Chapter 2

UniProtKB/Swiss-Prot, the Manually Annotated Section of the UniProt KnowledgeBase: How to Use the Entry View

Emmanuel Boutet, Damien Lieberherr, Michael Tognolli, Michel Schneider, Parit Bansal, Alan J. Bridge, Sylvain Poux, Lydie Bougueleret, and Ioannis Xenarios

Abstract

The Universal Protein Resource (UniProt, http://www.uniprot.org) consortium is an initiative of the SIB Swiss Institute of Bioinformatics (SIB), the European Bioinformatics Institute (EBI) and the Protein Information Resource (PIR) to provide the scientific community with a central resource for protein sequences and functional information. The UniProt consortium maintains the UniProt KnowledgeBase (UniProtKB), updated every 4 weeks, and several supplementary databases including the UniProt Reference Clusters (UniRef) and the UniProt Archive (UniParc).

The Swiss-Prot section of the UniProt KnowledgeBase (UniProtKB/Swiss-Prot) contains publicly available expertly manually annotated protein sequences obtained from a broad spectrum of organisms. Plant protein entries are produced in the frame of the Plant Proteome Annotation Program (PPAP), with an emphasis on characterized proteins of *Arabidopsis thaliana* and *Oryza sativa*. High level annotations provided by UniProtKB/Swiss-Prot are widely used to predict annotation of newly available proteins through automatic pipelines.

The purpose of this chapter is to present a guided tour of a UniProtKB/Swiss-Prot entry. We will also present some of the tools and databases that are linked to each entry.

Key words Swiss-Prot, TrEMBL, UniProt, Protein database, Amino-acid sequence, Manual annotation

1 Introduction

In late 2002 the SIB Swiss Institute of Bioinformatics (SIB), the European Bioinformatics Institute (EBI) and the Protein Information Resource (PIR) (*see* **Note 1**) joined forces by creating the Universal Protein Resource (UniProt) consortium [1]. The aim of this consortium is to provide high quality protein databases that are freely accessible to the scientific community.

The centerpiece of UniProt is the UniProt Knowledgebase (UniProtKB, http://www.uniprot.org), a comprehensive and

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annotated protein sequence knowledgebase, which consists of two sections: UniProtKB/Swiss-Prot, containing manually expertly annotated entries, and UniProtKB/TrEMBL, containing computer translation and annotation of CoDing Sequences (CDS) extracted from the European Molecular Biology Laboratory nucleotide sequence database (EMBL) [2, 3] as well as sequences and annotation imported from Ensembl (http://www.ensembl.org), EnsemblGenomes (http://ensemblgenomes.org) including EnsemblPlants (http://plants.ensembl.org), and in the future, from RefSeq (http://www.ncbi.nlm.nih.gov/refseq/). Taking advantage of the expertly curated UniProtKB/Swiss-Prot section, automatic annotation procedures based on well described proteins are created and maintained to improve the annotation of related proteins in the UniProtKB/TrEMBL section. UniProtKB entries contain information curated by biologists or produced by annotation rules, and provide users with cross-links to about 140 external databases and give access to additional information or tools. UniProtKB/Swiss-Prot contributes actively to the "Gene Ontology" (GO, 10) annotation effort of proteins by manually assigning GO terms during the annotation process.

UniProtKB/Swiss-Prot is characterized by extended expert annotation (sequence properties, corresponding literature, etc.), minimal redundancy (separate entries for the same gene product in a given species and same cultivar/isolate are merged into a single protein entry), integration with other databases (cross-links to other life science databases including sequence-related databases as well as specialized data collections) and documentation (large number of index files and specialized documentation files) (*see* **Note 2**).

UniProtKB/TrEMBL, a computer-annotated database, mainly consists of translations of all coding sequences (CDS) proposed by the submitters to the EMBL/GenBank/DDBJ nucleotide databases, which are not integrated into UniProtKB/Swiss-Prot, and by proteomes imported from Ensembl and EnsemblPlants. Some additional protein sequences are also extracted from the literature or directly submitted to UniProtKB. In addition to the preliminary information given by the submitters, UniProtKB/TrEMBL entries are processed according to automatic annotation procedures such as: (i) transfer of general annotation, domains and functional sites from well-characterized UniProtKB/Swiss-Prot entries belonging to protein family groups defined by InterPro [4], (ii) removal of redundancy by merging identical full-length sequences from the same organism, (iii) attribution of evidence to identify the source of individual data items (*see* **Note 3**).

