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Meta-analysis of functional expression and mutational analysis of c-Met in various cancers

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ABSTRACT

Comprehensive genomic profiling is expected to revolutionize cancer therapy. c-Met signaling is responsible for tumorigenesis in various cancers. In this prospective, we present the prevalence of c-Met mutations and copy number alterations across various solid tumors. We used major databases like cBioportal, PubMed, and COSMIC for c-Met mutation and amplification data collection from various cancers. Our result shows complete details about c-Met mutation and its clinical data of various cancers. Hotspot mutation of human c-Met protein reveals that repeatedly and most mutated regions and these hotspots may be a diagnostic tool for cancer confirmation. Amino acid and nucleotide changes and their prevalence were reported in a number of individual cancers. However, we collectively present the amino acid and nucleotide changes in various cancers in this review. Our collection of data for c-Met mutation and its distribution in different cancer tissue is showing that the missense mutation is the major one in all type of cancers. Copy number

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variation data showing amplification and deletion of human c-Met from various tumor types, lung and central nervous system tumors showing high amplification comparatively other types.

ARTICLE INFO

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Introduction

The human c-Met was first identified in the early 1980s, in a human osteosarcoma cell line treated with the *N*-methyl-*N*-nitro-*N*-nitrosoguanidine on the basis of its transforming, which caused by a gene rearrangement where sequences from the promoter region (TPR) of chromosome 1 were translocated to Met sequence on chromosome 7 (TPR-Met).[1] Met is a receptor tyrosine kinases (RTKs) and are normally direct many vital cellular progressions including cell proliferation, survival, motility, invasion and morphogenesis, wound healing, and tissue homeostasis. This RTK gene is expressed in epithelial cells of many organs during both embryogenesis and adulthood.[2,3] It is normally stimulated by its distinct natural ligand hepatocyte growth factor (HGF) is a scatter factor (SF) located on chromosome 7q21-31, which provoke different phenotypes of cell proliferation and angiogenesis, forming micrometastases, and clear metastases in cancer.[2,4]

Expression of c-Met and HGF has been observed in several solid tumors and its signaling has been documented in different types of malignancies.[2,5] Various alterations occurred in this gene which includes gene amplification, protein overexpression, and mutations of this gene in juxtamembrane and semaphoring domains.[6-8] Aberrant c-Met signaling is involved in the progression and extends of several cancers, and this has led to the development of a variety of c-Met pathway antagonists with potential clinical applications. Pathway-selective anticancer drug development is an important method to target the gene; it is of 3 types included antagonism of ligand/receptor interaction, inhibition of RTK catalytic activity, and obstruction of the receptor/effectors interaction.[7] Several c-Met antagonists are now under clinical investigation; however, the RTK-targeted agents such as trastuzumab, imatinib, Tivantinib, Capecitabine, bevacizumab, crizotinib, cabozantinib, and gefitinib inhibit this protein for the treatment of selected cancers.[9-12] c-Met as a potential therapeutic target, using small interfering RNA (siRNA) downregulation of the receptor expression by above 50% in NSCLC cells,[13] and additionally siRNA combined with other targeted drugs can give important insights into the biological roles of c-Met and HGF.[14]

Currently, several early-stage clinical targeting agents of c-Met were rising and entirely changed treatment approach. In the present study, we performed an in-depth analysis of c-Met in cancer and we used 3 databases (cBioportal and COSMIC and PubMed) which provides exploring, visualizing, and multidimensional analyzing of cancer genomic data, and an easily understandable molecular profiling data of clinical preclinical primary and metastatic tissues and also cell lines.

C-met structure and its function

The c-MET is a proto-oncogene primarily occurs in epithelial-derived cells of different organs including hepatocytes, renal tubule cells, gastric, and intestinal epithelium.[15] The transcription of the c-Met gene is regulated by E-twenty six (Ets), paired box 3 (Pax3), activator protein-2 (AP2), and transcription factor 4 (Tcf-4),[16,17] and is expressed as multiple mRNA transcripts.[18] Finally, it produces the protein c-Met tyrosine kinase. It mostly expressed in many organs like liver, pancreas, prostate, kidney muscle, and bone marrow. Its receptor is initially formed as a

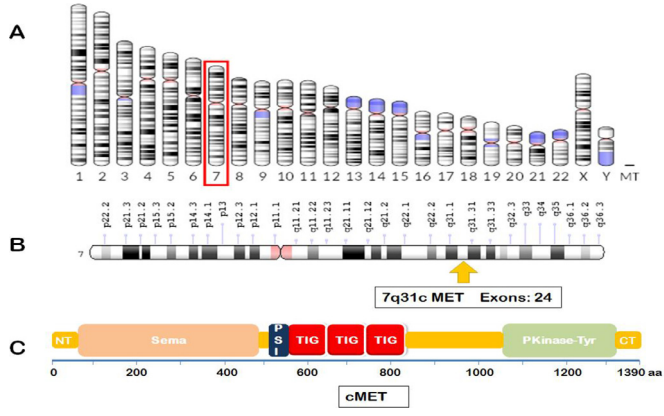


Fig. 1. c-Met structure and its location in chromosomes. (A) shows 24 chromosomes included sex chromosomes and the seventh chromosome was highlighted. (B) A seventh chromosome and the arrow mark point out c-Met gene position within the chromosome. (C) c-Met protein structure. Sema, semaphorin domain; PSI, plexin semaphorin integrin; IPT, immunoglobulin plexin transcription; PKinase-Tyr, tyrosine kinase catalytic domain; AA, amino acid; NT, N terminal; CT, C terminal.

single-chain precursor; it proteolytically cleaved at a furin site finally to shape disulfide-linked extracellular α-subunit and a transmembrane β-subunit.[2] The extracellular region of c-Met is comprised of 3 domains, the large N-terminal semaphoring (Sema) contain α and β subunit, the plexin semaphorin integrin (PSI) connected to the Sema, and PSI is joined to the transcription factor immunoglobulin (TIG), which are related to immunoglobulin-like domains. The intracellular portion of the protein encloses a tyrosine kinase catalytic domain. The domain of the cytoplasmic tyrosine kinase possesses key serine and tyrosine phosphorylation sites that are the key in the conscription of SRC-homology-2-domain (SH2) comprise signaling transducers and intermediaries. The stromal and mesenchymal cells producing HGF is a ligand of c-Met, which promotes cell proliferation, survival, motility, dispersion, and morphogenesis, and in addition, it plays a defensive role in various syndromes. The HGF is an initially inert precursor when the extracellular proteases cleave the bond between Arg494 and Val495 is transformed into biologically active form. The matured HGF consists α and β chains; however, α chain is comprised N-terminal hairpin loop followed by 4 kringle domains, and connected with the β chain it is homologous to serine proteases, these 2 chains are held together by a disulfide bond. c-Met location in chromosome 7 and its structural schema (Fig 1).

The Met receptor and HGF ligand are normally expressed in several tissues in an adult. HGF binding to c-Met and autophosphorylation takes place within the cytoplasmic domain by using intrinsic ATPase. In this result, c-Met assisting the development of protein GAB1 and GRB2 is the signaling complex that activates multiple downstream pathways and different effectors molecules involved in this signaling cascade. The c-Met-mediated pathway positively influences proliferation, migration, and survival of cells. In early embryogenic stage, HGF and c-Met are co-expressed by progenitor cells, suggesting signaling of autocrine is a homeostatic mechanism for stem cell survival.[19] Although, the Met signaling is crucial for the growth and survival of placental trophoblast cells, embryonic hepatocytes, migration of muscle progenitor cells, and embryonic nervous system formation.[15,16] and latterly signaling play a critical role in organogenesis. HGF-Met signaling has a major role in inflammation and wound healing of several injuries. Essentially, the HGF-c-Met signaling incriminates to the protection, regeneration, and antifibrotic activity of several tissues in response to injury. In the pancreas, the beta cells responsible for insulin secretion which dependent on HGF-Met signaling. Generally, the HGF-Met signaling pathway promotes pancreatic beta cell proliferation and development.

