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TOM1L2 as a Potential Regulator of Tumor Progression in Brain and Colorectal Cancers

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ABSTRACT

TOM1-like protein 2 (TOM1L2) is an adaptor protein that is associated with vesicular transport and endosomal transport that is essential in maintaining cellular signaling and homeostasis. Despite the possibility of TOM1L2 to be involved in a regulation role in the intracellular transport pathways, the relationship between TOM1L2 and cancer development and progression is not well understood. The aim of the current study was to analyze the trends and clinical significance of tumor TOM1L2 expression in multiple cancers with particular focus on tumors of the brain/central nervous system (CNS) and bowel. Initially, tumor-normal expression comparisons were studied to reveal the pattern of differentiation expression of TOM1L2. This was followed by an all-inclusive pan-cancer examination comparing the degree of gene expression, genetic changes, Oncoprint, and survival studies in different tumor categories. Consequently, the Brain/CNS and bowel-related malignancies were investigated in detail to investigate the expression, mutation and the potential prognostic value of TOM1L2 in these cancers. The results demonstrated variable, although significant changes in TOM1L2 expression in various types of cancers, and a different pattern was observed in the cases of some CNS and colorectal tumors. Survival analyses suggested possible trends between TOM1L2 genetic alteration status and patient outcomes in selected cancer types; however, these associations require further experimental validation Altogether, this paper demonstrates that TOM1L2 could be one of the biomarkers in cancer biology and offers a background of new experimental and clinical research to better understand its application and a therapeutic target in cancer development.

Keywords: TOM1L2, prognostic marker, GBM, colorectal cancer

1. INTRODUCTION

Cancer is among the major causes of morbidity or death across the world and tumors of the central nervous system (CNS) and colorectal area are the major contributors to the global cancer burden [1]. One of the most complicated malignancies with heterogeneous molecular properties and a few treatment options is brain and CNS tumors, whereas colorectal cancer is one of the most diagnosed cancer types and a significant cause of cancer-related deaths in the world [1][2]. Although a lot has been discovered in the field of genomic and transcriptomic profiling, the biological processes involved in the regulation of tumor initiation and progression in these cancers are still not fully understood [3].

Genes have a pivotal role in cancer development and progression where they control the key biological processes of cell proliferation, apoptosis, differentiation, DNA repair, and immune responses [4][5]. Oncogenes and tumor suppressor genes can be activated or inactivated by mutations, copy number variations and aberrant gene expression, which stimulate uncontrolled cell growth and tumor development [4]. Moreover, the dysregulation of genes involved in the signaling pathways, translocation of cells, and communication within cells can also contribute to the advancement of tumors, their dissemination, and treatment resistance [5]. Therefore, it is of high importance to identify and characterize these genes that play a role in various biological processes in order to understand tumor biology and come up with effective measures of diagnosis and treatment. Discovery of new genes in tumor biology is thus imperative in enhancing diagnostic, prognostic and therapeutic interventions [4].

Vesicular transport and intracellular trafficking systems are central to the upkeep of cell homeostasis. These mechanisms mediate receptor recycling, protein degradation, and signal transduction, which affect cell proliferation, immunogenicity, and apoptosis [6]. Endosomal transport and vesicle-mediated signaling disruption has also been increasingly identified as an important aspect of cancer cell development and progression [7]. The proteins that are involved in these pathways may regulate the localization, stability, and activity of growth factor receptors and other signaling molecules [7][8].

TOM1-like protein 2 (TOM1L2) is a member of TOM1 family of adaptor proteins with the VHS (Vps27, Hrs, and STAM) and GAT (GGA and TOM1) domains of endosomal trafficking and ubiquitin-mediated protein sorting [9]. The members under this family are involved in vesicular transportation, modulation of receptor transportation, and intracellular signaling pathways that are linked with immune regulation and cell communication [9][10]. TOM1L2 has been identified to have an interaction with proteins that are part of endosomal sorting and vesicle formation implying a participation in an intracellular transport system, which is essential in the maintenance of healthy cellular functions [10]. Since vesicular trafficking pathways mediate many signaling events, a failure in the regulation of these adaptor proteins can be implicated in pathological diseases, such as cancer [7].

Even though a number of studies have addressed the roles of proteins in endosomal trafficking, the biological function of TOM1L2 in human disease is yet to be fully explored. It has been experimentally indicated that TOM1L2 can affect immune architecture and cellular signaling events and changes in relevant trafficking signatures have been associated with tumorigenesis [11][12]. Moreover, genomic and transcriptomic data on a grand scale have continued to show that genes that are involved in vesicular movement can have their expression patterns altered in various types of cancers [9][11]. Nevertheless, the possibility of TOM1L2 being involved in the biology of tumors has not been systematically explored.

