VISDB User Manual

[V1.0]

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Catalogue

1 Homepage	3
1.1 Menu Bar	3
1.2 Hotspot genes button	3
1.3 Virus button	
1.4 Search button	6
2 VIS information	7
2.1 VIS visualizing zone	
2.2 Proximate DNA elements visualizing zone	
2.3 Gene and miRNA expression zone	
2.4 Text information region	
2.5 Gene, fragile site, miRNA and pathway	
3 Browse	
3.1 Browse all	
3.2 Browse by fragile site	
3.3 Browse by disease	
3.4 Browse by experimental assay	
3.5 Browse by chromosome	
3.6 Browse by literature	
4 Search	
4.1 Basic search	
4.2 Advanced search	
5 Curation	
6 Gene	
7 miRNA	
8 Download	22

Notes: Words with blue color mean they are hyperlinks, clicking on the words will navigate to another next page or pop out another page.

1 Homepage

1.1 Menu Bar

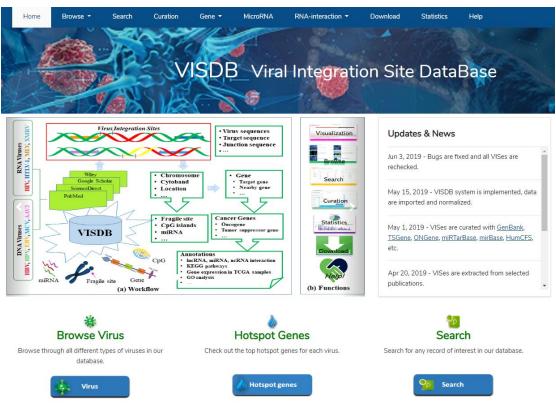


Figure 1. Homepage of VISDB

The homepage of VISDB (Figure 1) gives a summary of our knowledgebase, lists the functions of VISDB in the menu bar and provides some quick entries for accessing VISDB. Functions in VISDB consist of browse, search, curation, gene, miRNA, RNA-interaction, download, statistics and help.

1.2 Hotspot genes button

When clicking blue "Hotspot genes" button (Figure 2), a window pops out, listing the most 5 frequential genes targeted by HBV, HPV, EBV, MCV, AAV2, HIV and HTLV-1 respectively (Figure 3). Clicking on the "Close" button turns off the window while clicking on the hyperlinks of each gene name will create a new page to display all VISs targeting the gene (Figure 4).



Check out the top hits across the hotspot gene of the each virus.



Figure 2. Hotspot gene button

Hotspot genes

HBV: TERT FN1 KMT2B ALB LOC110806263

HPV: FHIT LRP1B RAD51B CDK13 KLF12

EBV: BACH2 DPP6 LOC100132154 CNTN4 KHDRBS2

MCV: ECH1 CDKAL1 PTP4A2 PTPRG

AAV2: CCNA2 CCNE1 KMT2B TNFSF10

HIV: MKL2 BACH2 HORMAD2 PACS1 STAT5B

HTLV-1: ROBO2 LRP1B EYS MACROD2

Close

Figure 3. All hotspot genes

Gene Information	
Gene ID	7015
Name	TERT
Alias	CMM9, DKCA2, DKCB4, EST2, PFBMFT1, TCS1, TP2, TRT, hEST2, hTRT
Description	telomerase reverse transcriptase
Location	5p15.33
Chromosome	chr5
Start	1253167
End	1295047
MicroRNAs	hsa-mir-138-5p; hsa-mir-498; hsa-mir-193b-3p; hsa-mir-335-5p; hsa-mir-12-5p; hsa-mir-1207-5p; hsa-mir-126 6-5p; hsa-mir-1182; hsa-mir-181a-5p; hsa-mir-6776-3p; hsa-mir-197-3p; hsa-mir-6740-3p; hsa-mir-6760-3p; hs a-mir-532-5p; hsa-mir-3064-5p; hsa-mir-422a; hsa-mir-1366; hsa-mir-1226-3p; hsa-mir-1255a; hsa-mir-1255b-5p
Annotations	ENCODE; GeneCards; KEGG; NCBI



Figure 4. VISs related to hotspot gene

1.3 Virus button

Clicking on the blue "Virus" button (Figure 5) lists 9 viruses curated in our knowledgebase. When clicking on virus name, the table on the bottom of the page change, listing the summary of 9 viruses (Figure 6).



Browse through all type of virus in our database.