HGF/SF and met in tumorigenesis

Tumorigenesis is a multistep progression that induces different phenotypes like cell proliferation and angiogenesis in primary tumors; motivating need a sequential selection of specific malignant phenotypes triggering motility to form metastasis.[4] The HGF and c-Met interaction can leads to initiate several downstream signaling pathways and tumor progressions. Zhang et al[20] discussed in detail about the HGF/c-Met aberrant activation and some c-Met-associated interlinked genes (PI3K/AKT, Ras/MAPK, JAK/STAT, SRC, Wnt/β-catenin, EGFR, and RON) which are involved in signaling pathways and tumor progression. Consequently, c-Met-associated gene signaling pathways are clinically more important therapeutic targets in various cancers. c-Met pathway interconnected with other signaling pathways are included HER2 family and vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR).[21] c-Met and HER family members interacted tumors acquired resistance to treatment and increased mechanism of tumor progression, and the signaling with VEGF A promotes angiogenesis and endothelial cell growth. PAX5 (paired box) gene is a nuclear transcription factor and its expression was studied in pancreatic and upper aerodigestive cancer by immunoblotting. In small-cell lung cancer (SCLC), the PAX5 expression was relatively strong and regulates the transcription of c-Met and a potential target for therapy in SCLC.[22] Therefore, the c-Met has become an attractive potential target for cancer therapy.[23]

Deregulation of Met pathway occurs in human tumors by various mechanisms like amplification, translocation, and point mutations or overexpression[2,24] and it causative to malignant transformation and metastasis. Soman et al[25] found that the TPR-MET translocation in primary gastric tumor and adjacent normal mucosa, this result suggests this genetic lesion may predispose to the development of gastric carcinomas. Gene amplification with consequent protein overexpression and constitutive kinase activation of c-Met has been reported in several human primary and metastatic tumors include liver metastases from colon cancer,[26] oesophageal,[27,28] medulloblastomas,[29] papillary renal cancer,[30] and predominantly in gastric and lung cancers.[31,32] One evidence showing that c-Met kinase domain with both sporadic and inherited forms of human renal papillary carcinomas.[33,34] Researchers found a mutation in the juxtamembrane domain and Sema domain.[35,36] A number of the literature confirmed that the overexpression and amplification of c-Met in non–small-cell lung cancer (NSCLC).[37-39] Lung cancer subtype of adenocarcinomas and female patients has frequent c-Met overexpression; however, its expression is associated with the epidermal growth factor receptor (EGFR) signaling cascade.[40,38,41]

Materials and methods

Databases and patient data

We scrutinized some public open-access databases and mainly the cBioPortal (http://www.cbioportal.org/public-portal/) and Catalogue of Somatic Mutations (COSMIC) (http://cancer.sanger.ac.uk/cosmic) provide a large scale human cancer genome datasets.[35,42-44] The cBioportal comprise comprehensive integrated genome data from The Cancer Genome Atlas (TCGA; http://cancergenome.nih.gov/), The Wellcome Trust Sanger Institute's Cancer Genome Project (http://www.sanger.ac.uk/research/projects/cancergenome/), The Cancer Genomics Hub (CGHub; https://cghub.ucsc.edu/), and the International Cancer Genome Consortium (ICGC https://icgc.org/). Especially, the TCGA is collaborative with the National Cancer Institute (NCI; http://www.cancer.gov/) and the National Human Genome Research Institute (NHGRI; https://www.genome.gov/) and publically available. These containing copious of genomic data and this genomic information assist to improve the cancer research community. These databases encompass publications, reporting large-scale genome screening data and imported data from other databases such as TCGA, ICGC etc., and also provide molecular profiling and finding of novel driver genes in cancer. In these databases, the c-Met gene was uploaded to search for patients' clinical cancer data

like personal information, mutations, and other related changes in all cancer studies. There are 78,842 tumor samples were analyzed and 1303 c-Met mutation were identified from various cancers. Patient's clinical data (age, gender, race, smoking history, tissue, and vital status) also collected from c-Met-mutated samples. However, some patient's data are not completely provided; there is paucity of all the information in the databases.

Biocomputational data and cell signaling network analyses

The National Center for Biotechnology Information (NCBI) (http://www.ncbi.nlm.nih.gov) is a gene database, it was used for identification of official gene symbols and basic gene functions. STRING is a biological search tool for the retrieval of interacting genes/proteins (at http://string-db.org/; default mode), here we used this for cell signaling pathway analysis.[45] When we input our desired gene symbol into the tool that provides interlinked genes with gene signaling.

Results

c-Met mutation analysis from different types of cancer

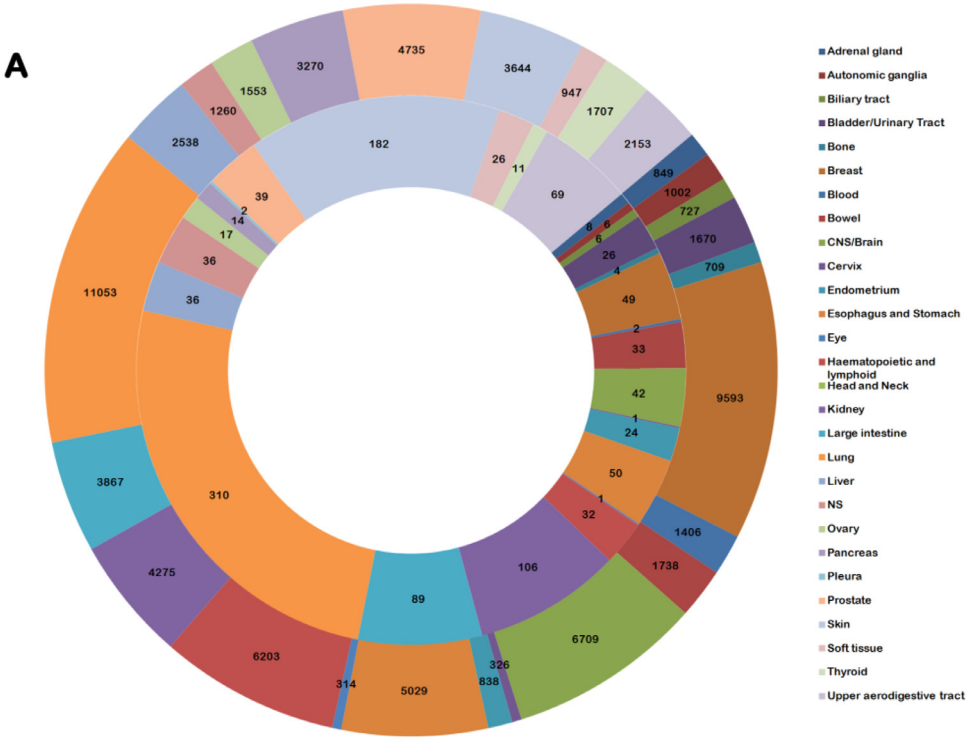
cBioportal, COSMIC and PubMed to analyzed various cancer types and specifically for c-Met mutation and these databases comprises 78,842 patients samples, in that 1303 (about 2%) patients samples had detected c-Met mutations (Fig 2A). The outer circle shows different cancer with the total sample in number, particularly the lung has the highest number of analyzed samples (11,053) and within this 310 Met mutation was identified followed by skin 3644 cases with 182 mutations and kidney had 4275 cases with 123 mutations. Other cancers have a lower number of c-Met mutation comparatively to these 3 cancers. From patients' data, we collected the gender wise mutation data, comparatively male is highly affected by cancer with c-Met mutation than female. Some gender-specific cancer like bladder (19) and prostate (42) in male and breast (49) endometrium (31), and ovary in female (26) were also mutated. Overall lung and skin cancer highly mutated by a c-Met mutation in both the sex (Fig 2B). However, in this database, many patients' history data are not included or not available.

The clinical characteristics like sex, age, race, smoking status, histology, and performance or living status were analyzed in c-Met-mutated cancer cases. However, the databases have too little-registered data of patient's performance or living status and other details. Table 1 shows that the mean ages of several cancers are above 50 and a few cancers are below 50. The race category evinces white people are greatly affected by c-Met mutation followed by the Black, Asian, and other categories (Table 1).

