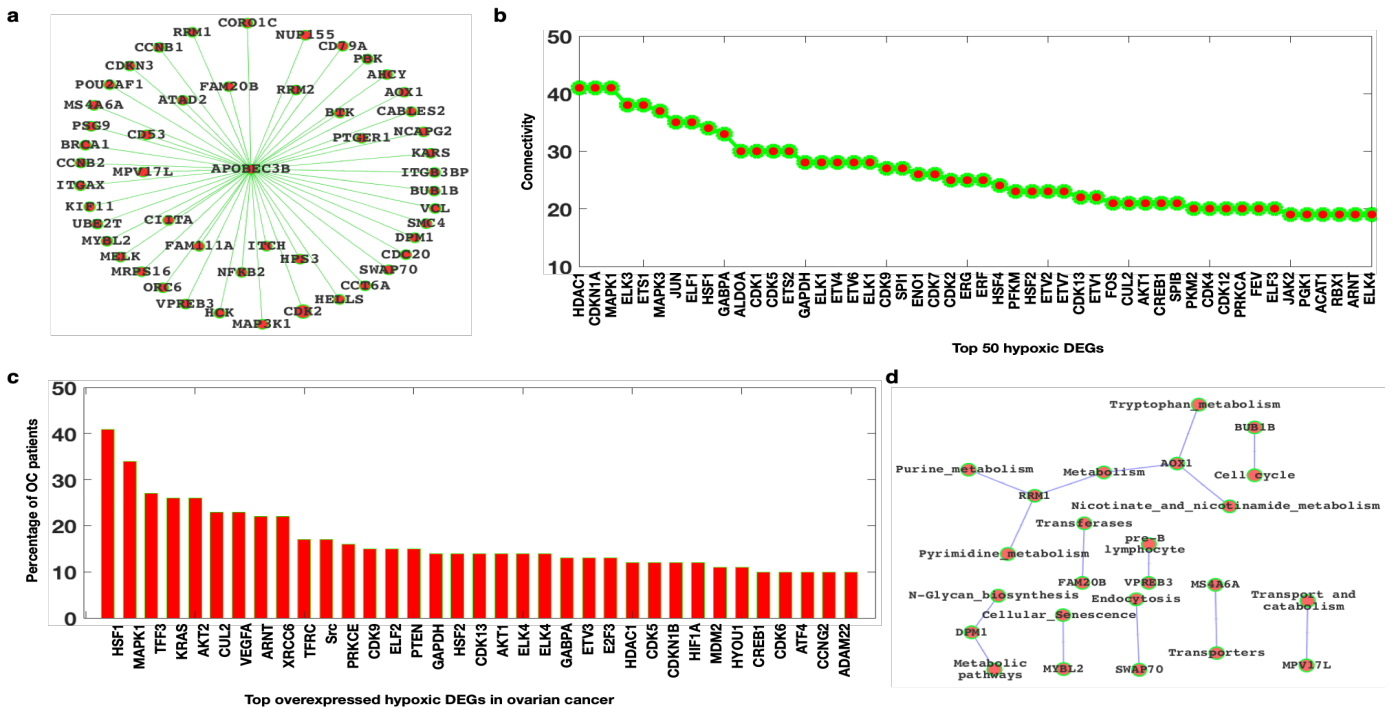
GEO2R has been used to analyse DEGs, and lists of DEGs have been extracted. We have used the KEGG pathway database and network database (FunCoup) to present a network of both the pathways and their directly associated components, i.e., directly APOBEC3B-associated genes, after establishing the fundamental relevance of the APOBEC3B and its association with other genes and pathways[39, 40].

For the list of mutated genes obtained for large datasets of ovarian cancer from TCGA and pathway enrichment analysis has been performed and the cutoff p-values were 0.05 and the steps implemented was similar to DAVID database and for network drawings cytoscape has been used and for enriched pathways, basic enrichment approach has been used. In survival curve analysis, we have presented the overall list of genes with significant p-values[41-43].