Figure 5. Virus button

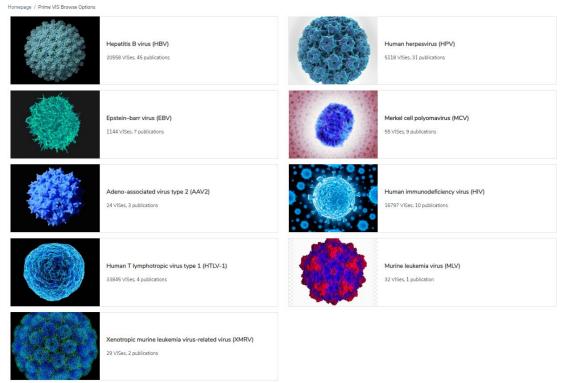


Figure 6. VIS summary of 9 viruses

Clicking on the icon of each virus activates virus-related pathway, GO analysis and VISs list (Figure 7). For HBV, HPV, HIV, HTLV-1 and EBV, virus pathway information is provided. GO analysis is available for HBV, HIV, HTLV-1 and HPV, other viruses have VISs list only.

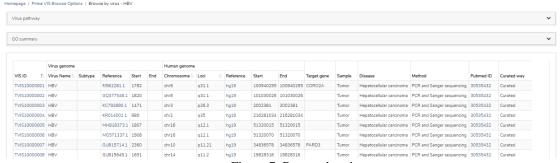


Figure 7. Browse by virus

Clicking on the Virus pathway unfolds virus metabolic pathway (Figure 8). Pathway information was downloaded from KEGG, we only retained the networks and genes of pathway entries.

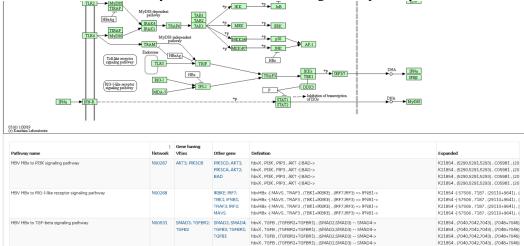


Figure 8. Virus pathway and its details

We divide pathway genes into two subsets, one is the set of genes targeted by VIS, the other is gene set of not being targeted by VISs. Clicking on the target gene name activates a new page displaying VISs in a table, clicking on non-target gene create a page display the gene information in KEGG. Clicking on the network code creates a new page displaying the sub pathway in KEGG.

Clicking on the "GO summary" link in Figure 7 unfolds the GO analysis result including BP table, BP bar chart, MF table and MF bar chart (Figure 9). Each part can unfold or fold independently.



Figure 9. GO analysis result

1.4 Search button

The blue "Search" button (Figure 10) is an entrance of searching all VISs in our database as well the menu item "Search" in the menu bar. The webpage will be navigated to the basic search page (Figure 11) when clicking on "Search" button.



Search the interested records in our database.



Figure 10. Search button

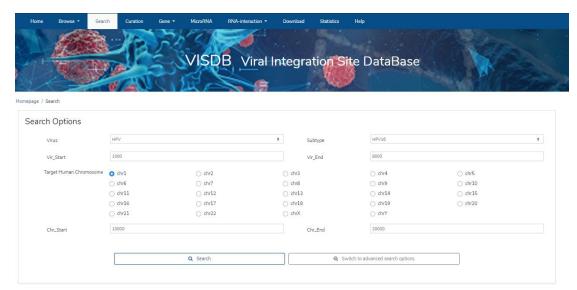


Figure 11. Basic search page

The basic search function provides user searching of specific virus and the integration sites on the chromosome.

Tips:

- 1) For virus with subtype, the default option is ignoring subtype and the user can click the dropdown box to choose the specific subtype. For virus without subtype, no other choice is provided. The "Start" and "End" mean the breakpoint in virus reference genome, their value must be integers.
- 2) User can search for multiple chromosomes at the same time by checking the chromosome checkbox. Clicking "Select all" link on the left of checkbox chooses all chromosomes, while "Deselect all" cancels all check.
- 3) "Advanced search options" link provides an entrance for using more complex query conditions, please refer to 3.2.
- 4) "Example option" link give users an example to fill in the search item.