In addition to UniProtKB, the UniProt consortium maintains several other protein databases, including:

– **The UniProt Archive (UniParc),** which stores and maps all publicly available protein sequences from numerous databases, including UniProtKB, RefSeq, Patent offices, etc. (obsolete data excluded from UniProtKB are also present in UniParc)

– **The UniProt Reference Clusters (UniRef),** which consists of clusters of sequences sharing 100 % identity for UniRef100, 90 % for UniRef90 and 50 % for UniRef50 (*see* **Note 4**). These databases are based on both UniProtKB and UniParc.

The Swiss-Prot group has initiated the Plant Proteome Annotation Program (PPAP) in 2001 [5] (http://www.uniprot.org/program/plants/). The current priority of this program is to annotate the proteomes of *Arabidopsis thaliana* and *Oryza sativa*, but without neglecting to annotate the proteins from other plant species. Our goals are the annotation of characterized plant specific and plant family proteins according to the Swiss-Prot standards [3]. At the beginning of March 2014 (UniProt release 2014_02), 34,824 plant sequence entries are present in UniProtKB/Swiss-Prot. Among them 12,665 are from *A. thaliana* and 3130 from *O. sativa*. In UniProtKB/Swiss-Prot, more than 1976 different plant species are present with at least one annotated protein (up-to-date statistics are available at http://www.uniprot.org/statistics/, http://web.expasy.org/docs/relnotes/relstat.html and http://www.uniprot.org/program/plants/statistics).

To cope with the large and growing amount of sequenced genomes, UniProt assigns unique proteome identifiers giving the possibility to select proteins of a given organism. A subset of well-studied or biomedically and biotechnologically interesting organisms, selected to provide broad coverage of the tree of life, are manually defined as standard for a particular user community, and their proteome are "Reference proteomes" (*see* **Note 5**).

2 Materials

UniProtKB is hosted by uniprot.org (*see* **Note 6**). This chapter will always refer to the UniProtKB interface format used by the uniprot.org server (http://www.uniprot.org/), and will focus on UniProtKB/Swiss-Prot entries. The database is updated every four weeks. It is possible to download a local version of UniProtKB (*see* **Notes 7** and **8**).

2.1 UniProtKB Entries

2.1.1 Download and Display Content

The main distribution format of UniProtKB is a custom text-based format. Entries are represented by lines beginning with a two-letter code that identifies the type of data contained in the line. Each line follows a strictly defined format and the lines themselves are organized in such a way as to be easily legible to human users and simple to parse by computer programs (http://www.expasy.org/sprot/userman.html#entrystruc). However, UniProtKB proteins are also available in the more modern and structured XML/RDF format for computational use (http://www.uniprot.org/docs/uniprot.xsd).

2.1.2 Web View of an Entry

When accessing UniProtKB entries from the uniprot.org server, the default format is topic-wise organized in a user-friendly format when compared to the text-based format (*see* Fig. 1). The general elements of an entry in the uniprot.org view format are (from top to bottom): (i) UniProt header and search tool, (ii) UniProt tools (BLAST, alignment, mapping/retrieval in batch), (iii) general help, contact and basket tools, (iv) the header of the UniProtKB entry, (v) tools applicable to the current UniProtKB entry, (vi) current UniProtKB entry centric comment, feedback and external data tools, (vii) UniProtKB entry's section navigation bar organized by topics, (viii) the content of the current UniProtKB entry, (ix) details about the history of the current UniProtKB entry.

2.1.3 Content of an Entry

In most cases, each entry corresponds to a protein sequence encoded by a single gene locus (*see* **Note 9**). However, a few protein entries contain different coding loci merged into a single record when these loci are highly similar (e.g., histones, ubiquitins). References to residue positions within a sequence are made using sequential numbering starting with 1 at the N-terminal position. Displayed sequences correspond to the precursor forms of proteins, before posttranslational modifications and processing.

2.2 Tools and Databases Linked to UniProtKB

The uniprot.org website provides dedicated tools designed to exploit both protein sequences (BLAST, [6], alignments, database identifier mapping tool) and functional annotations (friendly but advanced search tool). SIB has developed the **Ex**pert **P**rotein **A**nalysis **Sy**stem proteomic server (ExPASy), which is another entry point to UniProtKB [7–9]. On http://www.expasy.org/, tools are available to deal with several aspects of protein analysis, including BLAST search, proteomics and sequence analysis, and take into account all splice variants as annotated in UniProtKB (*see* **Note 10**). Results obtained by these tools or links from other specific databases points to the corresponding UniProtKB entries.