3. Results

3.1. Understanding the role of APOBEC3B and the associated genes and pathways in ovarian cancer: The big datasets (expression and mutation) from GEO and TCGA were acquired for our work in order to accomplish the objective described in the preceding section, and for its analysis, we used an in-silico approach. We used a protein-protein interaction database to map out all the genes and to map out the genes directly connected with APOBEC3B. Figure 1a shows the integrated network of all these genes. Here, we see that there are many genes that interact directly with APOBEC3B, and the bulk of these genes are recognised to be a direct component of established cancer pathways, such as those that lead to breast and ovarian cancer. We also matched the DEGs with the list of APOBEC3B genes, and we've displayed them as a network in Figure 1b along with the related pathways. The pathways included the cell cycle, cellular senescence, metabolic, and endocytosis. After examining the direct APOBEC3B components, we moved on to the study's original objective, which is the function of hypoxia genes in cases of OC. To achieve this, we combined the list of hypoxia genes we had compiled from the KEGG pathway database or other studies with the DEGs from the GEO dataset of gene expression OC. We then created and evaluated a network of these hypoxic genes, and the top 50 hypoxic DEGs were shown in Figure 1c. HDAC1, CDKN1A, MAPK1, ELK3, ETS1, MAPK3, JUN, ELF1, HSF1, GABPA, ALDOA, CDK1, CDK5, ETS2, GAPDH, ELK1, ETV4, ETV6, ELK1, CDK9, SPI1, ENO1, CDK7, CDK2, ERG, ERF, HSF4, PFKM, HSF2, ETV2, ETV7, CDK13, ETV1, and FOS were among top-ranked hypoxic genes which appear to be connected with more than 20 genes leading to the conclusion that the alteration in the gene expression patterns of these genes could greatly affect in case of OC.

Figure 1. APOBEC3B targets and gene expression profiling. (a) APOBEC3B interactors, (b) top 50 DEGs based on connectivity within the DEGs



network, (c) top hypoxic genes overexpressed in case of OC patients, and (d) DEGs matched with the targets of APOBEC3B.

Further, extending our analysis we classified positive and negative co-expressing genes but threshold we have applied for correlation value was either greater than +0.5 or less than -0.5 and such negative and positive correlation in expression provides important information regarding the dependence of gene expression on each other.

3.2. Overexpression of hypoxic genes and their functional impact in clinical ovarian cancer patients: After analyzing the hypoxic genes in case of OC, we used TCGA database and analyzed the genes which show mutation in larger number of patient samples (Figure 1d). Here, the genes showing mutation in 10% percent or more number of OC patients are HSF1, MAPK1, TFF3, KRAS, AKT2, CUL2, VEGFA, ARNT, XRCC6, TFRC, SRC, PRKCE, CDK9, ELF2, PTEN, GAPDH, HSF2, CDK13, AKT1, ELK4, ELK4, GABPA, ETV3, E2F3, HDAC1, CDK5, CDKN1B, HIF1A, MDM2, HYOU1, CREB1, CDK6, ATF4, CCNG2, and ADAM22. Majority of the top-mutated genes seems to be the part of critical pathways such as hippo, cell cycle, RTK-RAS-PI3K, and AKT-KRAS-HRAS pathways (Figure 2a, 2b, 2c, and 2d). There

are also a number of genes which belong to more than one pathways and are highly mutated such as PIK3CA = 42.3%, STK11 = 27.7%, KRAS = 25.7%, AKT2 = 26.3%, and PTEN = 15.3%.

3.3. Functional of the overexpressed genes in ovarian cancer: We did the pathway enrichment analysis for the DEGs after examining the APOBEC3B-related genes,

