High Frequency Mutant Genes in Urothelial Carcinoma Based On Genomic Landscape

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Abstract

Objective

The new generation of sequencing technology has been applied to the study of genomic genetic characteristics of urothelial carcinoma for 20 years. Researchers at home and abroad have done a lot of research work. Analyzing and summarizing the research results, we can clarify the genes with high-frequency mutations, which is of great significance for the screening of biomarkers and molecular targets of urothelial carcinoma.

Method

We will adopt the PICOS analysis method of evidence-based medicine; follow the principles of systematic evaluation and meta-analysis; formulate literature retrieval keywords and retrieval strategies; determine the inclusion criteria; and statistically analyze the name, mutation frequency, quantity, and the total number of times in repeated reports of significant mutant genes in the genomic landscape.

Results

A total of 6254 cases of urothelial carcinoma were sequenced in the 27 theses selected. Sequencing methods include whole genome sequencing, whole exome sequencing, and target exome sequencing. 27 genomic landscapes of urothelial carcinoma showed that the number of significant mutant genes was 5-58, with an average of 26 reported in each paper. There were 273 genes with significant mutations in urothelial carcinoma, 65.57% (179 / 273) of which were reported only once and 34.43% (94 / 273) were reported more than twice. The top 7 genes most frequently reported were TP53, PIK3CA, FGFR3, KDM6A, ARID1A, RB1 and STAG2.

Conclusion

There were 273 genes with significant mutations in the genome of urothelial carcinoma, and biomarkers may be selected from 94 genes with high-frequency of mutations.

Introduction

Urothelial cells stretch across the renal pelvis, ureter, bladder, and parts of the urethra. Urothelial carcinoma (UC) can be divided into Upper tract urothelial carcinoma (UTUC) and lower urinary tract epithelial cancer[1]. Lower urinary tract urothelial carcinoma is mainly bladder cancer (Bladder cancer, BC), the incidence of which is higher and is divided into non muscle invasive bladder cancer(Non-muscle invasive bladder cancer, NMIBC) and muscle invasive bladder cancer (Muscle invasive bladder cancer, MIBC). In the past 20 years, the new generation of sequencing (NGS) has been used to analyze a large number of genomic genetic characteristics of the UC, and many mutations which are associated with the occurrence and development of tumor, tumor biological characteristics, and clinical prognosis have been found[2,3]. Many important research reports have described genomic landscape (GL) in detail. However, we found significant differences in the types and frequencies of mutated genes reported in these literatures. Meanwhile, we also found that the genomic mutation landscape of UTUC, BC, NMIBC and MIBC also had their own significant characteristics. Therefore, using the method of evidence-based medicine Picos analysis[4], this paper systematically evaluated and meta-analyzed the literature on UC genomic detection in recent 10 years. Through the statistical analysis of the number and mutation frequency of significantly mutated genes displayed by GL in the literature, we attempted to obtain the key genes and mutation rules of common mutations in different histopathological types of UC, which will provide a theoretical basis for the screening of UC biomarkers and the study of molecular imaging targets.

Results

1. Basic data included in the paper

A total of 5643 relevant literatures were retrieved and excluded one by one, of which 27 original literatures with GL and influencing factors > 5 were included. A total of 6254 cases of urothelial carcinoma were studied in these 27 papers, including 919 cases of UTUC and 5335 cases of BC. In addition to NMIBC and MIBC, BC also included bladder inverted papilloma and urothelial papilloma, bladder adenocarcinoma, micropapillary urothelial carcinoma, and neuroendocrine BC. Metastatic urothelial carcinoma of the upper and lower urinary tracts was also included.

Sequencing methods include whole genome sequencing, whole exome sequencing, and target exome sequencing. In this paper, the genes with mutation frequency > 10% were identified as significant mutation genes. GL was drawn according to the significantly mutated genes. The map mainly showed the name, mutation frequency, mutation type of mutated genes, and their correlation with tumor clinical characteristics (Table 1).