3 Methods

3.1 Introduction

The main goal of UniProt is to provide a central resource for protein sequences and functional annotation. Together with UniProtKB/TrEMBL, UniProtKB/Swiss-Prot contains all known proteins, without species restriction. Currently the plant protein entries represent about 20 % of eukaryotes proteins and 7 % of the total content of UniProtKB/Swiss-Prot and our main effort is focused on the annotation of plant specific proteins characterized in literature from *Arabidopsis thaliana* and *Oryza sativa*. Any new genome fully sequenced, deposited in the public nucleotide database (EMBL/GenBank/DDBJ) and for which a gene prediction

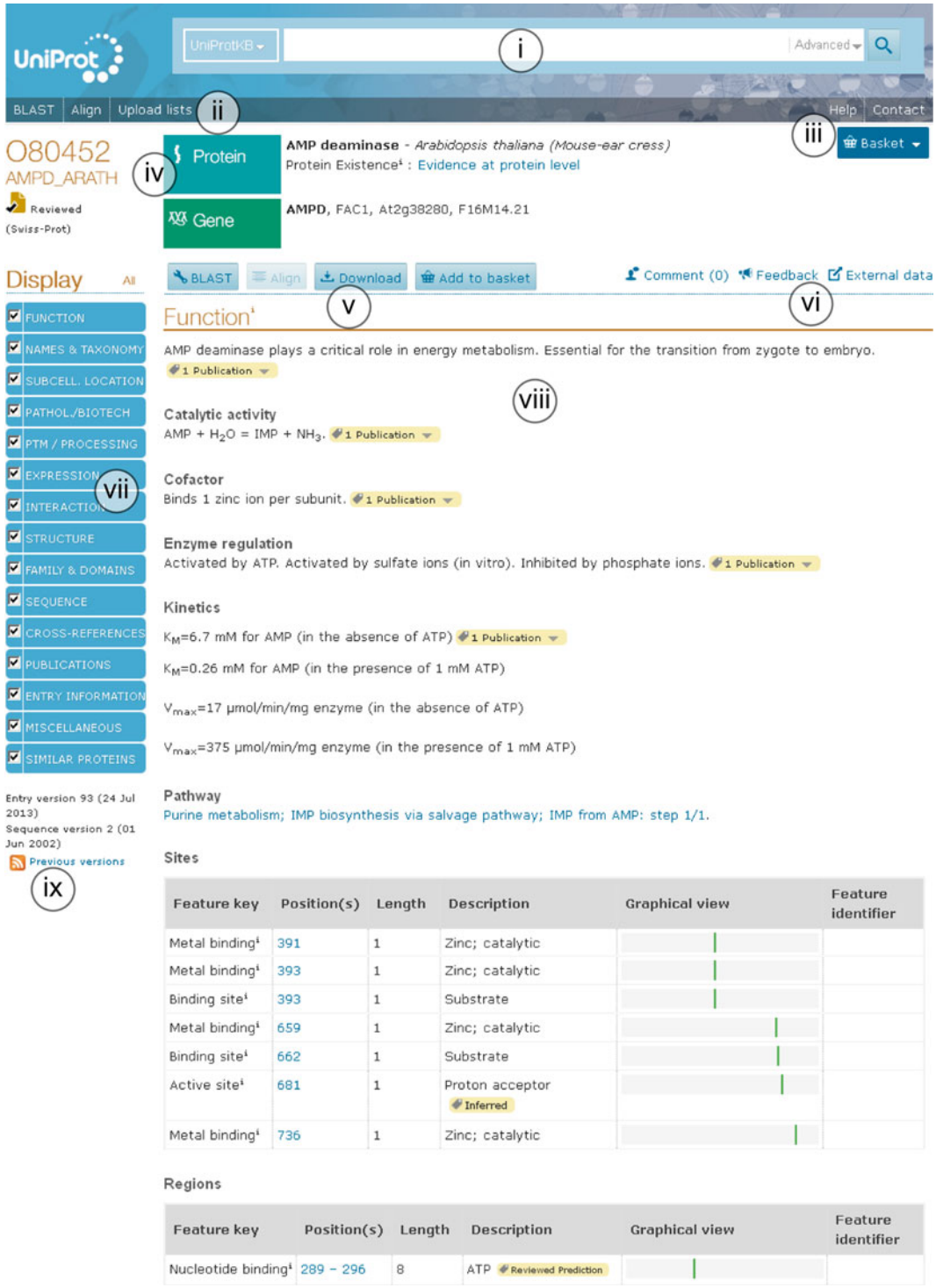


Fig. 1 Header of a UniProtKB entry in the uniprot.org display format; partial view (http://www.uniprot.org/uniprot/O80452)

has been performed will be processed automatically. The predicted set of proteins is added to the UniProtKB/TrEMBL section as soon as the data is publicly available.