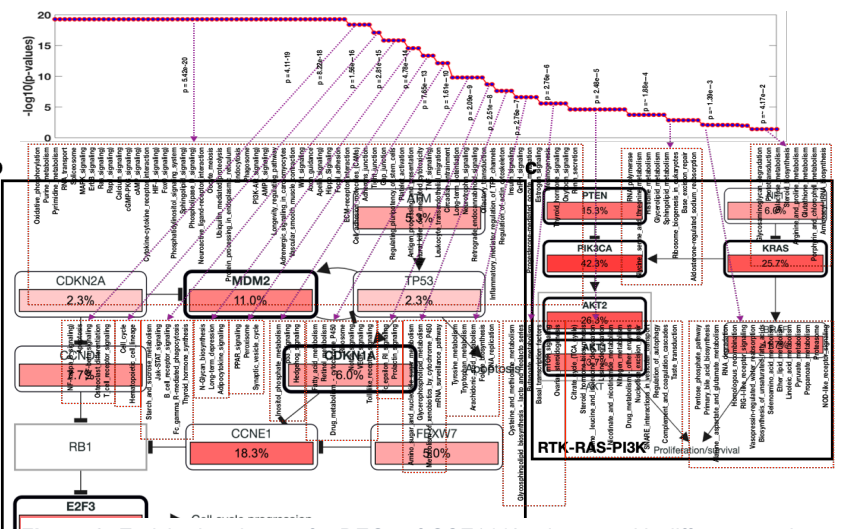
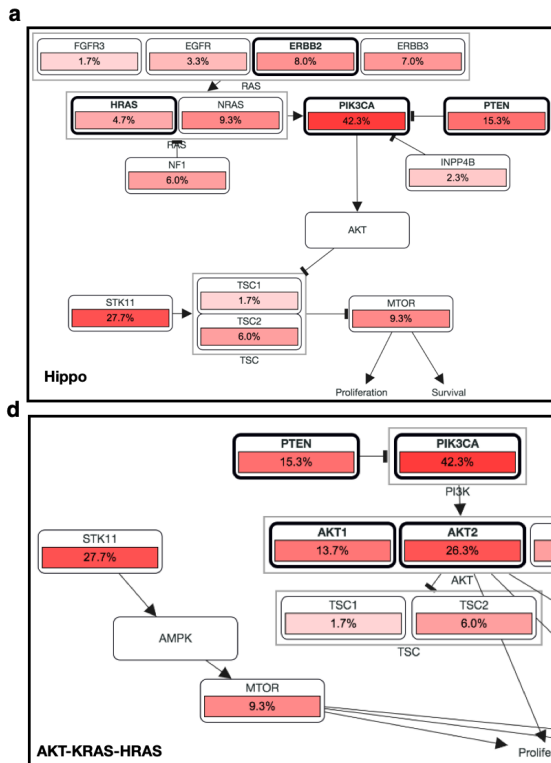


Figure 3. Enriched pathways for DEGs of GSE14407 dataset with different p-values. The plot was carried out by converting p-values into $-\log_{10}(p\text{-values})$.

Figure 2. Top-ranked overexpressed genes in case of OC belonging to different pathways. Genes with increased red color (means more number of patients showing the overexpression) in different pathways (a) Hippo signaling pathway, (b) cell cycle pathway, (c) RTK-RAS-PI3K pathway, and (d) AKT-KRAS-HRAS signaling pathway.

genes affected by hypoxia, and genes with mutations. As seen in Figure 3, there are numerous paths in this area that were significantly enriched. The p-values were transformed using $-\log_{10}$ as $-\log_{10}(p\text{-values})$ so that we could more easily understand that higher $-\log_{10}(p\text{-values})$ indicates higher enrichment and lower $-\log_{10}(p\text{-values})$ indicates lower enrichment. We have also labeled the respective p-values ranges. Oxidative phosphorylation, metabolism, RNA transport, spliceosome, MAPK, ErbB, Ras, Rap1, calcium, cytokine, HIF-1, Foxo, PI3K, ubiquitination, wnt, hippo, focal adhesion, ECM, cell adhesion, adherens junction, tight junction, gap junction, platelet activation, antigen processing and presentation, NK cell-mediated cytotoxicity, TNF signaling, neurotrophin, melanogenesis, and regulation of actin cytoskeleton signaling pathways were among the highly enriched pathways which have p-values $< 1e-20$. Overall, we conclude that there are the highly significant pathways which are enriched here such as NF- κ B, apoptosis, TGF- β , TCR, BCR, JAK-STAT, p53, cell cycle, VEGF, Notch, TLR, and PPAR signaling pathways. These pathways are well-known to be associated with almost all types of cancers. For more clarity, in terms of p-values, lower the p-values higher the number of DEGs overlapping with the respective pathways.