2. Mutant genes displayed by the genome landscape

The genome landscape of 27 papers were sorted out one by one, and the author, publication date, name of significant mutant genes, the number of mutant genes, pathological type of tested tissues, journals, and influencing factors were shown in Table 1.
| Author [Ref] | Year | Mutant genes in the genome landscape | Tissue types (n) |
|-------------|------|-------------------------------------|-----------------|
| Guo[9]      | 2013 | KDM6A, TP53, ARID1A, CREBBP, EP300, HRAS, RB1, PIK3CA, STAG2, FGFR3, SYNE1, KMT2A, KRAS, ERCC2, NF1, SYNE2, ELF3, ANK3, ESP1,1, CSM3D, LRF2, TSC1, TRAK1, NFE2L3, PDZD2, ERBB3, TRRAP, PIK3R4, LAM4A, NCO1R, ERBB2, KALRN, ATM, CHD6, ANK2, KMT2D, FAT4 (n=37) | 99 TCC |
| Cancer Genome Atlas Research Network[9] | 2014 | CCND3, ROH3, ZFPE3L61, HRAS, BTG2, PAIP1, FOX1, RHOB, CDKN2A, FOXQ1, TXNIP, KLF5, TSC1, NFE2L2/ELF3/RXRA/FBXW7/ERBB3/STAG2/FGFR3/ERCC2, RB1, CDKN1A/EP300:PIK3CA/KDM6A/ARID1A/MLL2/TP53 (n=29) | 131 UC |
| Yap[7]      | 2014 | TP53, KDM6A, TSC1, ATM, UNC5C, BRCA2, ERCC2, FANCD2, FANCD2, PALB2, BRCA1 (n=11) | 81 MIBC |
| Ross[9]     | 2014 | ERBB2, TP53, RB1, MCL1, ARID1A, CCND1, RICTOR, MYCL1, MLL2, EGFR, RUNX1, RAF1, P1TEN, P1TCH1, PIK3R1, PIK3CA, NF2, MSH2, MDM2, KRAS, JAK2, IR52, ID2, HRAS, FBXW7, EPHA3, CNE1, CCND3, BAP1, AURKA, AKT2, AKT1 (n=32) | 15 MPUC |
| Sfakianos[9] | 2015 | FGFR3, KMT2D, KDM6A, KMT2C, STAG2, CDKN2A, TP53, CDKN2B, CREBBP, TSC1, PIK3CA, ARID1A, CCND1, HRAS (n=14) | 83 UTUC 102 UCB |
| Hedegaard[10] | 2016 | FGFR3, KIA1109, SYNE2, AHN4K, DST, RNF213, BIRC6, DYNCH1H, AKAP9, NF1, NIPBL, MACF1, PIK3CA, PLEC, KDM6A, BPTF, DSP, VPS13D, SRRM2, HUWE1, RANBP2, CEP350, SPTBN1, LMO7, MAST4, GIGYF2, ERBB2, TP53, PBRM1, C10orf137, SMAD3, SEMA5F, SMG5, WDR70, MAP2K5, PSD4, NAP5X, P1T1, FAT1, MLL3, MLL, STAG1, MYCBP2, EP300, ATM, ARID1A, ASH1L, CREBBP, MLL2, WNK1, ERBB3, BRD1, ELF3, INADL, RB1, RHOB, RBM10, RXRA (n=58) | 460 early-sta UC |
| Longo[11]   | 2017 | FGFR3, PIK3R1, TP53, P1TEN, TSC1, BRAF, KRAS, NF1, ALK, EGFR, ERBB2, FGFR3, KMT2D, SETD2, SMARCB1, TET2, ATM, BRCA1, BRCA2, CDKN2A, JAK1, RB1, TP53 (n=23) | 50 BC |
| Pietzak[12] | 2017 | FGFR3, KRAS, HRAS, ERBB2, ERBB3, PIK3C, TSC1, NF1, TP53, MDM2, RB1, CDKN2A, CDKN1A, CCND1, STAG2, KDM6A, KMT2D, ARID1A, KMT2A, KMT2G, EP300, CREBBP (n=22) | 105 NMIBC |