2 VIS information

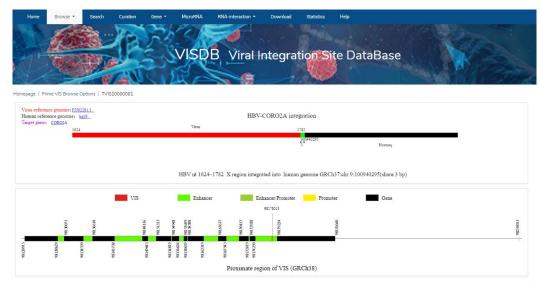


Figure 12.VIS information page

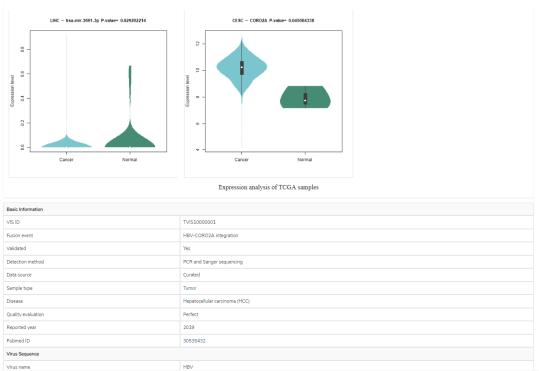


Figure 13.VIS information page

Perfect		
	Disease	Hepatocellular carcinoma (HCC)
	Quality evaluation	Perfect
us sequence Us name HBV ference genome FI562281.1 glon type X ut 1782 gegrated sequence TCAACGACCGACCTTCAAGCATACTTCAAAGACTGTTTGTT	Reported year	2019
HBV	Pubmed ID	30535432
FISE 228.1 1 gloin type X yt 1 TCAACGACCGACCTTCAAGCATACTTCAAAGACTGTTTGTT	Virus Sequence	
yolon type X tht 1782 TCAACGACCGACCTTGAGGCATACTTCAAAGACTGTTTGTT	Virus name	HBV
1782 TEAACGACCGACCTTGAGGCATACTTCAAAGACTGTTTGTTT	Reference genome	FI562281.1
TCAACGACCGACCTTGAGGCATACTTCAAGGACTGTTTGTT	Region type	X
ATTGGTCTGTTCACCAGCACCATGCAACTTTTCACCTCTGCCTAATCATCTCATGTTCATGTCCTAAGCCTCAAGCTGTGC at Sequence consistence drip drip doband q3.1.1 ference genome GRCh37/hg19 driv driv 100940295/98178013 (Hg38) driv function type Intronic	Start	1782
composition chr9 toband q3.1.1 ference genome GRCh37hg19 srt 100940295/98178013 (Hg38) d 100940295/98178013 (Hg38) cation type Intronic	Integrated sequence	
defence genome	Host Sequence	
ference genome GRCh37/hg19 urt 100940295/98178013 (Hg38) d 100940295/98178013 (Hg38) cation type Intronic	Chromosome	chr9
10040295/98178013 (Hg38) d 100940295/98178013 (Hg38) tation type Intronic	Cytoband	q31.1
d 100940295/98178013 (Hg38) Lation type Intronic	Reference genome	GRCh37/hg19
Intronic Intronic	Start	100940295/98178013 (Hg38)
	End	100940295/98178013 (Hg38)
	Location type	Intronic
get gene CORO2A	Target gene	CORO2A
RNAs that regulate target gene hs-mir-124-5p : hsa-mir-21-5p : hsa-mir-678-3p : hsa-mir-1976 : hsa-mir-1976 : hsa-mir-583-5p : hsa-mir-6747-3p : hsa-mir-6727-3p : hsa-mir-6722-3p : hsa-mir-6814-5p : hsa-mir-891-3p : hsa-mir-4291 : hsa-mir-6215 : hsa-mir-627-5p : hsa-mir-937-5p : hsa-mir-937-5p : hsa-mir-937-5p : hsa-mir-937-5p : hsa-mir-937-5p : hsa-mir-938 : hsa-mir-938-3p : h	miRNAs that regulate target gene	mir-4722-3p; hsa-mir-6814-5p; hsa-mir-3691-3p; hsa-mir-4279; hsa-mir-8081; hsa-mir-1231; hsa-mir-627-5p; hsa-mir-937-5p; hsa-mir-516b-5p; hsa-mir-797; hsa-mir-3120-5p; hsa-mir-5699-3p; hsa-mir-4421; hsa-mir-6748-3p; hsa-mir-6736-3p; hsa-mir-5588-3p; hsa-mir-29b-2-5p; hsa-mir-3187
arest mIRNA hsa-let-7a-1/Upstream/814332; hsa-mir-12126/Downstream/51136;	Nearest miRNA	hsa-let-7a-1/Upstream/814332; hsa-mir-12126/Downstream/51136;
arest TSS ENST00000422679(Upstream/5129; ENST00000610463)(Downstream/14627;	Nearest TSS	ENST00000422679/Upstream/5129; ENST00000610463/Downstream/14627;
arest CpG islands None/Target, chr9-CpG: 64/Upstream/58635, chr9-CpG: 24/Downstream/13991	Nearest CpG islands	None/Target, chr9-CpG: 64/Upstream/58635, chr9-CpG: 24/Downstream/13991
wnstream sequence GCTCTCTACTTTTTTTAAATTTATTTTATAAAAACATTTTTT	Downstream sequence	${\tt GCTCTCTCACTTTTTTTTAAATTTATTTTTATAAAAACATTTTTT$
ACGCCACTGGAACCTGCCCAAGGTCTTACATAAAAGGACTCTTGGACTCTCAGCAATGTCAACGACCGAC	Junction sequence	GGAGGAGTTGGGGGAGGAGATTAGGTTAATGATCTTTGTACTAGGAGGCTCTCTCACTTTTTTTCTTTTTTAAATTTATTT
ference	Reference	