One of the great strengths of the UniProt Knowledgebase is the extensive integration and interconnectivity of numerous tools and external databases. The knowledgebase is cross-linked to about 140 other databases while most of the tools are adapted to allow analysis of all spliced isoforms described in the entry.

The UniProt Knowledgebase is constantly evolving and all recent modifications are detailed at http://www.uniprot.org/help/?query=*&fil=section:news while the forthcoming modifications are listed in http://www.uniprot.org/changes.

To further improve the quality of our annotation, we encourage users to submit comments and update requests (http://www.uniprot.org/update?entry= *primary accession number* accessible by the buttons and links present in each UniProtKB entries, *see* Fig. 1 iii and vi).

3.2 Accessing and Analyzing UniProtKB Entries

1. Quick and advanced text search (*see* Fig. 1 i) can be accessed directly from the UniProt home page (http://www.uniprot.org) (*see* **Note 11**). The advanced text search is designed to help users in writing complex queries by restricting terms to specific fields of the database (*see* Fig. 2 i), organized in the same topics of entry's sections. "Intelligent" filters are suggested to restrict the query with most likely terms (*see* Fig. 2 ii). Proteins of interest can be stored in the "basket" by checking boxes (*see* Figs. 2 iii and 3 i) and clicking on the button "Add to basket" for later comparison or download. When accessing the basket (*see* Fig. 3 ii), previously selected entries are listed and different actions are available: "Align", "BLAST", and "Download" (*see* Fig. 3 iii). The result table can be customized to fit user's requirement (*see* Fig. 4). A drag and drop

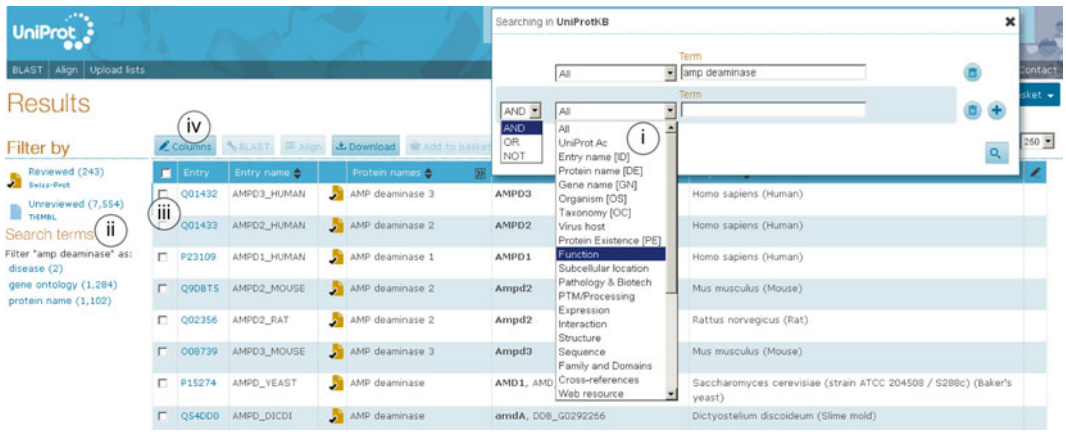


Fig. 2 Text search result; partial view. Partial view of the result of a text search made on UniProtKB with "amp deaminase" as query