| Roy[13]     | 2017 | TP53, KRAS, TERT, PIK3CA, CTNNB1, APC, SMO, FEXW7, IDH2, PDGFR3, RB1 (n=11) | 15 BA |
| Glase[14]   | 2017 | ARID1A, BRD1D, C3orf70, CCND1, CDKN1A, CDKN2A, CDKN2B, CHIT1, CREBBP, ELF3, EP300, ERBB2, ERBB3, ERBB4, ERCC2, FAM47C, FGFR3, HRAS, IRS4, KDM6A, KMT2C, KMT2K, KRAS, MBD1, NFE2L2, PIK3CA, RB1, ROH3, ROHOB, RXA, STAG2, TGFB1, TP53, TSC1, TXNIP, TYRO3, ZFPE3L61 (n=38) | 487 MIBC, NMIBC |
| Robertson[15] | 2017 | TP53, KMT2D, KDM6A, ARID1A, PIK3CA, KMT2C, RB1, EP300, FGFR3, STAG2, ATM, FRT1, ELF3, CREBBP, ERBB2, SPTAN1, KMT2A, ERBB3, ERCC2, CDKN1A, ASXL2, TSC1, FBXW7 (n=23) | 412 MIBC |
| Moss[16]    | 2017 | FGFR3, KMT2, PIK3CA, TP53, KDM6A, CDKN2A/B, ATM, ZFH4, ADY2, ARID1A, ERBB3, ERCC2, NPHS1, RHOB, SPTB, TSC1, CCND1, CREBBP, STAG2, SH3KBP1 (n=20) | 31 UTUC |
| Hurst[17]   | 2017 | FGFR3, PIK3CA, KDM6A/STAG2/KMT2D/ARID1A/EP300/KMT2C/CREBBP/RHOB/Hras/KMT2A/TSC1/BRC2/CO111A1/RBM10, UNC80, CEP290, CLT06, MECOM, UTY, MAGI3, DYNCH1H1, KIF16, REB1, USP47, ZFVEY26 (n=27) | 140 Ta NIBC |
| Nassar[8]   | 2018 | FGFR3, KDM6A, TP53, RB1, HRAS (n=5) | 472 NMIBC, NMIBC, U1 |
| Shen[19]    | 2018 | TP53, RB1, PRUNE2, NOTCH1, TMEM132D, EP300, CREBBP, MLL2, ARID1A, PIK3CA, MEN1, DAXX/ATRX, CTNNB1, KRAS, P1TEN, ALK, CDKN2A, BRCA2, FGFR3, CDKN1B, TERT, SMAD4, MYCN (n=24) | 12 NEB |
| Agarwal[20] | 2018 | TP53, PIK3CA, ARID1A, ERBB2, EGFR, FGFR3, TERT, NF1, EGFR2, BRCA1, BRCA2, BRAF, CCNE1, FGFR1, FGFR3, KIT, MET, RAF1, FGR2, NOTCH1, APC, AR, KRAS, QNA6, KDM6A, KMT2C, TSC1, TRAK1, STK11, CDH1, FBXW7, ALK, CD4, CDK5, CDKN2A, PDGFA, TSC1, ATM, CCND1, MTO1, RB1, SMAD4, DHC2, HNF1A, JAK2, MAPK21, MLH1, NFE2L2, NARS, P1TEN, PTPN11, SMG, QATA3, MAP2K2, MAPK1, RET, RHOD, RIT1, ROS1 (n=58) | 369 mU |
| Wu[21]      | 2018 | FGFR3, TP53, PIK3CA, ZFPE3L61, HRAS, KDM6A, ELF3, KRAS, STAG2, ERBB2, RB1, CASP8, CDKN1A, PMS2, CRIPAK, ERCC4, RBM15, ZNF814, TERT, ADGR6, PLEXH1, TBC1D12, WDR74, LEPR1, PLCLDC1, CDKN2A, FHI1, TC28, LRP1B, MDM2, CDCC, FRS2, SHANK2, LRRC10, CDKAL1, PDE4D, FAGAD, CTT2, KCNB2, VPS13B, GPS5, ATP8A2, ELAVL2, RGB1X1, PTRPR, ITSN1, TNC2, CSE81 (n=46) | 32 NMIBC 33 MIBC |
According to the analysis in Table 1, there were great differences in the number of significant mutant genes displayed in 27 urothelial carcinoma genome landscapes. The number of significant mutant genes was 5-58, with an average of 26 reported in each paper.

