H-InvDB in 2009: extended database and data mining resources for human genes and transcripts

Chisato Yamasaki1, Katsuhiko Murakami2, Jun-ichi Takeda1, Yoshiharu Sato1, Akiko Noda1, Ryuichi Sakate1, Takuya Habara1, Hajime Nakaoka2,3, Yusuke Todokoro2,4, Akihiro Matsuya2,5, Tadashi Imanishi1 and Takashi Gojobori1,6,*

1BIRC, AIST, 2JBIC, 3C’s Lab Co. Ltd, 4DYNACOM Co. Ltd, 5Hitachi Ltd, 6CIB-DDBJ, NIG Waterfront Bio-IT Research Building, 4-7 Aomi, Koto-ku, Tokyo 135-0064, Japan

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ABSTRACT

We report the extended database and data mining resources newly released in the H-Invitational Database (H-InvDB; http://www.h-invitational.jp/). H-InvDB is a comprehensive annotation resource of human genes and transcripts, and consists of two main views and six sub-databases. The latest release of H-InvDB (release 6.2) provides the annotation for 219765 human transcripts in 43159 human gene clusters based on human full-length cDNAs and mRNAs. H-InvDB now provides several new annotation features, such as mapping of microarray probes, new gene models, relation to known ncRNAs and Glycogene information. H-InvDB now also provides useful data mining resources—‘Navigation search’, ‘H-InvDB Enrichment Analysis Tool (HEAT)’ and web service APIs. ‘Navigation search’ is an extended search system that enables complicated searches by combining 16 different search options. HEAT is a data mining tool for automatically identifying features specific to a given human gene set. HEAT searches for H-InvDB annotations that are significantly enriched in a user-defined gene set, as compared with the entire H-InvDB representative transcripts. H-InvDB now has web service APIs of SOAP and REST to allow the use of H-InvDB data in programs, providing the users extended data accessibility.

INTRODUCTION

We held the first international workshop entitled ‘Human Full-length cDNA Annotation Invitational’ (abbreviated as H-Invitational or H-Inv) in Tokyo, Japan, from 25 August to 3 September 2002, and constructed a novel, integrative database of human transcriptome called H-Invitational Database (H-InvDB; http://www.h-invitational.jp/) (1). H-InvDB is a comprehensive annotation resource of human genes and transcripts. On 20 April 2009, we marked the fifth anniversary of the opening of H-InvDB to the public. During this period, we released six major updates, namely H-InvDB 1.0(1), 2.0(2), 3.0, 4.0(3), 5.0 and 6.0. The latest release (release 6.2) provides annotations for 219765 human transcripts in 43159 human gene clusters based on human full-length cDNAs and mRNAs. The increases in the number of entries in H-InvDB are summarized in Table 1.

For these human transcripts, proteins and genes, we now provide several new annotation features, such as mapping of probes, new gene models, relation to known ncRNAs and glycogene information. H-InvDB now also provides useful data mining resources—‘Navigation search’, ‘H-InvDB Enrichment Analysis Tool (HEAT)’ and web service APIs. Here, we report on the extended database and data mining resources newly released in H-InvDB.

THE EXTENDED DATABASE OF H-InvDB

RELEASE 6.2

In our latest release of H-InvDB release 6.2, we annotated 162395 human mRNAs extracted from the International Nucleotide Sequence Databases (INSD)(4) in addition to 54927 human FLcDNAs that were available on 9 May 2008. We mapped these human transcripts onto the human genome sequences (NCBI build 36.2) and determined 43159 human gene clusters. For these human gene clusters, we defined 34511 (80.0%) protein-coding and 7747 (17.9%) non-protein-coding loci, whereas...
901 (2.1%) transcribed loci overlapped with predicted pseudogenes. We then followed functional and further comprehensive annotation procedures as described previously (1–3). The statistics of manually curated representative human proteins are summarized in Table 2.

In H-InvDB, we now include annotation for two kinds of high-quality predicted transcripts: eHITs and pHITs. The eHIT transcripts are computationally and manually annotated gene models whose exon–intron structures are synthetically predicted by integrating the information of EST and mRNA sequences. pHIT transcripts are the novel gene candidates predicted from human genome sequences using CAGE tags and several gene prediction programs summarized using JIGSAW (5). In H-InvDB release 6.2, we provided 612 eHIT and 1831 pHIT predicted transcripts. For eHIT gene models, we assigned HIT ID prefixed ‘e’ (e.g. eHIT000000001) and for pHIT gene models, we assigned HIT ID prefixed ‘p’ (e.g. pHIT000000001). For example, pHIT000015735 is mapped on chromosome 9p13.3 and consists of 18 exons. The functional description for pHIT000015735 is ‘Interleukin-11 receptor alpha chain precursor (IL-11RA), Isoform HCR2’ which is classified as H-InvDB similarity category I, Identical to known human protein. For pHIT000015735, HIX0153289 is assigned as cluster ID and HIP000180408 is assigned as protein ID. It is a newly identified isoform of a known UniProtKB/Swiss-Prot entry, Q14626-2, which is a soluble form of Interleukin-11 receptor alpha chain (sIL11RA). In HIX0153289, pHIT000015735 is an only member and no other human mRNA, RefSeq nor Ensembl transcripts are included, suggesting that this is a novel human transcript candidate with a support of UniProtKB/Swiss-Prot entry. An example screen shot of G-integra for pHIT000015735 is shown in Figure 1.