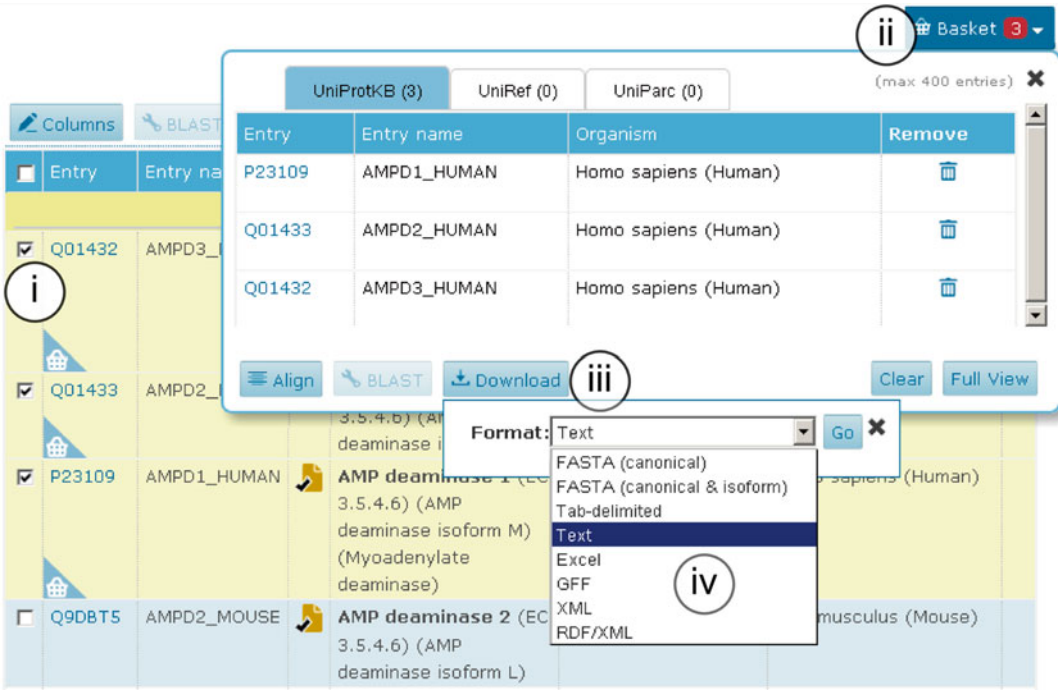


Fig. 3 The UniProt basket. View of the UniProt basket containing three UniProtKB protein entries (e.g., P23109, Q01433, and Q01432)

Fig. 4 The UniProt customization interface. View of the UniProt customization tool

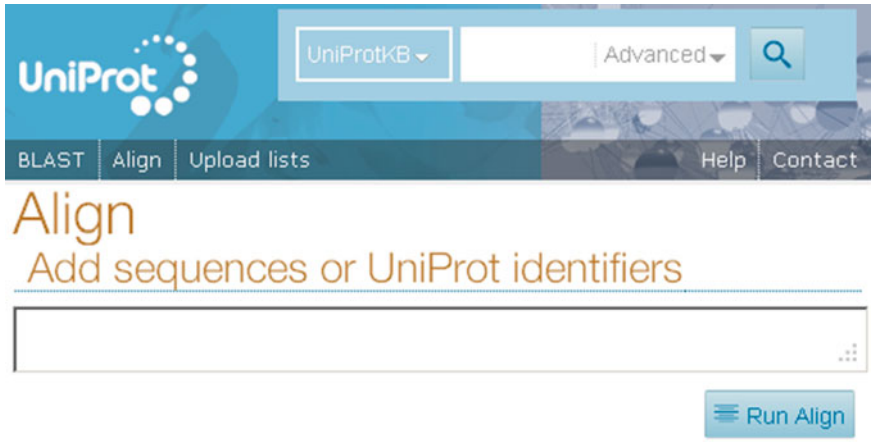


Fig. 5 The UniProt alignment tool. View of the UniProt protein alignment tool

tool makes it possible to change column order (*see* Fig. 4 i). A search engine is available to select for a favorite topic to display in the result table (*see* Fig. 4 ii). Each entry section can also be browsed in details (*see* Fig. 4 iii). When downloading selected entries in "tab-delimited" format, the columns of the output file are the same as the personalized display (*see* Fig. 2 iv). UniProt web services follow the representational state transfer (REST) architectural style to help sharing or storing favorite requests; this also permits easy programmatic access (*see* http://www.uniprot.org/faq/28).

2. An alignment tool based on Clustal Omega (https://www.ebi.ac.uk/Tools/msa/clustalo/) is available at http://www.uniprot.org/align/ (*see* Fig. 5). The alignment output (*see* Fig. 6) is interactive and gives the possibility to highlight in different colors sequence features (*see* Fig. 6 ii) annotated in UniProtKB as well as amino acid properties by selecting properties of interest (*see* Fig. 6 i). When more than two protein sequences are aligned, an alignment tree is also available.
3. BLAST is available at http://www.uniprot.org/blast/ (*see* Fig. 7). Standard parameters can be modified, default settings being: UniProtKB for the data set, 10 for the E-threshold, Matrix auto, no low complexity filtering and gap allowed (*see* **Note 12**). The BLAST output (*see* Fig. 8) gives, on the top, a list of sequences classified by level of similarity to the query, displayed in a graphical view of the query sequence with a similarity-dependent color gradient, and linked to the corresponding UniProtKB entries (*see* Fig. 8 i). A mechanism to allow the user to toggle between similarity based graphics and e-value based graphics will be soon available. All splice variants