The recent developments in cancer genomics and bioinformatics platforms can now provide a comprehensive analysis of gene expression profiles, genetic changes and clinical relationships in various tumor types. Through the use of pan-cancer analyses, genes which have potential roles in tumor development have been very useful in assessing their expression patterns, mutative rates, and prognostic value in diverse malignancies [13][14]. These integrative methods can give significant answers into

already unknown genes and aid in finding new molecular targets of cancer diagnosis and treatment [14][15].

Since the vesicular trafficking regulators may have a role in the oncogenic processes, and little is known about TOM1L2 in cancer, it should be proposed to investigate this gene in a systematic way. The present research aims to explore the patterns of expression and the genomic features of TOM1L2 in various cancers which can help to better understand its biological roles and potentially its role in tumor development. In addition, its applicability to the brain/CNS and colorectal malignancies would aid in understanding whether TOM1L2 is a part of the molecular pathways related to these tumors and whether it is a promising biomarker or drug target [16].

2. MATERIALS AND METHODS

2.1 Data Access

The Cancer Genome Atlas (TCGA) data was accessed through two complementary platforms, cBioPortal for Cancer Genomics (https://www.cbioportal.org/) [14] and Gene Expression Profiling Interactive Analysis (GEPIA) (http://gepia2.cancer-pku.cn/#index). These platforms were used to analyse gene expression, Oncoprint, genetic alteration, and survival analysis of TOM1L2 across different cancer types.

2.2 Data selection

Total 11 studies comprising 101679 samples/100611 patients were selected on cBioPortal platform to study the role of TOM1L2 across different cancer types. Eleven studies are Cancer Therapy and Clonal hematopoiesis (MSK, Nat Genet 2020), China Pan-cancer (OrigiMed, Nature 2022), Metastasis Solid Cancers (UMich, Nature 2017), MSK MetTropism (MSK, Cell 2021), MSK-CHORD (MSK, Nature 2024), MSK-IMPACT Clinical sequencing Cohort (MSK, Nat Med 2017), MSS Mixed Solid Tumors (Broad/Dana-Farber, Nat Genet 2018), Pan-cancer analysis of whole genomes (ICGC/TCGA, Nature 2020), SUMMIT-Neratinib Basket Study (Multi-Institute, Nature 2018), TMB and Immunotherapy (MSK, Nat Genet 2019) and Tumors with TRK fusions (MSK, Clin Cancer Res 2020). For brain/CNS tumor research, 33 studies comprising 10009 samples/9038 patients and for bowel tumor research, 27 studies comprising 9770 samples/9466 patients were selected.

2.3 Gene expression analysis

The Gene Expression Profiling Interactive Analysis 2 (GEPIA2) web server (http://gepia2.cancer-pku.cn/) was used for gene expression analysis for ARHGAP35 that uses the RNA sequencing data from The Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx) projects. The gene symbol “TOM1L2” was subjected to GEPIA2 search and analyzed its expression levels between tumor and normal tissues.

The default GEPIA2 normalization pipeline (log2(TPM +1) transformed RNA-seq data) was used for the expression comparison between tumor and normal tissues. One-way ANOVA was used to perform differential expression analysis in the GEPIA2 platform. Differences between tumor and normal tissues

were considered statistically significant with default cutoff values of |log2 fold change| ≥1 and p-value<0.01.

2.4 Oncoprint analysis

Pan-cancer genomic alteration data were explored and visualized using the cBioPortal for Cancer Genomics. Gene of interest as TOM1L2 was entered into the Query by Gene option to retrieve Oncoprint across all cancer types.

An OncoPrint was generated to visualize the alteration profile of TOM1L2 across tumor samples. In the OncoPrint, each column represented an individual patient sample, while the row corresponded to the TOM1L2 gene. Different color codes were automatically applied by the platform to indicate distinct alteration types such as mis-sense, truncating mutations, gene amplifications, and deep deletions.

2.5 Analysis of distribution of somatic mutations

The distribution of somatic mutations in TOM1L2 across the protein sequence was analyzed using the mutation visualization tools available in cBioPortal for Cancer Genomics. Pan-cancer genomic datasets were queried by entering TOM1L2 in the Query by Gene section of the portal to retrieve somatic mutation data across all tumor samples.

To examine the positional distribution of mutations along the protein sequence, a lollipop plot was generated using the built-in mutation visualization module.

2.6 Analysis of survival prognosis

In cBioPortal, the “comparison” module was used to generate the data on the overall survival of TCGA cases with or without TOM1L2 alteration. Kaplan-Meier plot with log-rank p-value was generated.

2.7 Genetic alteration analysis

The cBioPortal platform was explored and “TOM1L2” was entered for queries of the genetic alteration. Alteration frequency, mutation type, and copy number alteration (CNA) results of all tumors were obtained from the “cancer types summary” module.