Tumor characteristics of various cancer types

Tumor characteristics are summarized in Table 2. Tumor types and stage of cancer is associated with the patient's outcome. Several primary tumor samples, some metastatic samples, and cultured cells were analyzed for c-Met mutation. In a tumor, stage analysis reveals that mostly the second-, third-, and fourth-stage tumor samples are having a higher c-Met mutation and few stages I samples also have the mutation.

In this study, we performed a tissue-specific distribution analysis of various types of c-Met mutations in different types of cancer (Table 3). Overall, we observed the missense mutation is highly present in the large intestine (171), lung cancer (159), and kidney (110) and all other types of cancer except endometrium, lymph, eye, and esophagus. The other mutations like nonsense, insertion, deletion, duplication, synonymous, nonsynonymous, splice site or Un-Translated Region (UTR) and Exon14skip are slightly mutated in all cancers. Table 4 summarized



B

MALE		FEMALE	
Adrenal gland	5	2	Adrenal gland
Bladder/Urinary Tract	19	1	Autonomic ganglia
Bowel	9	1	Bone
CNS/ Brain	24	15	Bowel
Esophagus and Stomach	42	49	Breast
Head and Neck	7	21	CNS/ Brain
Kidney	54	31	Endometrium
Large intestine	32	15	Esophagus and Stomach
Liver	22	2	Head and Neck
Lung	116	29	Kidney
Lymph	2	22	Large intestine
NS	13	11	Liver
Pancreas	6	147	Lung
Prostate	42	5	NS
Skin	95	26	Ovary
Soft tissue	7	5	Pancreas
Upper aerodigestive tract	42	34	Skin
		9	Upper aerodigestive tract
		4	Urinary Tract

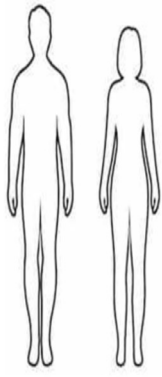


Fig. 2. c-Met mutation analysis from different types of cancer. (A) Outer circle showing a total number of sample analyzed for c-Met mutation to every cancer and the inner circle showing the number of c-Met mutation identified within the tissue types. Comparatively, these 3 cancers (lung cancer 310 mutations from 11,053 samples, skin 182 mutations from 3644 samples, and kidney 106 mutations from 4275 sample) are highly mutated with c-Met. (B) c-Met mutational frequencies of male and female; clinical data of various types of cancer patients with c-Met mutation in male and female; numbers indicate number of c-Met mutation in male and female on specific cancer tissue both the sex (male 116 and female 147) in lung cancer mostly altered by c-Met and skin cancer in male (95) having high mutation. CNS, central nervous system; NS, not specified.

Table 1
Summary of patient's history and tumor clinical characteristics of c-Met mutated various cancer types

Patients characteristics	Autonomic ganglia	Adrenal gland	Bladder/ urinary tract	Breast	Bowel	CNS/ brain	Head and neck	Endometrium	Esophagus/ stomach	Large intestine	Kidney	Liver	Lung	Lymph	NS	Ovary	Pancreas	Prostate	Skin	Soft tissue	Upper aerodigestive	Urinary tract
Total number	0	0	0	49	33	52	12	32	77	86	121	45	310	2	39	26	19	42	219	0	70	13
Sex	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Male	0	5	19	0	9	24	7	0	42	32	54	22	116	2	13	0	6	42	95	7	42	3
Female	1	2	0	49	15	21	2	31	15	22	29	11	147	0	5	26	5	0	34	0	9	1
Not reported	0	0	0	0	9	0	0	0	0	0	0	0	47	0	0	0	0	0		0	0	0
Age	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mean	42	52.3	0	52.1	69.4	41.3	63.7	55.7	64.7	58.4	63.3	56.5	65.2	40	52	0	66.1	69.2	0	56.7	0	0
Race	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0	0	0
White	0	0	1	8	0	9	7	0	15	0	22	0	42	2	1	2	6	2	25	0	0	0
Black	0	0	0	0	0	1	0	0	0	0	2	0	2	0	0	1	0	0	0	0	0	0
Asian	0	0	0	1	0	0	0	0	6	7	0	1	19	0	0	3	0	0	2	0	0	0
Irish	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	0	0	0
Other	0	0	3	0	0	0	0	0	4	0	0	0	1	0	0	0	0	0	0	0	0	0
Unknown	0	0	0	0	0	0	0	0	0	0	0	0	246	0	0	0	0	0	0	0	0	0
Smoking status	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Smoker	0	0	0	0	0	0	0	0	0	0	0	0	78	0	0	0	0	0	0	0	0	0
Ex smoker	0	0	0	0	0	0	0	0	0	0	0	0	56	0	0	0	0	0	0	0	0	0
Never smoker	0	0	0	0	0	0	0	0	0	0	0	0	81	0	0	0	0	0	0	0	0	0
Unknown	0	0	0	0	0	0	0	0	0	0	0	0	95	0	0	0	0	0	0	0	0	0
Histology	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Adeno carcinoma	0	0	0	0	27	0	0	0	28	85	0	0	170	0	1	0	0	12	0	0	1	0
Squamous cell carcinoma	0	0	0	0	0	0	0	0	7	0	0	0	19	0	0	0	0	0	0	0	65	0
NSCLC NOS	0	0	0	0	0	0	0	0	0	0	0	0	94	0	0	0	0	0	0	0	0	0
Small-cell lung cancer	0	0	0	0	0	0	0	0	0	0	0	0	16	0	0	0	0	0	0	0	0	0
Papillary renal cell carcinoma	0	0	0	0	0	0	0	0	0	0	46	0	0	0	0	0	0	0	0	0	0	0
Living	0	0	6	0	5	6	8	0	20	0	26	1	0	1	0	3	0	0	20	0	0	0
Dead	0	0	3	0	0	5	1	0	6	0	5	1	0	1	0	2	0		20	0	0	0

CNS, central nervous system; NSCLC, non–small-cell lung cancer; NS, not specified; LCC, large cell carcinoma.
The number denotes c-Met-mutated patients' characteristics number. The table displaying the c-Met-mutated patient's history data like sex, age, race, smoking status, tumor histology, and patient's performance status) of various cancer tissue. Comparatively, the mean ages in most of the cancers are above 50 and in few cancers, it is below 50. In the race category, the white people are highly affected by c-Met mutation specifically in lung cancer (42), skin (25), and kidney (22) followed by the Black, Asian, and other categories. Smoking status of lung cancer shows smoker (78), ex-smoker (56), and ever smoker (81).

Table 2
Summary of the c-Met-mutated cancer with clinical characteristics include sample type (tumor number and cultured cells number), tissue type and its stages

Cancer types	Sample types		Tumor types		Stage				
	Tumor #	Cultured cells #	Primary tumor #	Metastasis #	IA #	IB #	II (A&B) #	III (A&B) #	IV #
Biliary tract	0	0	0	0	1	0	0	1	0
Bladder/urinary tract	0	0	10	0	0	0	1	5	0
Breast	23	0	27	8	1		15	1	0
Bone	2	1	0	0	0	0	0	0	0
Bowel	0	0	0	0	0	0	1	0	1
CNS/brain	25	0	22	2	0	0	1	0	0
Head and neck	0	0	5	0	0	0	0	2	2
Hematopoietic and lymphoid	15	3	7	1	0	0	1	0	0
Endometrium	32	0	31	0	0	0	0	0	0
Esophagus/stomach	21	0	23	3	0	0	16	16	2
Large intestine	45	17	23	18	1	0	17	1	3
Kidney	53	3	57	1	17	0	2	7	2
Lung	176	7	110	36 (recurrent 9)	34	39	15	27	26
Lymph	0	0	2	0	0	0	1	0	1
NS	32	7	1	16	0	0	0	0	0
Ovary	11	0	12	0	0	0	2	5	2
Pancreas	8	0	11	0	0	0	7	0	0
Prostate	17	0	13	18	0	0	0	0	0
Skin	104	8	24	58 (recurred 3)	2	0	8	13	2
Soft tissue	71	2	2	0	0	0	0	0	0
Upper aerodigestive tract	31	0	2	3	0	0	0	0	0

Sample types; there are 2 sample types one is a tumor and the other is cultured samples, most of the sample are tumor types and cultured samples are few comparatively with all cancers. Tumors are categorized into 2 types: primary and metastatic tumor; comparatively, the primary tumor samples were largely analyzed for c-Met mutation and few metastatic cancer tissues also analyzed. The stages data reveal II, III, and IV stage tumors with c-Met mutations occur in most of the cancer. The number indicates a number of samples within cancer types.

the c-Met amplification or copy number variation (CNV) data from various cancer. There are 14466 cancer cases were studied within this 186 cases confirmed with c-Met amplification. Tissue wise the CNS/brain, esophagus & stomach, Kidney, lung and skin were highly altered with amplification.