3.4. Global mutational, CNAs, and SVs profiling for the genes in ovarian cancer: Finally, using bigger TCGA datasets, we investigated the mutant, CNAs, and SVs genes and provided the top 50 genes for each type of analysis

(Figure 4a). Here, we can also see that the top genes were shared by the mutated genes and CNAs genes. This comparison research thus reveals the additional importance of genes in the case of OC. Additionally, in order to comprehend the significance of the APOBEC3B gene, these genes were mapped to the list of APOBEC3B genes, and the three gene lists were then combined, resulting in the network depicted in Figure 4b. Here, we see that there are more instances of common genes in the case of CNAs than there are mutations and SVs, and a significant portion of these common genes are known to be linked to human disorders, including cancer. The network's highest levels of connectedness are displayed by CNAs and mutant genes, whereas a small number of SV genes have higher levels of linkage.

4. Discussion: Here, we examined the association between APOBEC3B and OC as well as the gene expression, mutational, CNA, and SV profiles in OC. A network-approach has also been employed. Here, we point out that p53 signaling, cell cycle, oocyte meiosis, major cancer signaling, ubiquitin-mediated proteolysis, TLR signaling, chemokine signaling, antigen processing and presentation, regulation of actin cytoskeleton, neurotrophine, MAPK, BCR signaling, a number of metabolism-related signaling, and calcium signalling are the pathways that could be impacted by changes in APOBEC3B. The regulation of the actin cytoskeleton pathway, the p53 signalling pathway, the MAPK kinase pathway, the neurotrophin and chemokine pathway, and the calcium signalling pathway, which, when altered in cancer cells, are involved in tumour initiation and angiogenesis, are all required for cell cycle progression and are regulated by increased GSH levels in a variety of cancer cells, both normal and malignant. These pathways, which are well-known to be highly specialised and to play a significant role in the migration and proliferation of cancer cells, were discovered to be significantly linked with APOBEC3B.

There have been numerous studies done in the past that have looked into genomic aberrations and their impacts, two of which are the genomic changes brought about by APOBEC3B in the human genome and mutation profiling[14, 44-51]. Mutations caused by APOBEC have occurred in active chromatin-containing early replicating areas. Due of the single state DNA present in these replicating areas, there are more substrates that are highly intriguing for APOBEC3B activity. According to our research, chromosome breakage results in copy number variation, chromosome rearrangements, fragility, and loss of heterozygosity in early replicating and highly transcribed regions of cancer genomes.

The pathway enrichment of the top mutant genes in the two cohorts revealed that APOBEC3B was largely altered to target cellular signalling pathways in ovarian cancer patients. Mutations in APOBEC3B are more likely to occur when DNA damage and repair are increased. Given the lack of known regulatory sequences, the prevalence of APOBEC-induced mutations in cancer genomes is unexpected. In contrast to 82% of AID-induced events, it has been discovered that only 6% of catastrophic events caused by APOBEC take place near transcriptional start sites. Additionally,