3. RESULTS

3.1 Gene expression analysis

The expression level of TOM1L2 in tumor tissues was lower than the corresponding control tissues of notably Bladder Urothelial Carcinoma (BLCA), Cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), Colon adenocarcinoma (COAD), Esophageal carcinoma (ESCA), Glioblastoma multiforme (GBM), Ovarian serous cystadenocarcinoma (OV), Rectum adenocarcinoma READ, Skin Cutaneous Melanoma (SKCM), Testicular Germ Cell Tumors (TGCT), Thyroid carcinoma (THCA), Uterine Corpus Endometrial Carcinoma (UCEC), Uterine Carcinosarcoma (UCS) as shown in Figure 1.

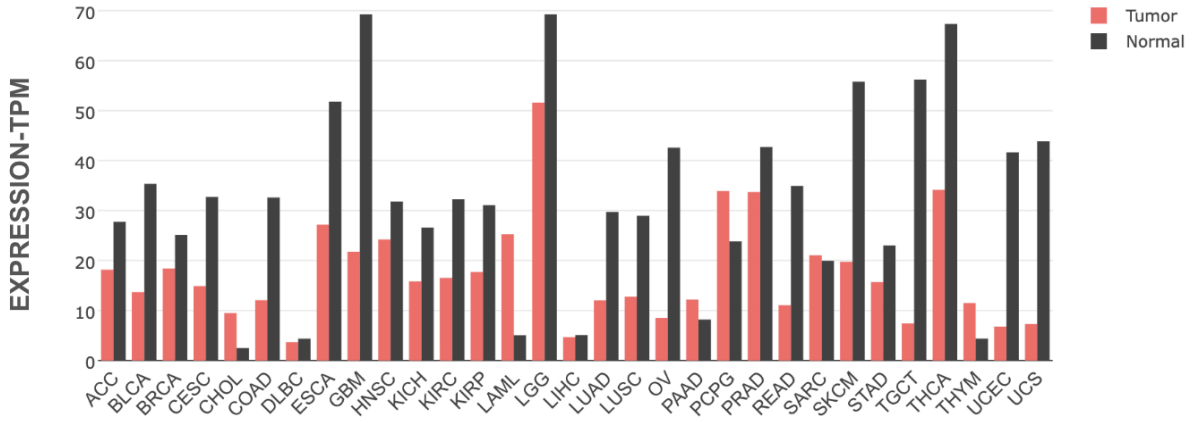

Fig. 1. Gene expression analysis. The bar graph indicates TOM1L2 expression (transcripts per million) in tumor tissues and their corresponding control tissue. The figure was created from GEPIA2.

3.2 Oncoprint analysis

Genomic alterations in TOM1L2 were assessed across multiple pan-cancer datasets using OncoPrint visualization (Figure 2). Overall, alterations in TOM1L2 were rare, occurring in less than 1% of the analyzed samples. The majority of detected events consisted of copy number alterations, including gene amplifications and deep deletions, while point mutations were infrequent. Among the mutations observed, only a few missense variants of unknown significance and rare truncating mutations were detected.

Fig. 2. Oncoprint analysis. Genomic alterations in TOM1L2 across multiple pan-cancer datasets. The figure was created from cBioPortal.

3.3 Genetic alteration analysis

The genetic alteration status of TOM1L2 in different tumor samples of the TCGA cohorts were analyzed. Figure 3 indicates that the highest alteration frequency of TOM1L2 appears for bone cancer patients with "amplification" as the primary type. The "mutation" type of CNA is the primary type in the uterine endometrial carcinoma cases and deep deletion type of CNA is the primary type in lung cancer patients.

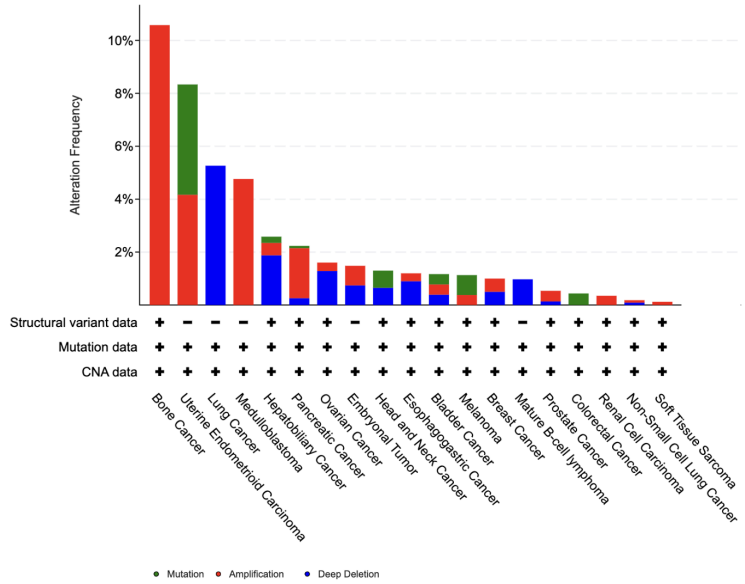

Fig.3 Genetic alteration analysis: The bar graph indicates alteration frequency of TOM1L2 in different cancer types. The figure was created from cBioPortal.