Figure 14.VIS information page

Figure 12-14 is the detailed description of VIS, the introduction of our VIS expressing model please refer to the online help page. For VIS downloaded from other databases, VISDB will navigate to the source website such as RID and HPVbase. The "Curate" button provides the user with the function of correcting or perfecting VIS for VISDB, and its usage is referred to "Curation" page. Here we just list the tips of using this page.

The detailed page is divided into 4 zones, zone one shows the visualization of single integration event, zone two shows the visualization of DNA elements proximate to VIS, zone three shows the gene and miRNA

expression of target gene targeted by current VIS, zone four is the description of VIS.

2.1 VIS visualizing zone

The uppermost of this page is the visualization of virus integration site.

- (1) The title such as "HBV-CORO2A integration" implies the integration is an event of HBV integrated into CORO2A gene.
- (2) The title such as "HBV-chr14: q22.3 integration" implies that the integration is an event of HBV integrated into cytoband 14q22.3.
- (3) The description of the demo briefly introduces the specific breakpoints and locations of this integration event.
- (4) Red block, black block, green block and gray block means the region belonging to virus sequence, human sequence block, both human sequence and virus sequence and unknown sequence separately.
 - (5) Coordinates above the red block mean they are the start and stop breakpoints of virus sequence.
 - (6) Coordinates below the black block mean they are the start and end locations on the human sequence.
- (7) The reference virus genome and human genome are displayed in the upper left corner if they are provided in the original publications.
- (8) Clicking on the link of Virus reference genome or red block navigates to the virus reference genome used in the original navigates.
- (9) Clicking on the link of Human reference genome navigates to the human reference genome used in the original publication.
- (10) Clicking on the link of gene name will open a new page describing the relation between gene, fragile site and miRNA (Figure 15).
- (11) Clicking on the black navigates to the precise region of the NCBI human reference genome with corresponding assembly and location (Figure 16).



Figure 15. Target gene-correlated entries

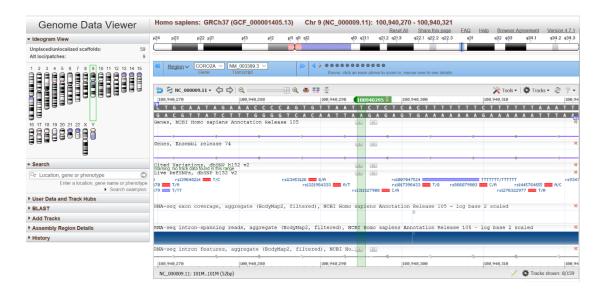


Figure 16. Displaying the precise location of "HBV-CORO2A integration" with NCBI Genome Data Viewer

2.2 Proximate DNA elements visualizing zone

The figure shows the relationship between VIS and other gene elements. On the top of the figure, there are five color blocks representing five different elements. Clicking the region on the gene will display the detail information about this region, such as the name of this region, the location in this chromosome and the score from the GeneHancer database (Figure 17).

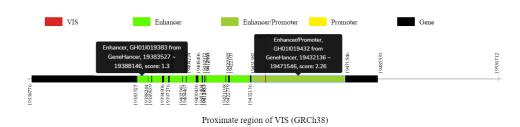


Figure 17. Proximate DNA elements visualizing zone

2.3 Gene and miRNA expression zone

This part shows the expression level of the target genes and miRNAs that regulate the target gene in The Cancer Genome Atlas (TCGA) dataset. The title of each figure shows the type of cancer in TCGA dataset, the symbol of the gene or miRNA and P-value. For miRNAs, only miRNAs with P-value less than 0.05 are shown (Figure 18).

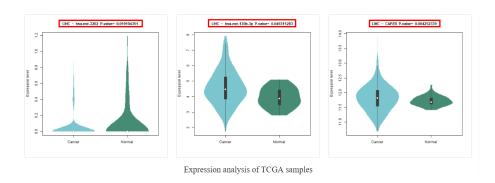


Figure 18. Expression of genes and miRNAs in TCGA dataset.