In base pair substitution data lung and kidney tissues were showing more or less all the base pair substitution mutation; notably in the skin and soft tissues has higher C > T and G > A base pair substitutions (Fig 3A). However, some tissues have very low nucleotide substitution. Overall, in all cancer comparatively G ≥ A, 25% followed by C ≥ T 23% and other showing the lower percentage (Fig 3B).

With better knowledge and understanding of c-Met mutations, we searched the overall amino acid (AA) changes in across various cancers. Most strikingly, in lung and skin, cancer has highly altered amino acids, and in lung leucine (L) (61) and skin proline (P) (31) cases (Fig 4A). Overall analysis of all cancer we found that 11% of cases with Leucine AA alteration, followed by Arginine (R) (8%), Threonine (T) (8%), Serine (S) (7%), valine (V), and Proline equally (6%) other AA alteration showing five or below five percentage of mutation (Fig 4B).

The protein comprises extra and the intracellular region called domains; here, we observed some regions of the protein were repeatedly or highly mutated that regions called as hotspots mutation (Fig 5). Consequently, Sema and protein kinase domains were highly mutated in all cancer so these 2 domains are the main hotspot for c-Met mutation, and other regions also slightly mutated. Overall, the result shows all regions of c-Met comprise mutation.

The c-Met interacting signaling network partners provide possible mechanisms involved in tumorigenesis. STRING is a network analysis database; it provides protein-protein interactions

Table 3
Various types of c-Met mutations in tissue-specific malignancies

Tumor types	Missense #	Nonsense #	Insertion #	Deletion #	Synonymous #	Splice site/UTR #	Exon14skip #
Autonomic ganglia	6	0	0	0	0	0	0
Adrenal gland	8	0	0	0	0	0	0
Biliary tract	5	0	0	0	0	0	0
Bladder/ urinary tract	23	2	1	0	4	1	0
Blood	2	0	0	0	0	0	0
Breast	43	2	3	6	9	2	0
Bone	3	0	0	0	0	0	0
Bowel	27	4	0	1	0	0	0
CNS/brain	41	7	2	0	6	1	0
Head and neck	8	0	0	1	0	1	2
Hematopoietic and lymphoid	29	0	0	0	7	0	0
Cervix	23	3	0	0	0	0	0
Endometrium	0	0	0	0	6	0	0
Esophagus/ stomach	41	17	5	3	14	4	0
Large intestine	171	1	5	2	18	0	0
Eye	0	1	0	0	0	0	0
Kidney	110	3	3	0	3	2	0
Liver	34	2	0	0	8	0	0
Lung	159	5	3	65	25	42	3
Lymph	0	0	0	0	0	0	0
NS	28	1	0	4	1	0	0
Esophagus	0	0	0	0	0	0	0
Ovary	24	0	0	0	2	0	0
Pancreas	16	0	0	0	3	0	0
Pleura	2	0	0	0	0	0	0
Prostate	39	8	2	0	2	1	0
Skin	158	9	1	0	40	2	0
Soft tissue	8	0	0	0	66	0	0
Upper aerodigestive	68	0	0	0	2	0	0

An overview of the types of mutation observed within the c-Met-mutated cancer types; numbers indicate that the number of cases within cancer with types of mutation. Comparatively, the missense mutation is highly present in the large intestine (171), lung cancer (159), and kidney (110) and all other types of cancer. The other mutations like nonsense, insertion, deletion, duplication, synonymous, nonsynonymous, splice site or UTR, Exon14skip (exon14 skipping), and others are very less in all cancers. Exon 14 skipping present in lung and head and neck cancer, respectively (3 and 2).

in both physical and functional. Hence, we used a STRING to demonstrate various networking between c-Met protein (Fig 6). Table 5 demonstrates the interlinked genes names and its functions.

Table 6 summarized the recent clinical study of patients' with c-Met alteration, clinical characteristics', and its treatment and outcomes in different cancers. c-Met mutation and higher expression were mostly identified at late stage in all cancers, it strongly states that c-Met alteration highly involve in tumor progression. Overall, this data reviewed from recent literature and it comprises the complete results of the individual article which related to the patients' with c-Met alteration, treatment outcomes, and other characteristics. The higher expression of c-Met or pc-Met was showed less PFS and OS rate comparatively to the lower expression in different cancers treated with various drugs. Many studies evaluated that the exon-14 Skip was highly occurred in lung cancer and which acquired resistance to dual ALK and c-Met inhibitor crizotinib and other drugs. Majorly EGFR and HER2 genes are mutated in c-Met altered or overexpressed cancers. Overall data showed that the c-Met amplification present in almost various Met positive cancers. The currently used targeted therapy (single and combination) highlighted with their status in clinical trials. Overall, the clinical data are revealing possible mechanism

Table 4
cMet amplification/copy number variations in various (CNV) cancer tissue types

Cancer type	Total # of cases across the study/ies	# of cases with CNV & Gain:Loss	Gender (M/F) #	Mean age
Total #	14466	186	128	
Adrenal gland	268	1 & 1:0		
Bladder/urinary tract	419	3 & 3:0	F3	61
Bone	170	1 & 1:0		
Breast	1544	10 & 6:4	F10	58.8
CNS/brain	1093	30 & 30:0	M13&F16	54.55
Cervix	313	1 & 1:0	F1	51
Endometrium	598	3 & 2:1	F2	62.5
Esophagus and stomach	1000	23 & 22:1	M7&F8	59.13
Hematopoietic and lymphoid	819	1 & 0:1	M1	59
Kidney	1027	20 & 20:0	M14&F4	58.94
Large intestine	771	5 & 5:0	M3&F2	67.8
Lung	1185	34 & 33:1	M22&F11	62.03
Liver	871	9 & 9:0	M7&F2	59.55
Ovary	729	4 & 4:0	F4	54.75
Pancreas	835	2 & 2:0		
Prostate	696	2 & 2:0	M2	70
Skin	630	24 & 24:0	M18&F6	59.75
Soft tissue	277	3 & 2:1	M1&F1	
Thyroid	506	1 & 1:0	F1	42
Upper aerodigestive tract	563	4 & 4:0	M3&F1	68
Testis	152	1 & 1:0	M1	

Minor allele: the number of copies of the least frequent allele, for example, if ABB, minor allele = A (1 copy) and major allele = B (2 copies), copy number: the sum of the major and minor allele counts, for example, if ABB, copy number = 3, gain: average genome ploidy $\leq$ 2.7 and total copy number $\geq$ 5 or average genome ploidy $>$ 2.7 and total copy number $\geq$ 9, loss: average genome ploidy $\leq$ 2.7 and total copy number = 0 or average genome ploidy $>$ 2.7 and total copy number $<$ (average genome ploidy $-$ 2.7). CNVs are included high-level amplifications or homozygous deletions. There are 14,466 tumor samples from various cancers were analyzed for CNV within this 186 samples with CNV, and amplification (gain) highly occurs and loss is lesser in number. Male has high CNV compared with a female, and mean age is above 50 in almost all cancer.

of resistant to c-Met-targeted drugs. However, new approaches for the standard treatment of c-Met-derived cancers are very essential to extend or save lives.

Discussion

In the present study, we explored in detail the role of c-Met mutant in various types of cancer. We report comprehensive details of c-Met mutation in various cancers for this we used the 2 large open-access databases. In these databases, we collected details of c-Met mutation in various cancer types which comprised 1303 c-Met mutation from 78,842 tumor samples (Fig 2A).