3.4 Analysis of distribution of somatic mutations in TOM1L2

The lollipop plot illustrates the distribution of somatic mutations in TOM1L2 along the protein sequence (507 amino acids) across cancer samples (Figure 4). Mutations are rare and dispersed, with most variants occurring only in single patients. Several mutations are located within the annotated VHS (Vps27/Hrs/STAM) domain at the N-terminal region and the GAT domain in the central region of the protein, suggesting that some variants may affect functional domains involved in intracellular trafficking. There is one common mutation identified as N297T, which is found in the GAT domain. The bottom panel shows predicted post-translational modification (PTM) sites, such as various phosphorylation and ubiquitination sites scattered throughout the protein, some of which overlap or are adjacent to the sites of observed mutation. The exon structure shows that mutations are distributed across several exons rather than clustering within a single exon. Overall, the results suggest that TOM1L2 mutations are infrequent and scattered, with limited evidence of strong hotspot mutations in the analyzed datasets (Figure 4).

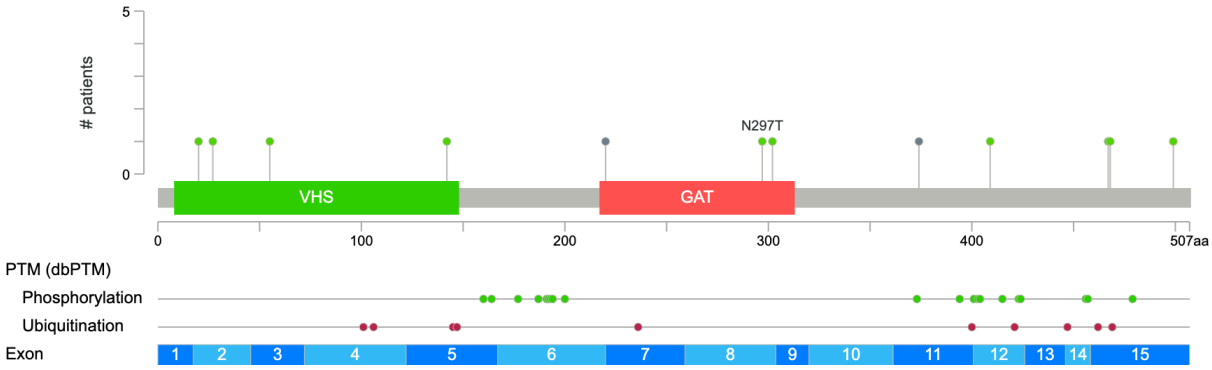

Fig.4 distribution of somatic mutations in TOM1L2: The lollipop plot illustrates the distribution of somatic mutations in TOM1L2 along the protein sequence (507 amino acids) across cancer samples. The figure was created from cBioPortal.

3.5 Analysis of survival prognosis

Figure 5 shows the probability of overall survival in an altered and unaltered group using cBioPortal platform. The median survival of patients in the unaltered group and altered group was 37.04 and 19.74 months respectively. The survival analysis comparing patients with and without TOM1L2 genetic alterations suggested differences in overall survival; however, these findings should be interpreted cautiously because statistical significance was not consistently observed.