2.4 Text information region

- (1) Clicking on the "PubMed ID" link navigates to the online download page in the NCBI PubMed database.
- (2) Clicking on the "Reference Genome" link navigates to virus genome or human genome.
- (3) Clicking on the "microRNA" link navigates to the corresponding microRNA introduction page in miRTarBase.
- (4) Clicking on the "Target gene" or "Nearby gene" or "Nearest cancer gene" (TSG means tumor suppressor gene, OG means oncogene) link navigate to the gene homepage in NCBI GenBank.
- (5) Clicking on the "Fragile site" link navigates to the corresponding chromosome fragile site/region in HumCFS database.
- (6) Clicking on the "Start" or "End" link of host sequence navigate to the precise region of NCBI human reference genome with corresponding assembly and locations (Figure 16).
- (7) For virus sequence, if the begin breakpoint, stop breakpoint and reference genome exists, the "integrated sequence" is the sequence between "begin breakpoint" and "stop breakpoint". Otherwise, the upstream 100bp of "begin breakpoint" or "stop breakpoint" is extracted and isolated by "||".
- (8) For target sequence, we try to provide the upstream 100bp of "begin location", the sequence between "begin location" and "end location" (denoted as "target sequence"), and the downstream 100bp of "end location" if the detailed locations and reference human genome are provided in the original publications. If only one location is provided, then the upstream 100bp and downstream 100bp of the point are extracted.

2.5 Gene, fragile site, miRNA and pathway

For the VIS-targeted gene, we also provide:

- 1) Fragile site the target gene located.
- 2) miRNAs that have influences on the target gene.
- 3) Pathways that target gene involved in KEGG database.
- 4) Carcinogenesis in ONGene database if the target gene is identified as an oncogene.
- 5)Cancer suppressor in TSGene database if the target gene is identified as a tumor suppressor gene.
- 6) Common gene database such as GenBank, Encode, GeneCards.
- In the target gene-correlated page:
- (1) Clicking on the "microRNA" link navigates to the corresponding microRNA introduction page in miRTarBase.
- (2) Clicking on the "Fragile site" link navigates to the corresponding chromosome fragile site/region in HumCFS database.
 - (3) Clinking on the "Reference" link navigates to ENCODE, KEGG, Genecards page about the target.

3 Browse

In VISDB, we provide six kinds of different ways to browse all virus integration sites (VIS), you may browse the VIS based on your rules, such as fragile sites, chromosome, disease, experiment and literature.

Choose the Browse module (Figure 19). You will see six options below and you can select one based on your interest.

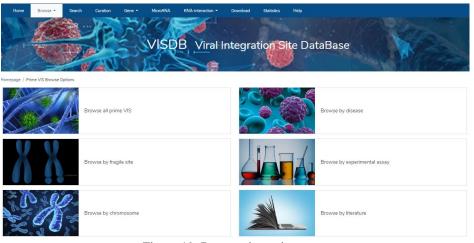


Figure 19. Browse the main menu.

3.1 Browse all

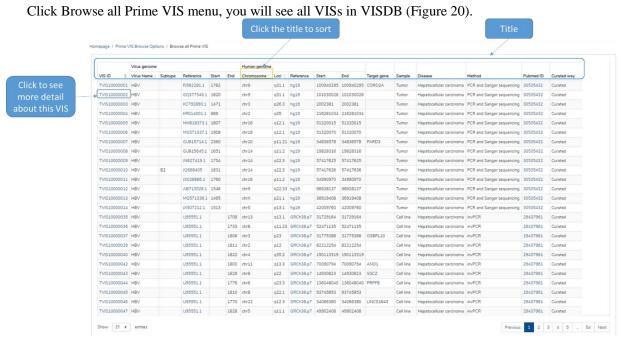


Figure 20. All VIS in VISDB

3.2 Browse by fragile site

Clicking Browse by fragile site, the page will display the name of each fragile site (Figure 21).



Figure 21. All fragile site name in VISDB.

You may select one of the interested fragile to see the detail information of this fragile site (Figure 22) and also the VIS which is located within this fragile site (Figure 23).

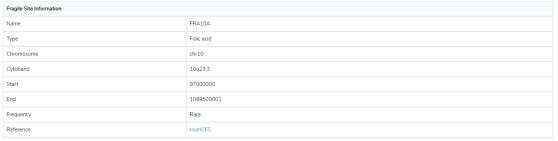


Figure 22. Detail information of one fragile site.