3. Frequency of mutant gene reported

To further compare the genes in Table 1 one by one and calculate the frequency of repeated reports (Table 2)
Table 2
frequency of significant mutant gene reports

| Number of repetitions | Repeat genes |
|-----------------------|--------------|
| 27                    | TP53(\(n=1\)) |
| 23                    | PIK3CA, FGFR3, KDM6A (\(n=3\)) |
| 22                    | ARID1A, RB1, STAG2 (\(n=3\)) |
| 18                    | CREBBP, KMT2D (\(n=2\)) |
| 15                    | TSC1, ERBB2 (\(n=2\)) |
| 14                    | KRAS, HRAS, EP300, (\(n=3\)) |
| 13                    | CDKN2A (\(n=1\)) |
| 10                    | ERCC2, KMT2C, ERCC2 (\(n=3\)) |
| 9                     | ERBB3, CCND1 (\(n=2\)) |
| 8                     | BRCA2, ATM, NF1, (\(n=3\)) |
| 7                     | FBXW7, PTEN, TERT (\(n=3\)) |
| 6                     | RHOB, CDKN1A, EGRF, ELF3, NOTCH (\(n=5\)) |
| 5                     | MDM2, KMT2A, MLL2, MDM2, RBM10, MDM2 (\(n=6\)) |
| 4                     | CDKN2B, ZFP36L1, ZFP36L1 (\(n=3\)) |
| 3                     | NCO1, RHOA, FOXQ1, NFE2L2, RXRA, BRCA1, RAF1, PIK3R1, CCNE1, FAT1, BRAF, APC, LRP1B, FRS2, FAT1, ALK, (\(n=16\)) |
| 2                     | SYNE2, CCND3, TXNIP, KLF5, MCL1, MSH2, IRS2, IDH2, BAP1, AKT1, DYNC1H1, MLL3, CTNNB1, SMAD4, FGFR1, MET, CDH1, ROS1, ASXL2, FGFR19, FGFR4, SPEN, ANK2, ASXL2, FANCD2, BRWD1, PDGFRA, CRIPAK, JAK2, FGF3, MLL3, MSH2, ZFHX4, TC2B (\(n=38\)) |
| 1                     | SYNE1, ANK3, ESPOCSM3D, LRP2, TRAK1, NFE2L3, PDZD2, TRRAP, PIK3R4, LAMA4, KALRN, CHD6, FAT4, BTG2, PAI1, FOXA1, UNC5C, PALB2, RICTOR, MYCL1, RUNX1, PTCH1, NF2, EPHA3, AURKA, AKT2, KIAA1109, AHNAK, DST, RNF213, BIRC6, AKAP9, NIPBL, MACF1, PLEC, BPTF, DSP, VPS13D, SRRM2, HUWE1, RANBP2, CEPI350, SPOTB1, LMO7, MAST4, G11G2F2, PBRM1, C10orf137, SMAD3, SEMA3F, SMG5, WDR70, MAP3K5, PSD4, NASSP, XPD, MYC, MYCBP2, ASH1L, WNK1, INAD1, SETD2, SMARC81, TET2, JAK1, FEXW7, C3orf70, CH1, ERBB4, FAM47C, IRS4, MBD1, TGFBR1, TYRO3, FRT1, SPTAN1, SH54BP1, COL11A1, CEPP90D, CLTC, MEGD1, UTY, MAG3, KIF16B, RBD1, USP47, ZFVVE29, PRUNE2, TME132D, MEN1, DAXX, ATRX, CDK4, CDKN1B, MYCN, KIT, QNAN, NTRK1, STK11, CDK5, MTROR, EZH2, HNF1A, MAP2K1, MLH1, NARS, PTPT2B, GATA3, MAP2K2, MAPK1, RET, RIT1, CASP8, PMS2, ERC2, RBB4, RBM15, ZNF814, ADGRG6, PLEKH5, TBC1D12, WDR74, LEPRTOL1, PLXDC1, FHIT, SHANK2, LRR1C9, CDKAL1, PDE4D, FOD4, CCT2, KCN82, VPS13B, GPC5, ATP8A2, ELAVL2, RBFOX1, PTPR8, ITSN1, TPCN2, CCES1R1, HLA-A, POM121C, ELMOD2, CDH17, PRK1, PCDH4A2, HHDIN, PDHA1, DZIP1L, FAM80A1, VPS13A, ACIN1, MED12, STOX3, RAD1, R2G2, ADNR2, TAF1, EMSY, ARID2, FOXP1, LZTR1, NOTCH3, RAD50, SF3B1, BCO1R1, CTCF, DNTM3A, FANCA, ZNF217, BRD4, GNAQ, KDR, INPPL1, ZFHX3, KMT5A, MDC1, ANKRD11, GANAB, SPTAN1, (\(n=179\)) |

According to the analysis of Table 2, a total of 273 genes with significant mutations were reported in 27 literatures, 65.57% (179 / 273) of which were reported only once and 34.43% (94 / 273) were reported more than twice.