The H-InvDB annotation resources consist of two main views: Transcript view and Locus view, and six sub-databases: the DiseaseInfo Viewer H-ANGEL (6), G-integra, Evola (7), the PPI view and the Gene family/group view with appropriate crosslinks. Here, we describe the viewers that we have extended since our previous report (3). The new annotation features in H-InvDB are summarized in Table 3.

New features in Transcript view and Locus view

Transcript view shows all annotations of the H-Inv transcript in 12 section tabs, and Locus view shows all annotations of a locus in 6 section tabs. At the ‘expression’ tab in Transcript and Locus view, the mappings of microarray probes to H-InvDB data are now available. The probes of DNA Chip Research AceGene, Affymetrix GeneChip and Agilent in DNAProbe Locator (http://h-invitational.jp/DNAProbeLocator/) were mapped, related to H-InvDB entries (both to HIT and HIX), and are shown. To qualify the transcript quality, we now provide two new features, truncation (8) and Kozak consensus sequence (9) at the ‘Transcript Info’ tab in Transcript view. We have also integrated the annotated information of the GlycoGene Database (10) and the Functional RNA Database (11) at the ‘function’ tab in Transcript view using web services.
The Transcript and Locus views also have links to related external public databases including DDBJ/EMBL/GenBank (4), RefSeq (12), UniProtKB (13), HGNC (14), GeneCards (15), InterPro (16), Ensembl (17), EntrezGene (18), CCDS (19), PubMed (20), dbSNP (21), GO (22), GTOP (23), OMIM (24) and MutationView (25).

New features in G-integra

G-integra is an integrated genome browser in which we can examine the genomic structures of transcripts. The genomic locations, gene structures and alignments against the human genome of H-Inv transcripts, and the corresponding RefSeq and Ensembl entries are shown. We now show the annotations for two types of high-quality gene models, pHIT and eHIT, for all human gene tracks (Figure 1). G-integra provides gene structure annotations for two new species (horse and medaka). In total, the gene structures for humans and 13 non-human species, namely Pan troglodytes (chimpanzee), Macaca sp. (macaque), Mus musculus (mouse), Rattus norvegicus (rat), Canis familiaris (dog), Bos taurus (cow), Monodelphis domestica (opossum), Gallus gallus (chicken), Equus ferus caballus (horse), Danio rerio (zebrafish), Tetraodon nigroviridis (tetraodon), Takifugu rubripes (fugu) and Oryzias latipes (medaka) can be optionally displayed for comparison. The reference gene structures of non-coding RNAs of fRNAdb, pseudogenes of Pseudogene.org (26) and consensus coding sequences of CCDS (19) are also shown.

Table 3. New annotated features in H-InvDB

| No. | Annotation item                                      | Area                          | Available at                                    |
|-----|------------------------------------------------------|-------------------------------|------------------------------------------------|
| 1   | Mappings of microarray probes to H-InvDB data        | Expression                    | ‘Expression’ tab in Transcript view            |
| 2   | New ID for gene families/groups (HIF)                | Gene family                   | ‘Function’ tab in Transcript view, Locus view, and Gene Family/groups view. |
| 3   | pHIT gene models                                     | Gene model                    | Transcript view, Locus view, G-integra and all the related viewers |
| 4   | eHIT gene models                                     | Gene model                    | Transcript view, Locus view, G-integra and all the related viewers |
| 5   | Truncation judgment                                  | Quality control               | ‘Transcript Information’ tab in Transcript view |
| 6   | Kozak sequence                                       | Quality control               | ‘Transcript Information’ tab in Transcript view |
| 7   | Anti-sense gene information                           | Gene structure                | ‘Gene structure’ tab in Locus view             |
| 8   | Detailed data of similarity to known ncRNA.          | ncRNA                          | ‘Function’ tab in Transcript view               |
| 9   | Two new species (horse and medaka) for comparative analysis | Comparative                   | ‘Evolution’ tab in Transcript view, G-integra and Evola |
| 10  | Detailed annotation for unmapped (UM) transcripts    | Gene structure                | Topic Annotation viewer                        |
| 11  | Remote integration of GlycoGene Database (GGDB)      | Function                      | ‘Function’ tab in Transcript view               |
| 12  | Remote integration of the functional RNA database (fRNAdb) | ncRNA                        | ‘Function’ tab in Transcript view               |
NEWLY RELEASED DATA MINING RESOURCES IN H-InvDB

H-InvDB now provides newly released useful data mining resources, namely ‘Navigation search’, ‘H-InvDB Enrichment Analysis Tool (HEAT)’ and web service APIs.