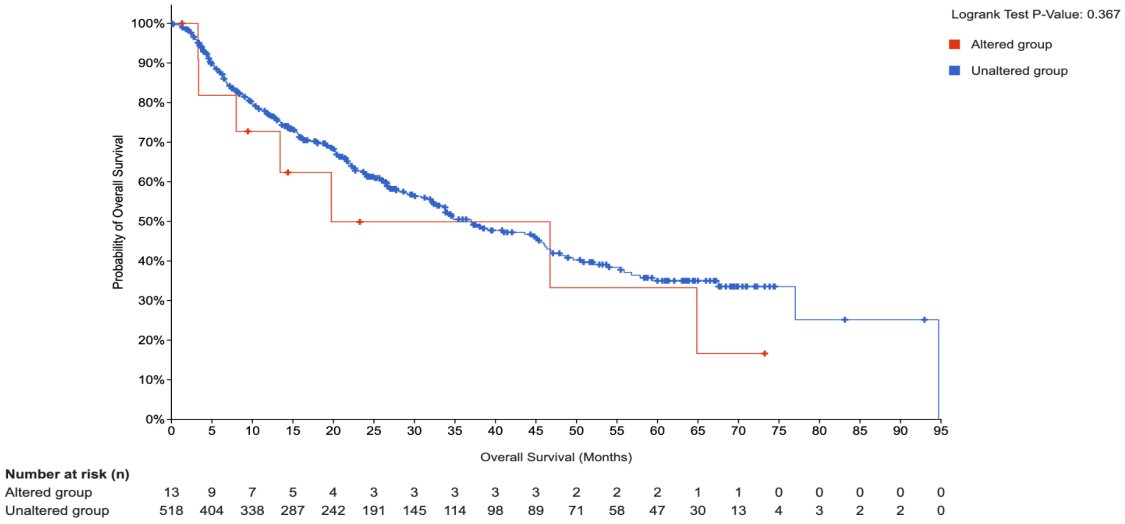

Fig. 5. Analysis of survival prognosis. The Kaplan-Meier plot indicates probability of overall survival in unaltered and altered groups. Logrank test P-value: 0.367 The figure was created from cBioPortal.

3.6 Role of TOM1L2 in brain/CNS related tumors:

The genetic alteration status of TOM1L2 in different brain/CNS related tumor samples of the TCGA cohorts were analyzed. Figure 6 indicates that the highest alteration frequency of TOM1L2 appears for meningioma patients with “deep deletion” as the primary type. The “mutation” type of CNA is the primary type in the glioma, embryonal patients cases. Figure 7 shows the probability of overall survival in an altered and unaltered group using cBioPortal platform. The median survival of patients in the unaltered group and altered group was 24.77 and 10.58 months respectively. The survival analysis comparing TOM1L2-altered and unaltered brain/CNS tumors suggested a trend toward differences in overall survival, although statistical significance was not consistently observed.

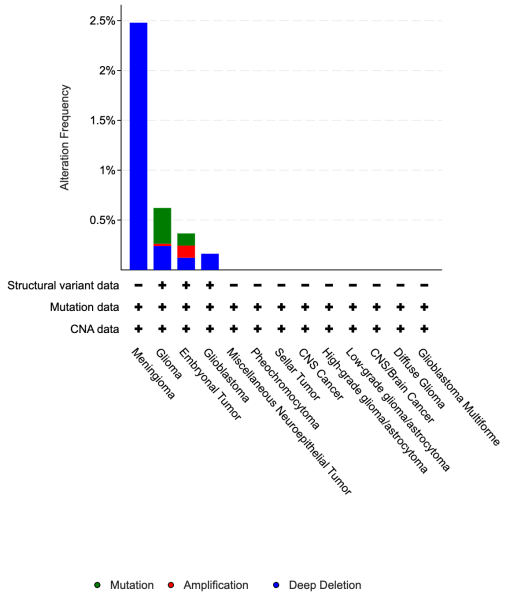

Fig.6 Genetic alteration analysis: The bar graph indicates alteration frequency of TOM1L2 in different brain/CNS related tumor types. The figure was created from cBioPortal.