4. Report frequency and mutation frequency

According to the analysis of Table 2, the four most frequently reported genes in 27 papers were TP53, PIK3CA, FGFR3 and KDM6A. The mutation frequencies of the four significant mutated genes in each paper were shown in Table 3.
| Author [Ref] | Year | Tissue types (n) | TP53(%) | PIK3CA(%) | FGFR3(%) | KDM6A (%) |
|-------------|------|------------------|---------|-----------|----------|-----------|
| Guo[^5]     | 2013 | 99 TCC           | 24      | 12        | 11       | 30        |
| Cancer Genome Atlas Research Network[^6] | 2014 | 131 UC          | 49      | 20        | 12       | 24        |
| Yap[^7]     | 2014 | 81 MIBC         | 40.7    |           |          | 21        |
| Ross[^8]    | 2014 | 15 MPUC         | 67      | 6         |          |           |
| Sfakianos[^9] | 2015 | 83 UTUC 102 UCB | 18      | 15        | 54       | 34        |
| Hedegaard[^10] | 2016 | 460 early-stage UC | 20      | 15        | 24        |           |
| Longo[^11]  | 2016 | 50 BC           | 52      | 40        | 2        |           |
| Pietzak[^12] | 2017 | 105 NMIBC      | 21      | 26        | 49       | 38        |
| Roy[^13]    | 2017 | 15 BA          | 47      | 20        |          |           |
| Glaser[^14] | 2017 | 487 MIBC, NMIBC | 29      | 19        | 29       | 33        |
| Robertson[^15] | 2017 | 412 MIBC       | 48      | 22        | 14       | 26        |
| Moss[^16]   | 2017 | 31 UTUC        | 22.2    | 25.9      | 47.1     | 22.2      |
| Hurst[^17]  | 2017 | 140 Ta NIBC    | 54      | 79        | 52       |           |
| Nassar[^18] | 2018 | 472 NMIBC, MIBC, UTUC | 41 | 15 | 26 | |
| Shen[^19]   | 2018 | 12 NEBC       | 83      | 25        | 33       | 25        |
| Agarwal[^20] | 2018 | 369 mUC     | 48      | 14        | 10       |           |
| Wu[^21]     | 2019 | 32 NMIBC 33 MIBC | 18      | 7         | 21       | 5         |
| Pietzak[^22] | 2019 | 245 primary MIBC secondary MIBC | 69 | 19 | 7 | 21 |
| Isharwal[^23] | 2019 | 22 11 IUP 11 UP | 9       | 9         | 9        |           |
| Author [Ref] | Year | Tissue types (n) | TP53(%) | PIK3CA(%) | FGFR3(%) | KDM6A(%) |
|-------------|------|-----------------|---------|-----------|----------|----------|
| Lawson[25]  | 2020 | Bladder         | 48      | 22        | 13       | 25       |
| Bellmunt[26]| 2020 | HGT1            | 40      | 13        | 13       | 24       |
| Necchi[27]  | 2020 | UTUC, 1984 BC, BC | 57      | 15        | 18       | 16       |
| Kim[28]     | 2020 | UTUC            | 25      | 14        | 47       | 38       |
| Pal[29]     | 2020 | 39 UCB, 7 UTUC  | 15      | 23        | 97       | 49       |
| Yang[30]    | 2021 | 45 UTUC, 73 UCB | 45      | 16        | 20       | 17       |
| Su[31]      | 2021 | UTUC, MIBC, NMIBC | 17      | 50        | 27       |          |

According to the analysis in Table 2, the mutation frequency range and average mutation frequency of the six genes with the most frequent occurrence in the 27 papers were TP53 (17-83%, 43.7%), PIK3CA (6% - 54%, 20.5%), FGFR3 (11% - 97%, 27.4%) and KDM6A (9-52%, 28.3%) respectively, indicating that the mutation frequency of each significant mutant gene was quite different in different cohorts (the blank space in the table indicates that the gene mutation was not detected).

According to overall analysis, many research teams worldwide have systematically studied the mutation characteristics of UC genome gene mutations. All studies have used similar sequencing technology, but the detection rate and types of mutant genes were very different in different research cohorts. The reasons for these differences may be related to the heterogeneity of tumor tissue, pathogenic factors, and ethnic and regional differences. The accuracy and scientificity of sequencing, however need to be further verified.