Navigation search

‘Navigation search’ is an extended search system that enables complicated searches by any combination of 16 different search contents. This system consists of three interfaces: search navigation menu, new advanced search and search results and the user interface images are shown in Figure 2. Search navigation menu: for every view in H-InvDB for example the top page, there is a link to ‘Navi’ on the black menu bar (Figure 2A). The search navigation menu provides a list of all searches available in H-InvDB (Figure 2B). New advanced search provide combination search of 16 search contents, for example, #2 gene structure, #3 alternative splicing (AS) variants, #10 genetic polymorphism and #13 relation to disease. The search results provide the list of HIX IDs, HIT IDs, Chromosome number, definition, HGNC gene symbol, and links to appropriate H-InvDB and related viewers.

Figure 2. ‘Navigation search’: powerful search tool of 16 search items. Example screen shot of the Navigation search system (http://www.h-invitational.jp/hinv/c-search/). (A) There are links to the Navigation system, ‘Navi’, at the black menu bar in all the viewers in H-InvDB including the top page. (B) Search navigation menu provide the list of all searches available in H-InvDB. (C) The new advanced search provide combination search of 16 search contents, for example, #2 gene structure, #3 alternative splicing (AS) variants, #10 genetic polymorphism and #13 relation to disease. (D) The search results provide the list of HIX IDs, HIT IDs, Chromosome number, definition, HGNC gene symbol, and links to appropriate H-InvDB and related viewers.
H-InvDB Enrichment Analysis Tool

H-InvDB Enrichment Analysis Tool (HEAT) is a data mining tool for automatically identifying features specific to a given human gene set. HEAT searches for H-InvDB annotations that are significantly enriched in a user-defined gene set as compared with the entire H-InvDB representative transcripts. This technique is called ‘gene set enrichment analysis’ and is popularly used for analysing the results of microarray experiments. The HEAT analysis requires three steps. (i) Gene-Set Submission: users must submit two or more human gene IDs. Acceptable IDs are H-InvDB Transcript IDs (HIT), Locus IDs (HIX), HUGO Gene Symbols, and accession numbers of INSD (DDBJ/EMBL/GenBank). (ii) Execution: the submitted IDs are converted into HIXs of H-InvDB release 6.0 representative transcripts by using the ID Converter System (27). (iii) Results: enriched features of the given gene set are shown. For each feature, the link to description of the feature, number of occurrences/gene of a submitted gene set, number of occurrences/gene among all H-InvDB representative transcripts and P-values are shown. Features with P-values smaller than 0.01 are shown and the list of results are sorted by P-value. Fisher’s exact probability is used in calculating the P-values. The following features of H-InvDB are analysed: InterPro, GO, the KEGG pathway, chromosomal band, gene family, structural domains (SCOP), subcellular localization prediction (using WoLF PSORT) and tissue-specific gene expression (10 tissue categories defined in H-ANGEL).

URL: http://h-invitational.jp/hinv/hws/search.php?lang=en.

H-InvDB web-service APIs: a new data retrieval service

The web service interface is becoming a major way for accessing biological databases (28). H-InvDB now provides a new data retrieval service, web service with APIs of Simple Object Access Protocol (SOAP) and Representational State Transfer (REST), to retrieval the H-InvDB entries of given IDs or keywords. Entries in H-InvDB can be retrieved in XML or sequence FASTA format. The current H-InvDB web service provides 26 SOAP and 28 REST APIs. To use the REST service, an HTTP connection (e.g. web browser) and a programming language (e.g. Perl, JAVA) are required. Although both the POST and GET methods of access are supported, the POST method is approved. To retrieve entries for a keyword, e.g. ‘cancer’, the method and parameters are as follows: http://h-invitational.jp/hinv/hws/keyword_search.php?query=cancer.

To use the SOAP service, users are requested to use the SOAP library of programming languages. Access to WSDL is via http://h-invitational.jp/hinv/hws/API?wsdl. The 12 representative SOAP APIs are listed in Table 5, and complete detailed descriptions are provided at the following URLs:

- REST APIs: http://www.h-invitational.jp/hinv/hws/doc/en/api_list.php
- SOAP APIs: http://www.h-invitational.jp/hinv/hws/doc/en/soap_api_list.php

The H-InvDB web service is already used for retrieving H-InvDB data by other databases. For example, in MutationView, a database for mutations in human disease genes (25), the InterPro domain data in H-InvDB are used to search for relations among of the functional domains, human genes and human disease-related mutations.

DATA AVAILABILITY AND FUTURE DIRECTIONS

H-InvDB is freely available for both academic and commercial use, and can be accessed online at http://www.h-invitational.jp/ (or hinv.jp). Annotated data can also be downloaded in FASTA sequence files, original-format flat files or XML files at HTTP and FTP servers. Major
updates are released once a year and minor updates are released a few times per year when necessary. For the next major update of H-InvDB by the end of this year, the annotations for the latest human genome assembly NCBI b37 will be provided.

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