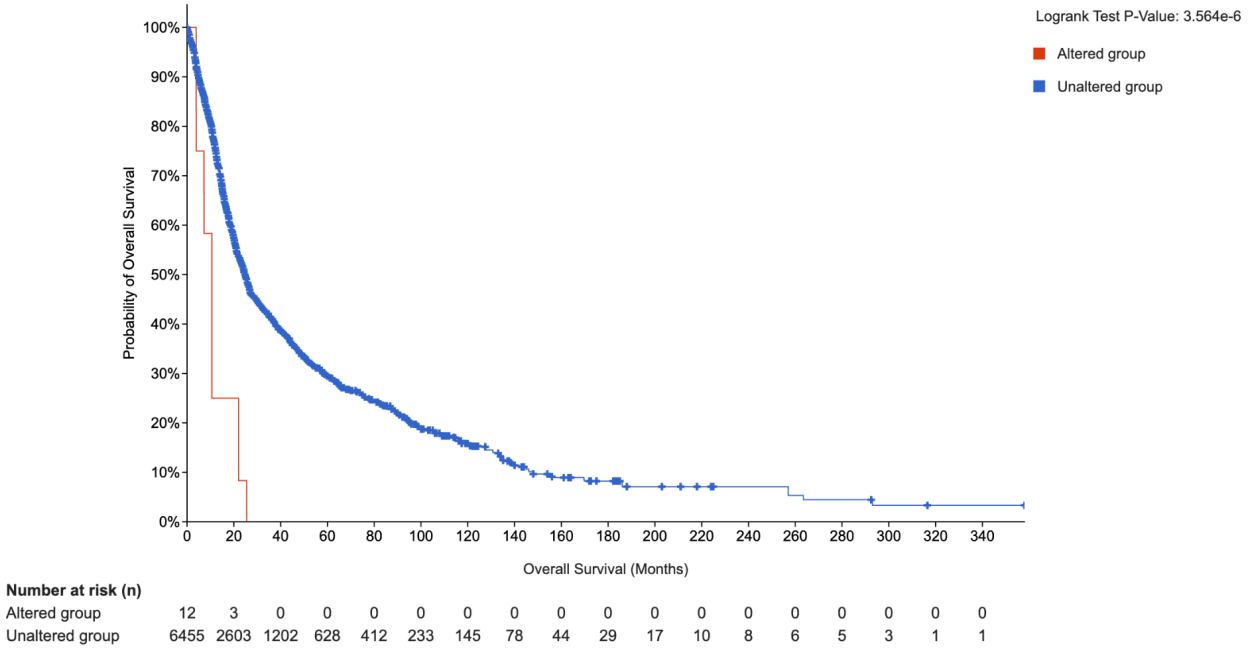

Fig. 7. Analysis of survival prognosis. The Kaplan-Meier plot indicates probability of overall survival in unaltered and altered groups. Logrank test P-value: $3.564e^{-6}$ The figure was created from cBioPortal.

3.7 Role of TOM1L2 in colon related tumors:

The genetic alteration status of TOM1L2 in different colon related tumor samples of the TCGA cohorts were analyzed. Figure 8 indicates that the highest alteration frequency of TOM1L2 appears for pre-cancer colorectal polyps and colorectal cancer patients with "mutation" as the primary type. The "amplification" type of CNA is the secondary type and deep deletion as tertiary type of CNA in the colorectal cancer cases. Figure 9 shows the probability of overall survival in an altered and unaltered group using cBioPortal platform. The median survival of patients in the unaltered group and altered group was 99.93 and 70.11 months respectively. The survival analysis based on TOM1L2 genetic alteration status suggested differences in overall survival between altered and unaltered colorectal tumors; however, these observations require further validation.

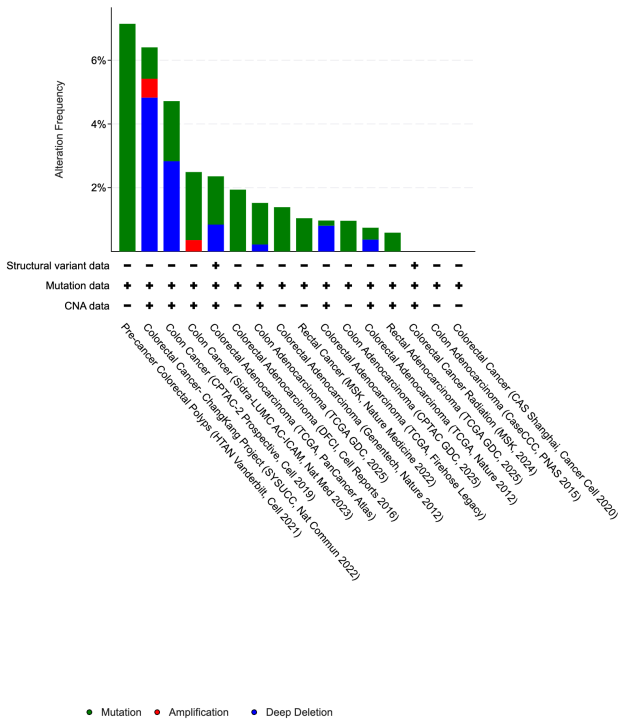

Fig.8 Genetic alteration analysis: The bar graph indicates alteration frequency of TOM1L2 in different colon related tumor types. The figure was created from cBioPortal.