**Discussion**

The human genome project (HGP) is a large-scale, transnational and interdisciplinary scientific exploration project. It aims to determine the nucleotide sequence of 3 billion base pairs contained in the human chromosome (haploid), draw the human genome map, identify the genes and sequences contained therein, and ultimately decipher human genetic information. For UC genome research, scientists from the Cancer Genome Atlas (TCGA), the International Cancer Genome Consortium (ICGC) and the Chinese Cancer Genome Consortium (CCGC) have participated in the research of the project and made unremitting efforts for 20 years. Remarkable research results obtained are worthy of summarizing.

Therefore, through literature retrieval, this paper obtained 27 valuable and high-level academic papers, following the PICOS method of evidence-based medicine for systematic evaluation and meta-analysis and trying to comprehensively understand the characteristics of gene mutations at the UC genome level so as to provide a theoretical basis for the screening of key molecules of UC and promote the clinical transformation of UC biomarkers, molecular imaging targets, and targeted therapeutic drugs.

In this study, 273 significantly mutated genes were reported in 27 papers. Unfortunately, 94 genes were reported twice or more in different literatures, accounting for only 34.43% of all significantly mutated genes, while 179 genes were reported only once in a single literature, accounting for 65.57%, indicating that the heterogeneity of UC genome mutation was very strong and the screening of UC key molecules may be limited to these 94 genes.

In terms of researchers and research objects, the research results mainly came from China, the United States, Germany, Britain, Spain, Canada, etc. It may be that the differences of race, region, and pathogenic factors will also attribute to the distinctions of UC gene mutation.
In addition, this paper studied the different histopathological types, including upper urinary tract urothelial carcinoma and bladder cancer. Bladder cancer includes NMIBC, MIBC, bladder inverted papilloma, urothelial papilloma, bladder adenocarcinoma, micro papillary urothelial carcinoma, neuroendocrine bladder cancer, and metastatic urothelial carcinoma of the upper urinary and lower urinary tract. Combined with the analysis of Table 3, the types and frequencies of tumor gene mutations in different histopathological types may also be distinct, and the analysis of different mutant gene combinations may be helpful for the diagnosis and molecular typing of different histopathological diseases. In 2016, Seiler et al. [32] established a clinicopathological classifier of KNN51 genome (51 genes) to predict positive lymph node metastasis. Kamoun et al. [33] established a MIBC classification system based on network analysis and divided MIBC into 6 molecular types. In fact, the detection of gene mutation alone cannot be used as a biomarker. The research method of protein genomics, the combination of genome and proteome, will facilitate to screen biomarkers.

In conclusion, although the 20-year study of urothelial carcinoma genomics has enabled us to have a profound interpretation of the molecular characteristics at the DNA level, we still lack a fundamental understanding of the heterogeneity and complexity of urothelial carcinoma genome.

Methods

1. Picos analysis method of evidence-based medicine

This study adopts the Picos method of evidence-based medicine. Picos stands for participants, intervention, control, outcome, and study design. The subjects (P) include urothelial carcinoma of upper urinary tract and bladder cancer; Intervention (I) means the method of genome sequence analysis involving whole genome, exon, and targeted sequencing technology; Control (C) is to compare and analyze the GL data of UTUC, BC, NMIBC, and MIBC; Outcome (O) includes gene name, mutation frequency, and other test data; Research design (S) mainly studies the original works with an impact factor greater than 5, excluding editorials, comments, and conference abstracts.

2. Thesis retrieval strategy

Based on the search keywords (Table 4), a systematic literature search of GeenMedical, PubMed, and Web of Science was conducted. We limited our searches to publication from January 2011 to January 2021.

| Search keywords | search strategies and search results |
|-----------------|-------------------------------------|
|                 | Total | 5≤IF<10 | 10≤IF<20 | IF≥20 |
| Genomic, Bladder Cancer | 5471 | 1415 | 420 | 139 |
| Whole-genome, whole-exome sequencing, bladder cancer | 13 | 4 | 3 | 2 |
| Molecular characterization, urothelial bladder carcinoma | 76 | 13 | 9 | 2 |
| Urothelial carcinoma, genome landscape | 23 | 6 | 3 | 2 |
| The genome, landscape, bladder cancer | 60 | 18 | 10 | 5 |
| Total | 5643 | 1456 | 445 | 150 |

3. Exclusion criteria

Following the principles of systematic evaluation and meta-analysis, all researchers participated in selecting papers. The exclusion criteria are original papers with similar research contents and impact factor < 5, excluding editorials, comments, and conference abstracts. The inclusion criteria are original papers with impact factor > 5 and including the standard detailed genome landscape map in the research results.

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