Our tumor stage findings were showed higher metastatic stage in skin cancer (58), lung cancer (36), and other cancers include large intestine, prostate, NS, and breast (18:18:16:8), and the late stage III and IV showed maximum patients in all cancer. Comparatively the late stage and metastatic tumor is higher than in early stage our result suggesting that the c-Met has lesser role in tumor development and more in progression (Table 2). Previous studies also evaluated and confirmed that the c-Met alteration to involve in tumor progression.[20,46] Patients with head and neck squamous cell metastatic cancer and higher HGF/c-Met expression correlated with worse outcome, when treated with a cetuximab-based regimen.[47] Many studies reported that the patients with advanced stage cancer correlated with worst prognosis.[48-50]

Table 5
c-Met-interlinked genes and its function in normal cell regulation

Gene symbol	Gene full name and function in cells
MET	Met proto-oncogene; receptor tyrosine kinase that transduces signals from the extracellular matrix into the cytoplasm by binding to HGF ligand. Regulates many physiological processes including proliferation, scattering, morphogenesis, and survival. Ligand binding at the cell surface induces autophosphorylation of MET on its intracellular domain that provides docking sites for downstream signaling molecules. (1408 AA)
HGF/SF	Hepatocyte growth factor scatter factor; potent mitogen for mature parenchymal hepatocyte cells, and acts as a growth factor for a broad spectrum of tissues and cell types. Activating ligand for the MET by binding to it and promoting its dimerization. (728 AA)
GRB2	Growth factor receptor-bound protein 2; adapter protein that provides a critical link between cell surface growth factor receptors and the Ras signaling pathway. (217 AA)
CDH1	Cadherin 1, type 1, E-cadherin (epithelial); cadherins are calcium-dependent cell adhesion proteins. CDH1 is involved in mechanisms regulating cell-cell adhesions, mobility, and proliferation of epithelial cells. (882 AA)
SH3KBP1	SH3-domain kinase binding protein 1; involved in the regulation of endocytosis and lysosomal degradation of ligand-induced receptor tyrosine kinases, including EGFR and MET/hepatocyte growth factor receptor, through an association with CBL and endophilins. (665 AA)
GAB1	GRB2-associated binding protein 1; adapter protein that plays a role in intracellular signaling cascades triggered by activated receptor-type kinases. Probably involved in signaling by the epidermal growth factor receptor (EGFR) and the insulin receptor (INSR). (724 AA)
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; phosphoinositide-3-kinase (PI3K) that plays a key role by recruiting PH domain-containing proteins to the membrane, including AKT1 and PDPK1, activating signaling cascades involved in cell growth, survival, proliferation, motility and morphology. (1068 AA)
CTNNB1	Catenin (cadherin-associated protein), beta 1, 88kDa; key downstream component of the canonical Wnt signaling pathway. (781 AA)
CBL	Cbl proto-oncogene, E3 ubiquitin protein ligase; adapter protein that functions as a negative regulator of many signaling pathways that are triggered by activation of cell surface receptors. (906 AA)
VEGFA	Vascular endothelial growth factor A; growth factor active in angiogenesis, vasculogenesis, and endothelial cell growth. Induces endothelial cell proliferation, promotes cell migration, inhibits apoptosis, and induces permeabilization of blood vessels. (412 AA)
PTPN11	Protein tyrosine phosphatase, nonreceptor type 11; acts downstream of various receptor and cytoplasmic protein tyrosine kinases to participate in the signal transduction from the cell surface to the nucleus. (593 AA)
HRAS	v-Ha-ras Harvey rat sarcoma viral oncogene homolog; Ras proteins bind GDP/GTP and possess intrinsic GTPase activity. (189 AA)
TP53	Tumor protein p53; acts as a tumor suppressor in many tumor types; induces growth arrest or apoptosis depending on the physiological circumstances and cell type. Involved in cell cycle regulation as a transactivator that acts to negatively regulate cell division by controlling a set of genes required for this process. (393 AA)
PAX3	Paired box 3; transcription factor that may regulate cell proliferation, migration, and apoptosis. Involved in neural development and myogenesis. (505 AA)
CRK	V-crk sarcoma virus CT10 oncogene homolog (avian); involved in phagocytosis of apoptotic cells and cell motility via its interaction with DOCK1 and DOCK4. May regulate the EFNA5-EPHA3 signaling. (304 AA)
PIK3R1	Phosphoinositide-3-kinase, regulatory subunit 1 (alpha); binds to activated (phosphorylated) protein-Tyr kinases, through its SH2 domain, and acts as an adapter, mediating the association of the p110 catalytic unit to the plasma membrane. (724 AA)
PTPN1	Protein tyrosine phosphatase, nonreceptor type 1; Tyrosine-protein phosphatase which acts as a regulator of endoplasmic reticulum unfolded protein response. May also regulate the hepatocyte growth factor receptor signaling pathway through dephosphorylation of MET. (435 AA)
PTPRJ	Protein tyrosine phosphatase, receptor type, J; plays a role in cell adhesion, migration, proliferation and differentiation. Involved in vascular development. Regulator of macrophage adhesion and spreading. (1337 AA)
INPPL1	Inositol polyphosphate phosphatase-like 1; plays a central role in regulation of PI3K-dependent insulin signaling, although the precise molecular mechanisms and signaling pathways remain unclear. (1258 AA)

(*continued on next page*)

Table 5 (*continued*)

Gene symbol	Gene full name and function in cells
PLCG1	Phospholipase C, gamma 1; mediates the production of the second messenger molecules diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3). Plays an important role in the regulation of intracellular signaling cascades. (1291 AA)
SRC	V-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (avian); nonreceptor protein tyrosine kinase which participates in signaling pathways that control a diverse spectrum of biological activities including gene transcription, immune response, cell adhesion, cell cycle progression, apoptosis, migration, and transformation. (536 AA)

AA, amino acid.
There are 20 genes with information related to c-Met protein action network. Table contains gene symbol with an explanation, and with a major role in cell signaling and amino acids number.

Here, we provided all the data collected from databases in the format of a table and image. These data provide a much more complete image of the c-Met gene in cancer, which gives formulate landscapes of all tumors. We presented data on various mutations like noncoding (splice site or UTR), synonymous, nonsynonymous, and other mutations (Table 3). Wood et al[51] found that a single-base substitution (92.7%) is hugely altered, with 81.9% missense mutation, 6.5% in stop codons, and 4.3% in splice sites or UTR.[52] Comparatively our results display that missense 70%, synonymous 14%, deletion 5%, nonsense and splice site or UTR equally 4%, and other mutations are below 4%.

National and international guidelines reported a variety of genetic alterations independent of race, age, sex or smoking status (NCCN guideline; ASCO guideline; ESMO guideline). In our results, Table 1 summarizes the patient's characteristics like gender, race, age, smoking history, and tissue histology data the results presented in numbers. One study reported that 26% African Americans, 22% never smokers, and 75% of patients had adenocarcinoma within that study population, and gender vise data also included.[53] The recent explosion of network analysis is making a significant contribution to study the biological networks, such as proteins interaction networks that help to understand the complex cellular phenotypes related to cancer. Our results of interacting signaling network of c-Met show interlinked genes with its function (Fig 6). The STRING database imports data from numerous resources, including public text collections, computationally predicted interactions from scientific texts, computed interaction from genomic features, and experimental repositories.[42,54]

The first c-Met genetic lesions were identified in human gastric cancer (amplification) and in renal cell cancer (Met activating point mutations) reviewed by Comoglio et al.[55] Later, these alterations were found in various cancers with different frequency and have been identified by whole genome-sequencing analysis.[56] These genetic alterations modify the c-Met protein structure and overexpression by the result of c-Met kinase activation which becomes independent or hypersensitive to ligand stimulation.[57,58] This leads to persistent signaling, uncontrolled cell proliferation, which is responsible for oncogene addiction.[55,59]