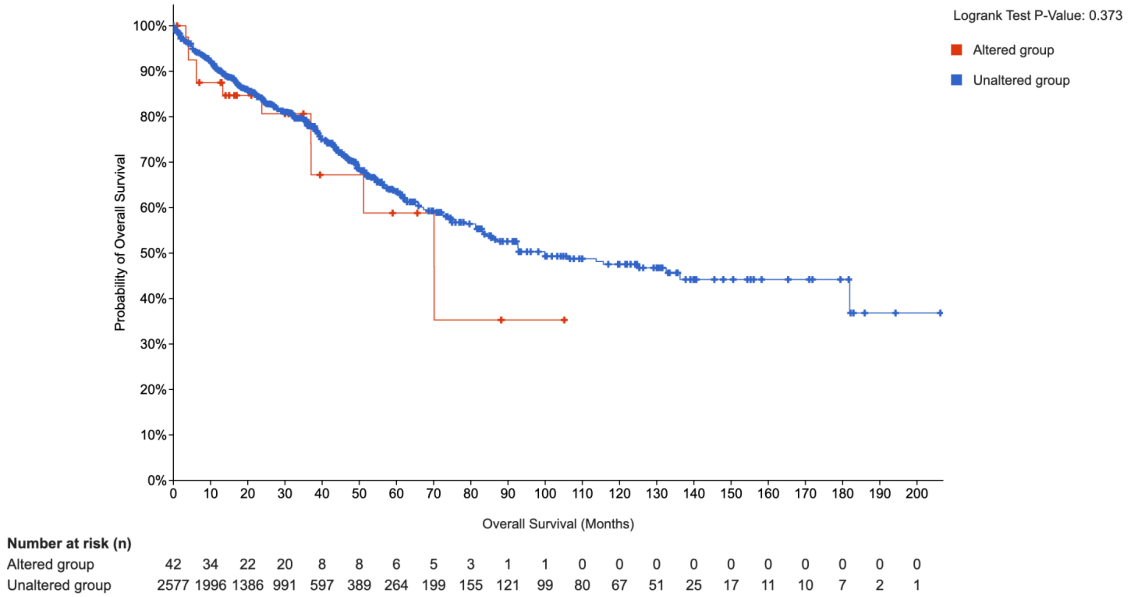

Fig. 9. Analysis of survival prognosis. The Kaplan-Meier plot indicates probability of overall survival in unaltered and altered groups. Logrank test P-value: 0.373 The figure was created from cBioPortal.

4. DISCUSSION

TOM1L2 (TOM1-like protein 2) is a protein belonging to the TOM1 family of adaptor proteins which is involved in intracellular traffic and endosomal sorting. The gene expresses a protein that has VHS domains and GAT domains, which are common structural motifs found in vesicular transport and ubiquitin-mediated processes [17][19]. TOM1L2 is involved with proteins, including clathrin, ubiquitin, and Toll-interacting protein (TOLLIP), which indicate that it plays a role in endosomal dynamics and receptor recycling in cytoplasm [18][19]. The trafficking processes play a critical role in cellular homeostasis, receptor signaling regulation and immune responses regulation. As such, interference with vesicular transportation routes has been gradually becoming an oncogenic transformation factor and tumor evolution [19].

Despite the fact that the biological functions of TOM1L2 have not been fully studied yet, there is evidence of experimental models that it is capable of affecting immune regulation and the predisposition to tumors. Indicatively, hypomorphic TOM1l2 mouse models display elevated incidence of infections and spontaneous tumor development, which show that defective TOM1L2 functions can deteriorate immune functions and lead to tumor development [11]. Localization experiments also indicate that TOM1L2 is associated with Golgi bodies, and it plays a role in intracellular trafficking networks which control cell signalling pathways [9][11]. Other TOM1 family members which are similar vesicular trafficking regulators have also been implicated in cancer progression by regulating membrane receptor signaling and extracellular matrix remodeling [19]. All of these findings are indicative of the possibility that TOM1L2 is a regulating molecule in pathways associated with tumor development.

In the current paper, we examined the possible implication of TOM1L2 in tumorigenesis, especially in brain/CNS and bowel-related cancer. Primary comparisons between tumor and normal tissues revealed that TOM1L2 was differentially expressed suggesting that TOM1L2 may be implicated in the transcriptional alterations associated with tumor formation. Later pan-cancer studies assessing gene expression patterns, genetic changes, Oncoprints, and survival relations showed that TOM1L2 has broad expression in numerous tumor types, which is similar to earlier transcriptomic studies where low cancer specificity but high rates of detection were found in human tissues [20]. Public cancer datasets have also shown that TOM1L2 expression could be associated with patient outcomes of various tumors, including renal, head and neck, pancreatic, and ovarian cancer [20].

Building on these observations, our study further focused on cancers originating from the central nervous system and bowel. Analysis of gene expression showed expression changes in TOM1L2 in a number of CNS tumors and colorectal malignancies indicating that vesicular trafficking process mediated by TOM1L2 can play a role in tumor progression in these tissues. Common mutations and copy number alterations found in the TOM1L2 gene by cBioPortal analysis indicate that changes in the tumor genome are distributed among selected tumor types, but with relatively low frequencies. These genomic changes are different from the differences in gene expression that are found in GEPIA2 analysis and could result in varying biological effects. Similarly, survival analyses were done based on the status of genetic

alteration, not gene expression levels, of TOM1L2. The associations observed should thus be considered as preliminary results, which need to be further investigated at the functional and clinical levels.

We find our result to be in line with the new literature, indicating that genes in vesicular transport and endosomal trafficking play an important role in cancer biology (21,23). The changes in the trafficking pathways could also affect the receptor reuse, the growth-factors and immune modulation-mechanism signals that depend on the centre of tumor growth and dissemination. Genomic studies have also shown fluctuations on the TOM1L2 locus that is associated with numerous physiological traits and metabolic activities suggesting that the gene has a broader regulation role besides vesicular transportation [21][22].