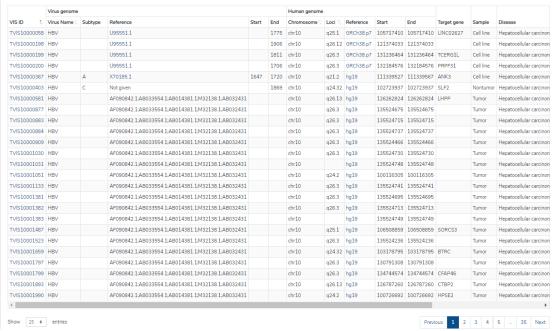


Figure 23. VIS located within this fragile site.

3.3 Browse by disease

Click Browse by disease menu, the page will display all the diseases in VISDB (Figure 24).



Figure 24. All diseases in VISDB.

You can click the interested disease name to see all VISs associated with this kind of disease (Figure 25).

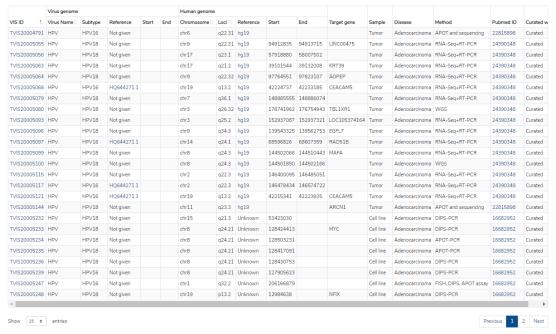


Figure 25. All VISs associated with one kind of disease.

3.4 Browse by experimental assay

Click Browse by experiment assay, the page will display all of the experiment assays in VISDB (Figure 26). It includes wet and dry lab assays that used to detect the virus integration on human genome.



Figure 26. All experiment assay in VISDB

You can click the interested experiment assay to check the VIS that was detected by this experiment assay (Figure 27).

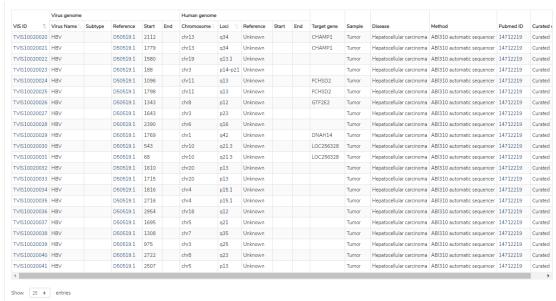


Figure 27. All VIS detected by the experiment assay.

3.5 Browse by chromosome

Click Browse by chromosome, the page will display all chromosome in VISDB (Figure 28).

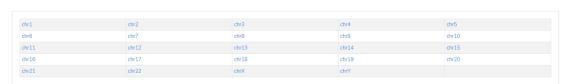


Figure 28. All chromosome in VISDB.

You may click the interested chromosome on this page, it will display all VISs located on this chromosome (Figure 29).

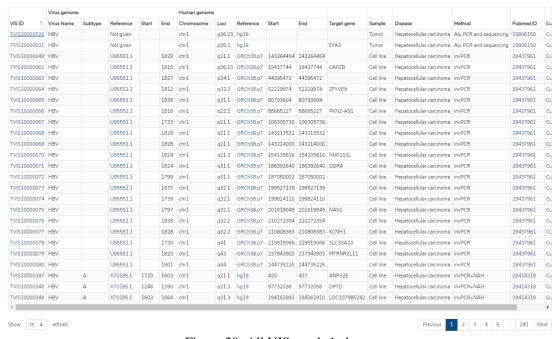


Figure 29. All VIS on chr1 chromosome.

3.6 Browse by literature

Click Browse by literature, the page will display all collected literature in VISDB (Figure 30).

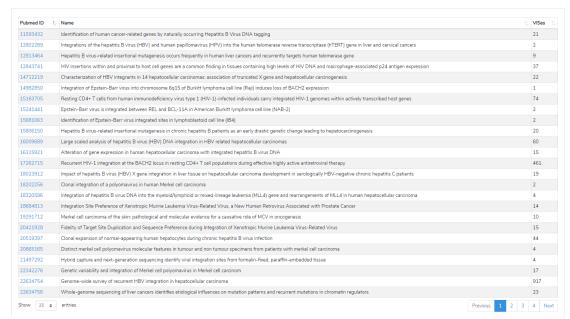


Figure 30. All literature collected in VISDB.

You can click the PubMed ID to browse all VISs collected from this literature (Figure 31).

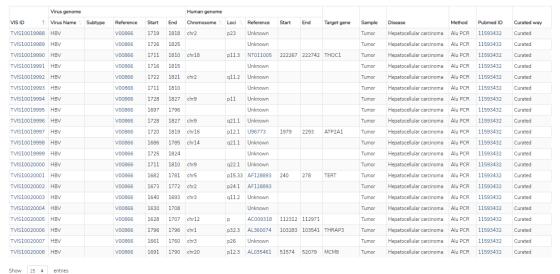


Figure 31. All VISs collected from one literature.