The oncogenic conversion of Met mutant's leads to upregulate the kinase activity, which is linked with catalytic domain, and the loss of mechanism of kinase downregulation is associated with juxtamembrane domain of the receptor. This domain contains serine residues (Ser985) which are phosphorylated by protein kinase C (PKC) and contribute to terminating the kinase activity of c-Met, and the tyrosine residue (Tyr1003) the domain linked with CBL (the E3 ubiquitin-ligase), which is necessary for c-Met internalization and degradation.[60,61] Mutation in tyr1003 residue prevents the receptor downregulation process and it leads to oncogenic activation of Met proto-oncogene.[60] However, c-Met point mutation in juxtamembrane domain of lung malignancy increased the tumorigenicity, and cell motility[36,58] reported that missense mutations in c-Met proto-oncogene tyrosine kinase domain (TK) caused constitutive phosphorylation of the c-Met protein and lead to malignant transformation in mouse NIH3T3 cells. And they identified and proved that this phosphorylation was stimulated by some missense muta-

Table 6
Summary of c-Met mutation, inhibitors, survival status, and other patient's clinical characteristics

References	Patients #	Primary tissue and histology subtype	Stages	Mutation types	Drugs name	Race	Gender M/F (#)	Age years #	Smoking status	Other genes mutations in same case or study	Median PFS months	Median OS months
Raghaw et al 2012[66]	257	Breast cancer	I, II, and III	Expression of c-Met (high c-Met (181) and low c-Met (76)) and pc-Met (high pc-Met (123) and low pc-Met (134))	Chemotherapy anthracycline based taxane anthracycline & taxane	NA	NA	51 (range 23-85 years)	NA	HER2 and HR (hormone receptor) positive	5-year relapse-free (RFS) survival (%) high (61.3) and low c-Met (78.9) and high (58.9) and low pc-Met (73.8)	5-year OS (%) high (61.3) and low c-Met (78.9) and high (58.9) and low pc-Met (73.8)
Dong et al 2016[67]	1	Lung (adenocarcinoma (recurrent))	IV	D1228N/H and Y1230H and Exon 14 skip	Car+AUC 5 and Pem and Criz	Chinese	F (1)	60	Nonsmoker	NA	NA	Crizotinib resistance
Spigel et al 2013[68]	66	Lung (adenocarcinoma, squamous, large cell, and branchioloalveolar)	IIIB/IV	MET IHC scores 2+ and 3+	Pla+Erl (n 31) and Ona+Erl (n 35)	White, Black or African American, Asian, and others	M (20) and F (11) and M (18) and F (17)	64 (44-82) and 66 (30-83)	Current/former smoker (53) and never-smoker (13)	KRAS and EGFR	NA	Place + 2+ (6.5 months) and 3+ (2.9) Onart+ (3+ 11.1 months)
Lu et al 2017[9]	1	Lung (adenocarcinoma (recurrent))	NA	Met-amplification D1228N, Y1230H, Y1230S and G1163R Exon 14 skip	Crizotinib	NA	F (1)	63	Nonsmoker	NA	NA	Crizotinib resistance
Kang et al 2018[10]	1	Lung (adenocarcinoma (recurrent))	IV	D1228N/H, Y1230H and D1231Y Met-amplificatio	Cab+osi and Cri+osi	NA	F (1)	44	NA	EGFR (L858R & T790M)	3	Resistance
Oddo et al 2017[69]	1	Colorectal cancer	Metastatic tissue	Met- amplification with over expression	Vem + pan and vem+cri	NA	NA	48	NA	BRAF (V600E)	After 4 months, acquired resistance	
Lennerz et al 2011[70]	10	Esophageal cancer (3), junctional cancer (3) and gastric cancer (4) (adenocarcinoma)	I (1) III (2) and IV (7)	Met-amplification	Crizotinb	NA	M (8) and F (2)	66	NA	HER2 and EGFR-amplified	Progression after 3.7 and 3.5 months.	7.1 months; P .001
Iveson et al 2014[71]	58	Gastric or oesophagogastric junction (adenocarcinoma)	NA	Met-amplification	Ril and pla	NA	NA	Median age 62	NA	HER2	5•1	11•5 months and 5•7 months
Catenacci et al 2017[12]	609	Gastric or gastrooesophageal junction cancer (adenocarcinoma)	I,II,III,IV	Met- over expression and amplification	Ril+epi, cis, and cap (n=304) and pla+epi, cis, and cape (305)	White, Asian, Black or African American, Native Hawaiian or other Pacific Island and others	M (425) and F (184)	Rilotumumab group (61 median age) placebo group (59)	NA	NA	Relotinib group (5.6) and placebo group (6.0)	Relotinib group (8.8 months) and placebo group (10.7 months)

(*continued on next page*)

Table 6 (*continued*)

References	Patients #	Primary tissue and histology subtype	Stages	Mutation types	Drugs name	Race	Gender M/F (#)	Age years #	Smoking status	Other genes mutations in same case or study	Median PFS months	Median OS months
Shah et al 2017[72]	76	Gastroesophageal (adenocarcinoma)	I,II,III,IV and V	IHC–positive (Met 2+/3+)	Plac+ flu, leu, and oxa (mFOLFOX6) (n = 109) and Onar (mFOLFOX6) (n = 105)	White, Asian, Black or African American and others	NA	Plac + mFOLFOX6 (58.0 (23-84))and Onar + mFOLFOX6 (60.0 (24-82))	NA	NA	Placebo (5.7) vs Onar + mFOLFOX (6.9)	Plac+ 9.7 and Onar+ 11.0
Madoz-Gúrpide et al 2015[47]	57	Head and neck cancer (squamous cell carcinoma) (recurrent or metastatic)	NA	Met-amplification, TGT Y1248 and Y1253 and Met:pMet:HGF IHC Low expression 24:47:20, Medium 21:8:27 and High 12:2:10	Cetuximab Test group (T group) and Control group (C group)	NA	M (49) and F (8)	T group 61 (38-80) and C group 64 (41-80)	Current smoker (20), former smoker 35, and Never smoker 2	NA	15	18
Choueiri et al 2017[73]	44	Advanced (papillary) renal cell cancer (locally advanced or metastatic)	NA	Met copy number gain Met-amplification, HGF gene amplification (>6 copies) and Met kinase domain mutations (allele frequency (>5%)	savolitinib	White 38, Black or African American 5 and other 1	F (12) and M (32)	64 (23-87)	NA	NA	6.2	NA
Twardowski et al 2017[11]	7	Papillary Renal cell carcinoma	I, II,III,IV	K1198I (1) and Met-amplification (6)	Tivantinib and Tiv+Erl	White and Black	NA	NA	NA	CDKN2A, PBRM1, SETD2, KDM6A, FAT1 and EGFR	Tivantini (2.0) and Tiv+Erlo (3.9)	10.3 and 11.3
Choueiri et al 2013[74]	11	Papillary renal cell carcinoma	I, II, III and IV	Four patients with same germline mutation H1094R, 5 somatic and 2 Amplification	NA	NA	NA	NA	NA	VEGF, RON, AXL, and TIE-2	9.3	NA
Shah et al 2016[75]	NA	Advanced stomach and gastroesophageal junction and (adenocarcinoma)	NA	c-Met positive IHC 2+/3+	Ona + mFOLFOX6 (16) and Pla + mFOLFOX6 (19)	NA	NA	NA	NA	HER2	Onar + mFOLFOX6 (5.95) vs mFOLFOX6 6.80	Onar + mFOLFOX6 8.51 vs mFOLFOX6 (8.48)

M, male; F, female; NA, not available; PFS, progression-free survival; OS, overall survival; Car, cacboplatin; Pem, pemetrexed; Cri, crizotinib; Pla, placebo; Erl, erlotinib; Ona, onartuzumab; Osi, osimertinib; Vem, vemurafenib; Pan, panitumumab; Ril, rilotumab; Epi, epirubucin; Cis, cisplatin; Cap, capecitabine; Flu, fluorouracil; Leu, leucovorin; Oxaliplatin; Cel, celuximab; Sav, savlotinib; Tiv, tivantinib.