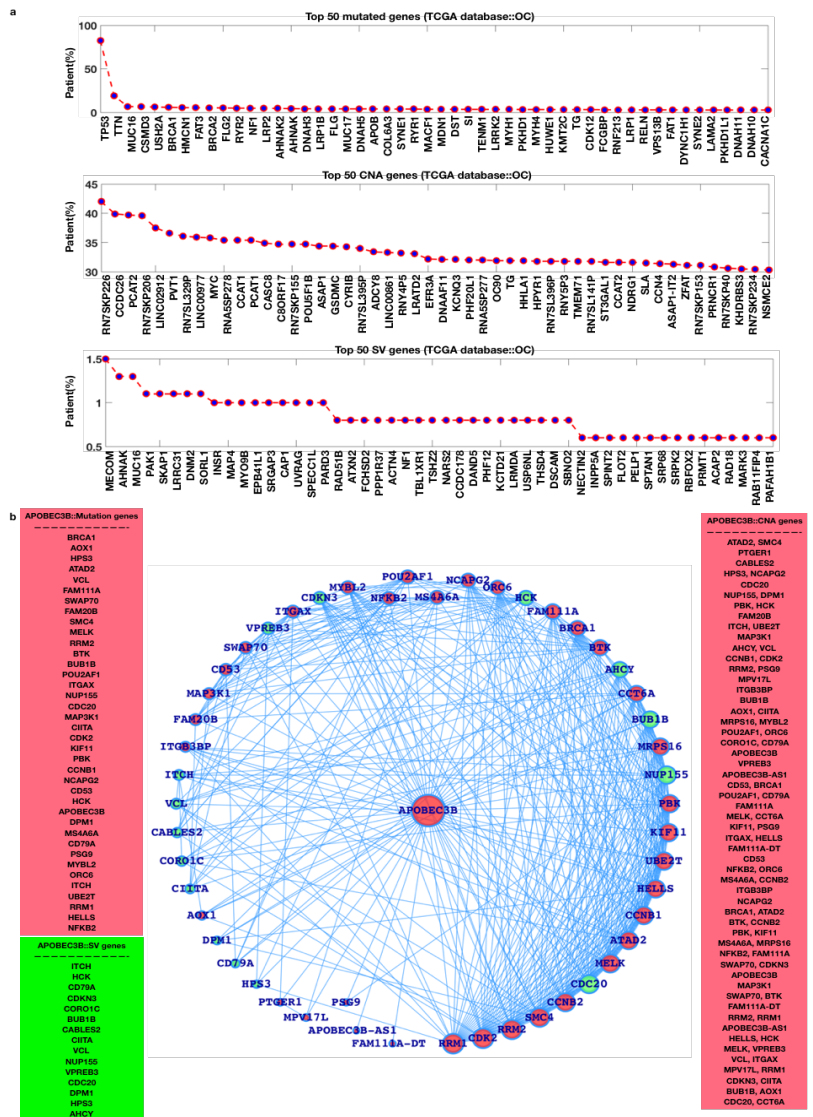


Figure 4. (a) Top 50 mutated, CNA, and SV genes and (b) mutated, CNA, and SV genes common to APOBEC3B target genes.

APOBECs favour early replicating regions of the genome, which are free of DSBs brought on by AID in B-cells. Previous research has also looked at a small number of variables that either directly or indirectly affect APOBEC3B expression. Reports claim that p53 and NF- κ B independently control the expression of APOBEC3B. In order to evaluate the association and impact of APOBEC3B in ovarian cancer, we have put considerable emphasis on an integrated investigation of APOBEC3B linked genes, functions, expression datasets, and clinical relevance. The work has mostly concentrated on the function of APOBEC3B as a standalone study up to this point. Here, we have used a variety of integrative study methods, including network-level understanding of the key genes and their associated functions, to thoroughly analyse APOBEC3B and the associated genes, as well as their roles[22-25, 27].

This work intends to define the clinical importance of APOBEC3B- and ovarian cancer connected genes in order to comprehend the relationship between variation in their expression, followed by the mutational profiling and the clinical significance of ovarian cancer associated genes. The enriched pathways, ovarian cancer mutational profiles, and ovarian cancer gene survival analyses are all displayed in the findings section along with the APOBEC3B associated genes and pathways. This study suggests that APOBEC3B may significantly influence ovarian cancer cases. Enhanced pathways and genes are reportedly major players in OC.

The APOBEC3B-related genes, ovarian cancer mutant genes, and clinically significant genes are among the pathways that may be known to be altered in cancer, specifically ovarian cancer. It is possible that APOBEC3B has a substantial direct or indirect role in the spread of ovarian cancer given the high correlation between this enzyme and the pathways for cancer cell migration and progression. According to co-relation patterns determined from expression datasets, APOBEC3B may have a significant impact on a number of genes. The spatial patterns of gene expression were revealed by the co-expressing study, proving that each DNA fragment was actively involved in transcription. Since transcription occurs on unfolded DNA, APOBEC3B has the potential to specifically target and mutate these exposed regions.

5. Conclusions: Based on this study, we conclude that the APOBEC3B associated genes and the pathways are very specific and play pivotal role in cancer cell migration and proliferation. MAPK, calcium signaling, cAMP, PI3K-AKT, focal adhesion, adrenergic signaling, thyroid hormone, oxytocin, ErbB, ubiquitin, apelin, tight junction, GnRH, Ras, cGMP-PKG, cell cycle, and pluripotency of stem cells are among the commonly enriched pathways. Network of the top-ranked overall survival analysis based genes and the associated functions, RRM1, CDK2, RRM2, SMC4, CCNB2, CDC20, MELK, ATAD2, CCNB1, HELLS, UBE2T, and KIF11 appear to affect more number of genes and thus could affect more biological functions. Among the overall functions associated with these top-ranked genes, majority of these pathways are known and well-established that they control major human diseases multiple types of cancers including ovarian cancer, neurodegenerative diseases, diabetes, and infection diseases.

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