4 Search

4.1 Basic search

Clicking the menu item in the menu bar acts the same as clicking the "Search" button on the homepage, please refer to 1.4 search button.

4.2 Advanced search



Figure 32. Advanced search page

Clicking the "Advanced search" in the basic search page will activate the advanced search page (Figure 32). As shown in Figure 32, the leftmost dropdown box provides the following searching options including:

Item	Suggested value
Virus	HBV, HPV, EBV, MCV, AAV2, HIV ,HTLV-1,MLV,XMRV
Chromosome	chr1~chr22,chrX,chrY
Paper	PubMed ID
Target gene	Official symbol of the gene in GenBank
Fragile site	Fragile site name such as FRA1A1
Disease	Adenocarcinoma, Adenosquamous carcinoma, Adult T-cell leukemia, AIDS dementia, AIDS-associated lymphoma, Anal intraepithelial neoplasia Angioimmunoblastic lymphadenopathy, B-cell lymphoma, Cervical carcinoma, Cervical intraepithelial neoplasia, Clear cell carcinoma, Extranodal natural killer T-cell lymphoma, Gastric carcinoma, Head and neck squamous cell carcinoma, Hepatocellular carcinoma, HIV-infected disease, Hodgkin lymphoma, HTLV-1 associated myelopathy/tropical spastic paraparesis ,Merkel cell carcinoma, Nasopharyngeal carcinoma, Neuroendocrine carcinoma, NK/T cell lymphoma, Oropharyngeal squamous cell carcinoma, Prostate cancer,Squamous-cell carcinoma, Vaginal cancer, Not given
Assay	Abbreviation of the assay, such as PCR, invPCR, NGS, etc. Approximate
	match is applied here.
Sample type	Tumor, Nontumor, PBMC, Cell line, Adjacent tissue

Users can choose any items in the above list or combine more items together to form complex searching conditions to reduce the scope of browsing. Figure 32 set "Virus" as the default searching item, users can change the item by clicking the drop-box and choose the item he or she prefers. The specific usages of advance are as follows.

Step1: choose items interested for search.

Step2: select comparing operation: equal or unequal (IS or IS NOT).

Step3: choose an item value by clicking drop-box or inputting data in the text box

Step4: add more conditions (click the "Add" link, clicking the "remove" link will delete a querying condition), and continue step 1~3.

Step5: click the "search" button.

In addition, clicking the "Back to basic search" link will navigate the page to the basic search page.

5 Curation

We provide the curation function for user to supplement or correct the VIS in our database. User uses curation function to submit their suggestion, and the final update will be validated only after checked by VISDB maintenance team.

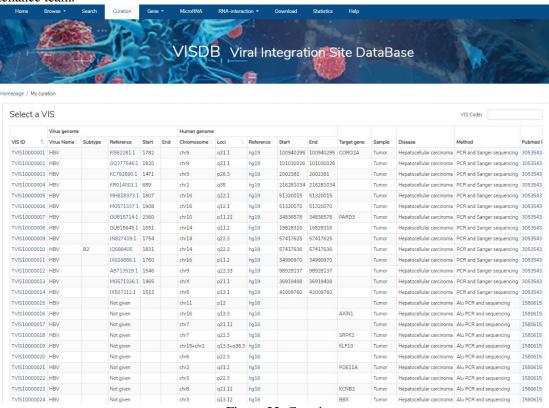


Figure 33. Curation page

To curate a VIS, the user needs to select a VIS by inputting the VIS ID in the text box in the upper right corner or click on the VIS ID link list in the table (Figure 33). The VIS curation page is shown in Figure 34.

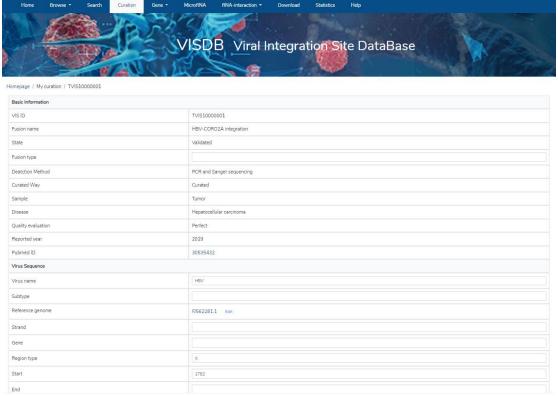


Figure 34. VIS curation page

In Figure 34, items that can be curated by user are displayed with the edit box or "Edit" link beside the value. For the former case, the user only needs to input the new value. For the latter, a small window containing the link name and URL will be popped out (Figure 35).