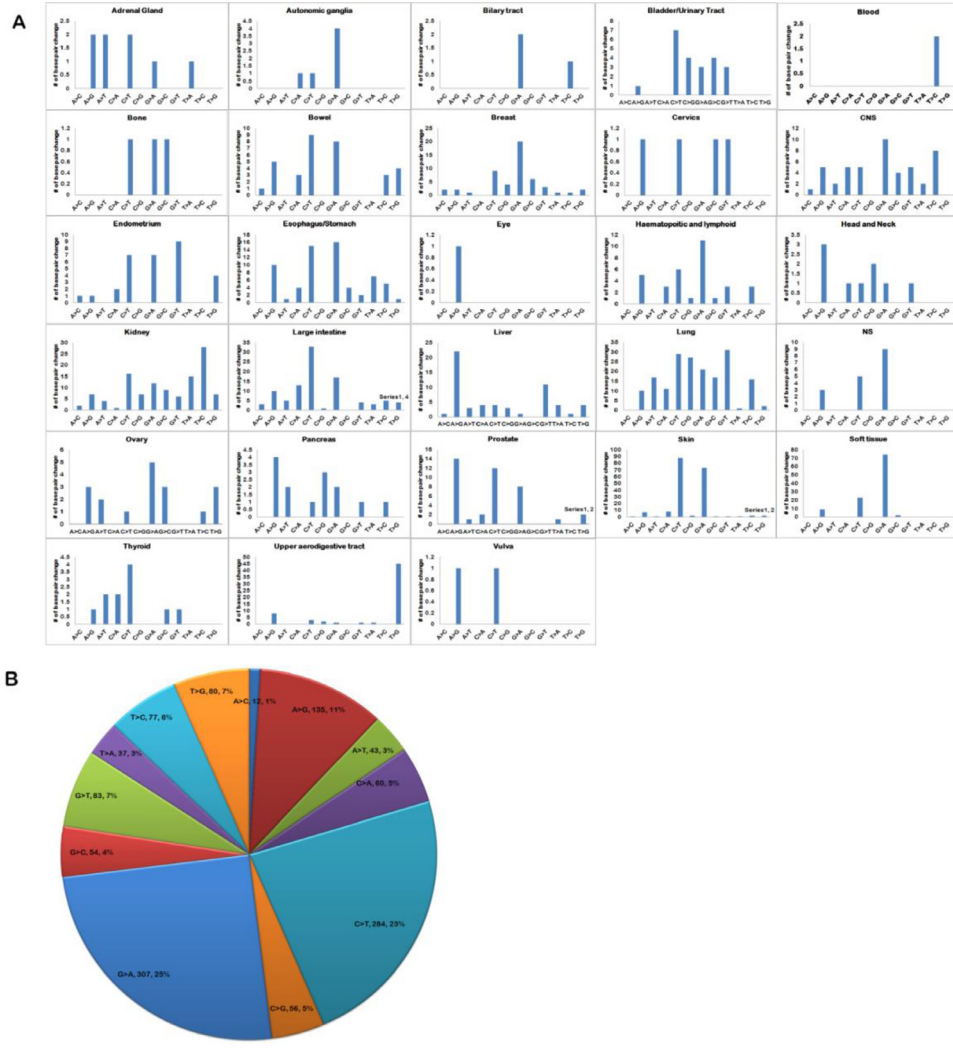


Fig. 3. Nucleotide sequence substitution or CDS mutation in different tissues. Nucleotide sequence substitution or CDS mutation in different tissues types; (A) shows tissue-specific cancer with DNA base pair substitution and most types of cancer largely having C > T and G > A substitution in c-Met mutation. (B) DNA base pair substitution mutation in all cancer, and G > A 307; 25% and C > T 282; 23% were highly altered. An, adenine; G, guanine; C, cytosine; T, thymine.

tions V1110I, H1112L, and H1124D in amino acids in TK domain. Schmidt et al[34] identified 15 different mutations which were missense and were located in the portion of exons 16-19 of the c-Met proto-oncogene in the TK domain. These mutations involved in 10 codons: V1110, H1112, H1124, M1149, V1206, L1213, V1238, D1246, Y1248, and M1268 and these codons to be mainly regulating tyrosine kinase activity and mutation in these codons produce malignant disease. Alterations were linked in the activation loop and the glycine rich-ATP binding region of the c-Met protein. Advances in genenome and protein sequencing provide landscape to identify the mutations and amplification on oncogenes or others. Our study provides comprehensive infor-

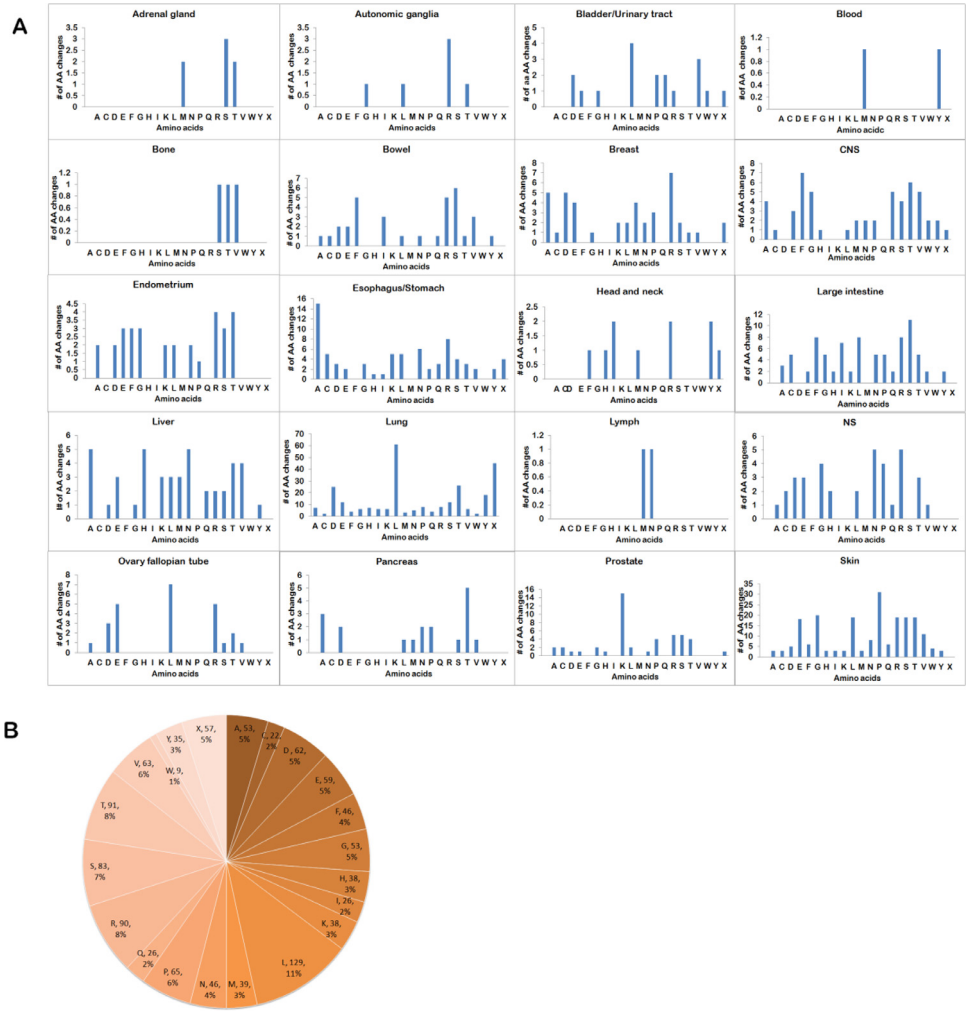


Fig. 4. Amino acid changes in MET mutation. AA changes in c-Met across all types of cancer (by # and percentage) Labeling: AA, number of cases, percentage. (A) AA changes in different cancer types most strikingly, in the lung (leucine 61) and skin (proline 31) cancer has highly altered amino acids. (B) AA changes in overall cancer types we found that 11% of cases with AA Leucine alteration, followed by Arginine (8%), Threonine (8%), Serine (7%), valine and Proline equally (6%) other AA alteration showing 5 or below 5% of mutation. X is a Splice site or UTR.

mation about c-Met role in normal cells and various cancers which helps researchers to easily understand.