In several cancer cohorts survival analyses showed differences between the medians of the overall survival in altered and unaltered groups, but these results were not always confirmed by log-rank tests with a statistically significant p-value. In conclusion, the present study suggests potential association between TOM1L2 genetic alteration status with clinical outcome but further validation in larger independent cohorts is needed to derive this association as a clinical prognostic.

While our data showed differential changes in TOM1L2 in several tumor types and different types of genetic changes, these results should be analysed cautiously. Genetic changes and changes in gene expression are different biological phenomena, and may play independent roles in tumor formation. Dysregulated expression might be the result of changes in transcription of the specific genes associated with the progression of a tumour, but genetic changes like mutations and copy number alterations are not necessarily associated with changes in gene expression or protein function. Moreover, patients with TOM1L2 alteration showed significant survival difference in various cancer types, although not all survival analyses were statistically significant. Thus, the present results should be considered as indicative of possible associations, and not as proof of TOM1L2 as an independent prognostic biomarker. In view of its known involvement in vesicles trafficking and in endosomal sorting, deregulated TOM1L2 may affect receptor recycling, intracellular signal transduction, ubiquitin-mediated protein trafficking and immune response, all known factors involved in tumor progression. These biological mechanisms are, however, only speculative with regards to the present study, and must be confirmed via functional experiments. Further research combining molecular, cellular and clinical approaches will be key to understanding the contribution of TOM1L2 to tumor initiation and progression as well as its role as a marker of altered cellular trafficking in cancer.

Overall, this study suggests that TOM1L2 may participate in molecular pathways associated with tumor biology. However, the current bioinformatics analyses alone are insufficient to establish TOM1L2 as a prognostic biomarker or functional regulator, and further experimental and clinical validation is warranted. Further experimental and mechanistic studies will be required so as to comprehend the role of TOM1L2-mediated trafficking in tumor biology and whether this gene has the potential to be a diagnostics or therapeutic biomarker in cancer.

5. LIMITATIONS

There are some limitations to this study that should be taken into account when interpreting the results of this study. First, all the analyses were conducted using only publicly available datasets from the TCGA, obtained through GEPIA2 and cBioPortal, with the results therefore not constituting experimental evidence of causality, but rather bioinformatics-based associations. Variations in the biochemical makeup of each sample, sequencing platforms, data processing pipelines, and clinical annotations may also affect the expression pattern and genetic changes observed. The results of the survival analyses should also be viewed with caution because not all trends were statistically significant. Further investigation of TOM1L2 *in vitro* and *in vivo* and larger independent clinical cohorts are needed to confirm the biological and clinical relevance of TOM1L2 as a biomarker and therapeutic target for brain and CRC.

6. CONCLUSION

The present study is an in-depth analysis of TOM1L2 as a potential tumor progression regulator particularly of brain/CNS and bowel cancers. Our findings based on tumor-normal comparison and pan-cancer analyses indicate that TOM1L2 has a different distribution among various types of tumors, which aids in concluding that TOM1L2 is a part of cancer-related molecular pathways. The combination of gene expression profiling and genetic alteration analyses, Oncoprint and survival analysis indicates that TOM1L2 may participate in cancer related molecular pathways. While variations in survival were found in some cohorts, these results were not statistically significant in all cohorts and could only be seen as preliminary findings to be further validated. Mutation and expression patterns are also relevant to support the idea that TOM1L2 changes may affect tumor progression and development of intracellular trafficking and signal transduction pathways. The findings have been in line with the former findings that revealed the applicability of vesicular transport regulators in the process of oncogenesis. Overall, this study identifies TOM1L2 as a candidate biomarker deserving further investigation.

7. FUTURE PERSPECTIVES

Despite the fact that the existing study provides valuable data on the potential role of TOM1L2 in cancer, the areas that can be explored in the future are still numerous. Functional studies are required to assist in revealing the precise molecular pathways through which TOM1L2 influences tumorigenesis, that is, the impact of TOM1L2 on vesicular transport, receptor-recycling and immunological signal-transduction. *In vitro* tests using models such as knockdown and overexpression of TOM1L2 in the brain and the colorectal cancer cell model, would help define its impact on cell proliferation, migration, invasion, and apoptosis. In addition, the animal models and *in vivo* experiments, would also lead to improved insights into the biological implication of the TOM1L2 dysregulation in the developing tumor. Integrating multi-omics measures, including proteomics and single-cell transcriptomics, might reveal a higher number of regulatory networks that are associated with TOM1L2. Future studies involving larger independent cohorts should determine whether TOM1L2 possesses independent prognostic value after

appropriate statistical validation. Collectively, these studies can be used to establish TOM1L2 as a clinically applicable biomarker and therapeutic target of brain and bowel malignancies.

Author's contributions
AV conceptualised the study, did literature survey, carried out bioinformatics analysis, analysed data, wrote and corrected the manuscript.

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Conflict of interest
There is no potential conflict of interest to disclose.

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