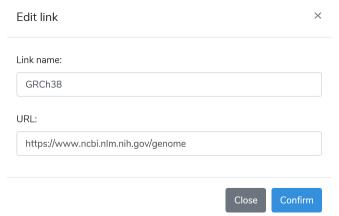


Figure 35. Page for editing link

In a word, the whole flow of curating a VIS for VISDB is as follows.

Step1: Choose the VIS to be curated

Step2: Edit items with accurate values.

Step3. Input a valid mailbox to get feedback from our team.

Step4. Click "Submit Curation" button to submit your update.

6 Gene

The "Gene" module provides target gene, nearby gene, target oncogene, nearby oncogene, target tumor suppressor gene and nearby tumor suppressor gene for users to browse by their interest. Here, we provide an example to show how to use the module to explore viral integration sites of each virus.

A particular gene can be specifically integrated with several viruses. How could we know the viral integration site that targets in the interested gene? Here, take "AKAP13" as an example, which has been reported associated with cancer in humans, other kinds of gene can be operated in the same way.

1. Choose the Target Oncogene sub-module under "Gene" module (Figure 36). VISUD VIrai Integration Site DataBase Homepage / Gene / Target gene Search gene by Name: ABL1 ADAMS ADAMTS18 ADAMI ADAMTS9-AS ADARB1 AFAP1L2 AFDN AFF1 AFF3 AGAP2 AGFG1 AGRN AGTR1 AHI1 AHR AJAP1 Show 25 ¢ entries Previous 1 2 3 4 5 ... 43 Next

Figure 36. Target gene page

2. Enter the gene name of "AKAP13" or click the "AKAP13" button. Then it will give the information about "AKAP13" gene and all VISs which can target "AKAP13" (Figure 37, 38).



Figure 37. Detail information of AKAP13

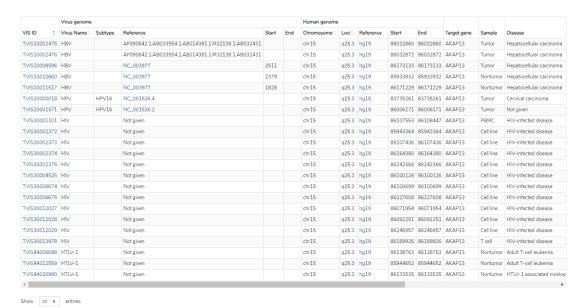


Figure 38. AKAP13-targeted VISs

3. Click the highlighted non-zero characters to browse more details. For example, click "TVIS10002475" in the VIS ID column, you can get more details about TVIS10002475 of HBV(VIS information).

7 miRNA

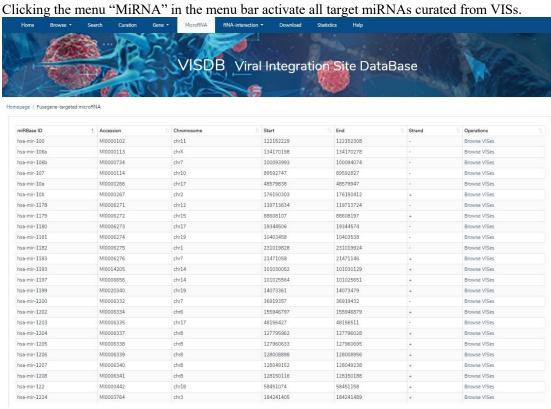


Figure 39. List of miRNAs target by VISs in VISDB

Figure 39 list part of information of miRNA targeted by VIS. Clicking the miRBase ID or Accession number navigates to miRBase to see detailed information of the miRNA.

Clicking the "Browse VISs" link in the operation column navigates to the list of VISs which are shown below the list of miRNA.

8 Download

We provide http download for VISs, Target genes and other kinds of data collected in the curation process. User can click the filename with right mouse click and select "save the object as" to save the file to local disk (Figure 40).

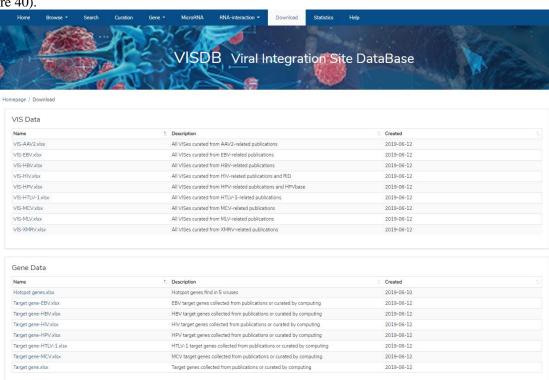


Figure 40. Data files for download