Kutzner et al[52] reported that the individual AA alteration in p60TRP across all different tissue and found that 24% AA glutamate (E) followed by alanine (A) and proline accounted for about 10% of cases each, and compared overall AA in all cancer. Ethnic differences and functional analysis of c-Met mutations in lung cancer from 141 Asian, 76 Caucasian, and 66 African American lung cancer patients, exons coding for MET identified R988C, N375S, I852F, and other.[62] Our results of AA changes in c-Met overall in different cancer show 11% of cases with AA Leucine alteration, followed by Arginine (8%), Threonine (8%), Serine (7%), valine and Proline equally (6%) other AA alteration showing 5 or below 5 percentage of mutation (Fig 4B).

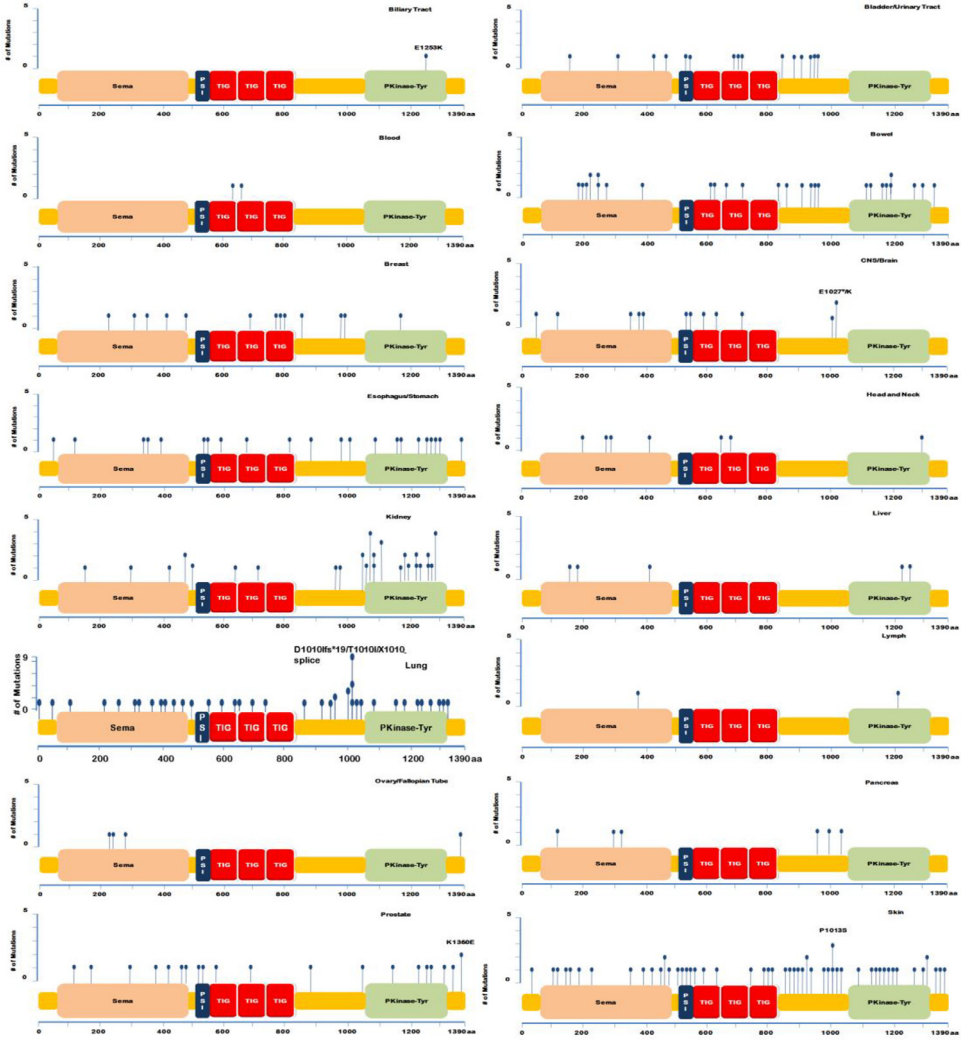


Fig. 5. Analysis of MET mutations according to AA position. AA mutation hotspots of c-Met protein and number of AA altered (stick like a point in protein structure) cases with different types of tissues. Some AA alteration in some cancer showing repeated and highly altered numbers include biliary tract E1253K, CNS/Brain E1027*/K, lung D1010lfs*19T1010I/X1010_Splice, prostate K1360E, and skin P1013S. Overall, the result shows all regions of c-Met comprise a mutation, consequently, Sema (semaphorin) domains and PKinase domains (protein tyrosine kinase domain) were highly mutated in all cancer, so these 2 domains are the main hotspot for Met mutation. Lung and skin cancer has a mutation in mostly all regions.

Krishnaswamy et al[62] reported that nucleotide substitution mutation of c-Met among the different ethnic groups identified 7 synonymous substitutions: 144G > A, 534C > T, 1113C > T, 1944A > G, 3912C > T, 4071G > A, and 4146G > A. In our study, we collected several nucleotide substitution data from various databases, comparatively G ≥ A substitution most repeated in various cancer in various position. Overall, in all cancer comparatively G ≥ A 25% followed by C ≥ T 23% and other showing the lower percentage (Fig 3). Various studies reported clinical characteristics like tumor types and its stages.[63,11,64,65]

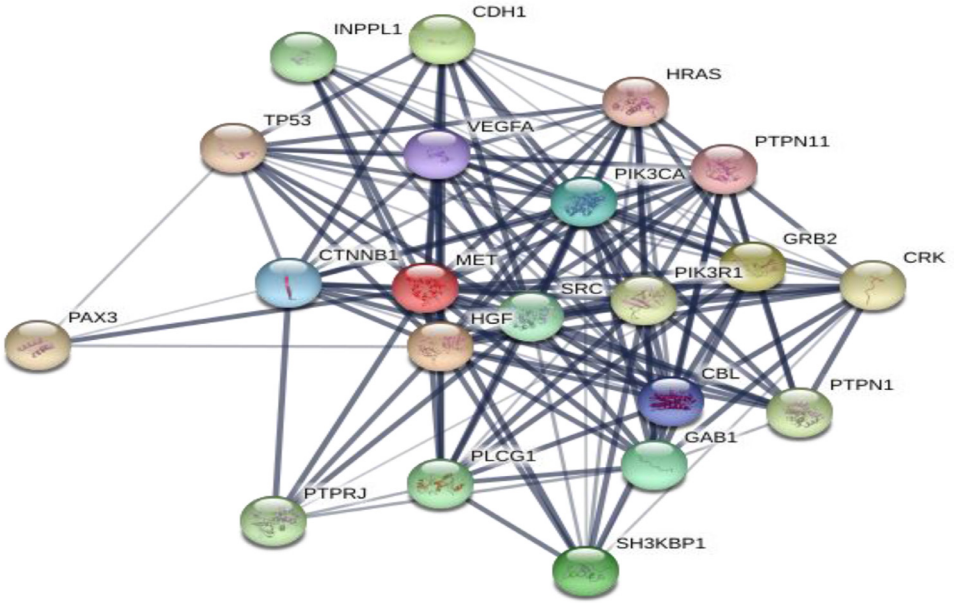


Fig. 6. c-Met biocomputational network analysis of interactive signaling pathways in tumorigenesis. The c-Met gene and its ligand HGF and also interlinked major protein network involved in tumorigenesis. Gene symbol and its explanation and other detailed information are given in the table.

Conclusion

We analyzed human cancer genome datasets for c-Met oncogene and its function in numerous types of cancer. c-Met and HGF gene expression are associated with various primary and metastatic cancer progression. The late stage identification of c-Met mutation, overexpression and amplification, highly promotes the tumor progression but lesser in development. Overall, the mutation and copy number variation of c-Met from various cancer types specifically lung, skin, and kidney are largely altered by this gene. Our data indicate that the c-Met is potential molecular marker and viable therapeutic target for different types of cancer. Our study provides comprehensive information about c-Met role in various cancers which helps researchers to easily understand.

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