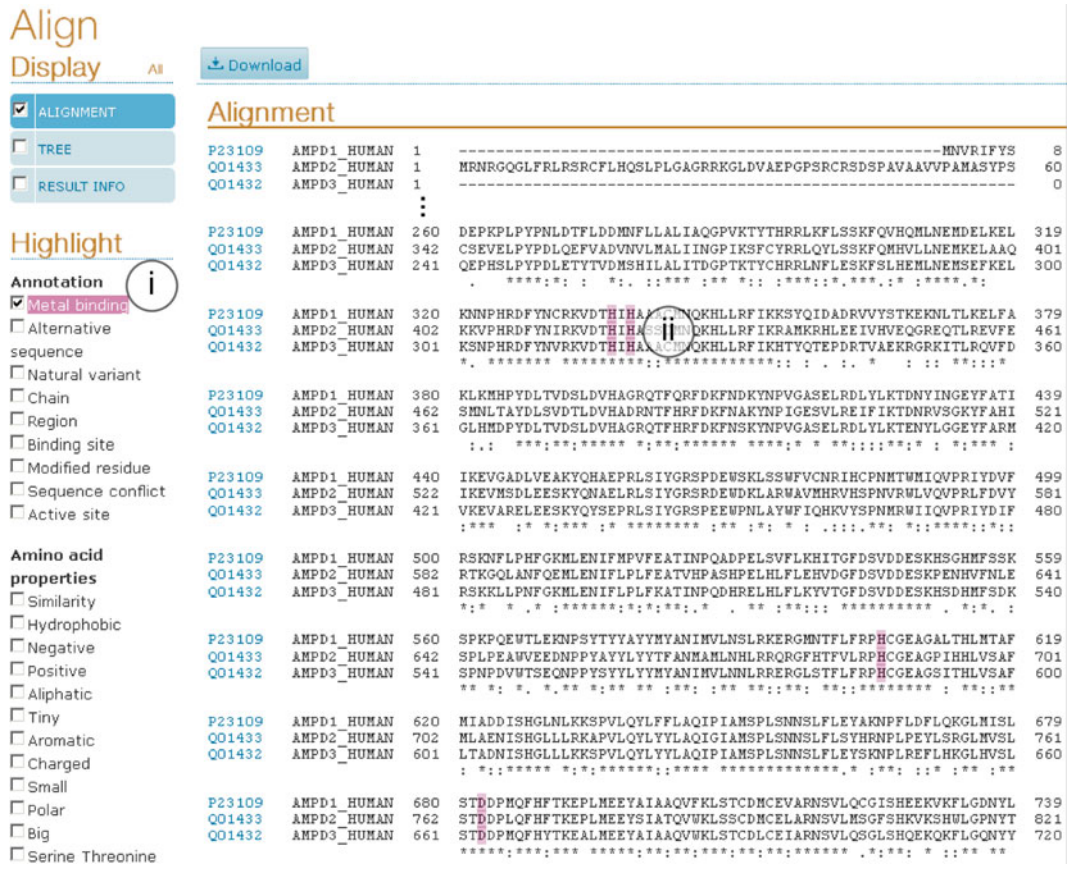


Fig. 6 Protein alignment result. Partial view of the protein alignment result made on UniProtKB between P23109, Q01433 and Q01432 protein entries

annotated in UniProtKB are considered during the BLAST (their UniProt accessions are followed by "-n" where "n" is a digit for Swiss-Prot alternative splicing products) (*see* Fig. 8 i). On the lower part of the output BLAST result, a detailed list of the matched proteins is displayed, with a graphical view of the best alignment for each hit represented in a graphical view with the color code described previously, and linked to all corresponding local alignments between the query and the hit sequences (*see* Fig. 8 ii). All options available for text search result are applicable to this list (*see* **Fig.** 4).

4. Database Entries can be downloaded in batch. Several sets of protein sequences are proposed for download at http://www.uniprot.org/downloads. Entries present in the basket can be retrieved in different formats (*see* Fig. 3 iv). A dedicated tool to convert and download a list of proteins is available at http://

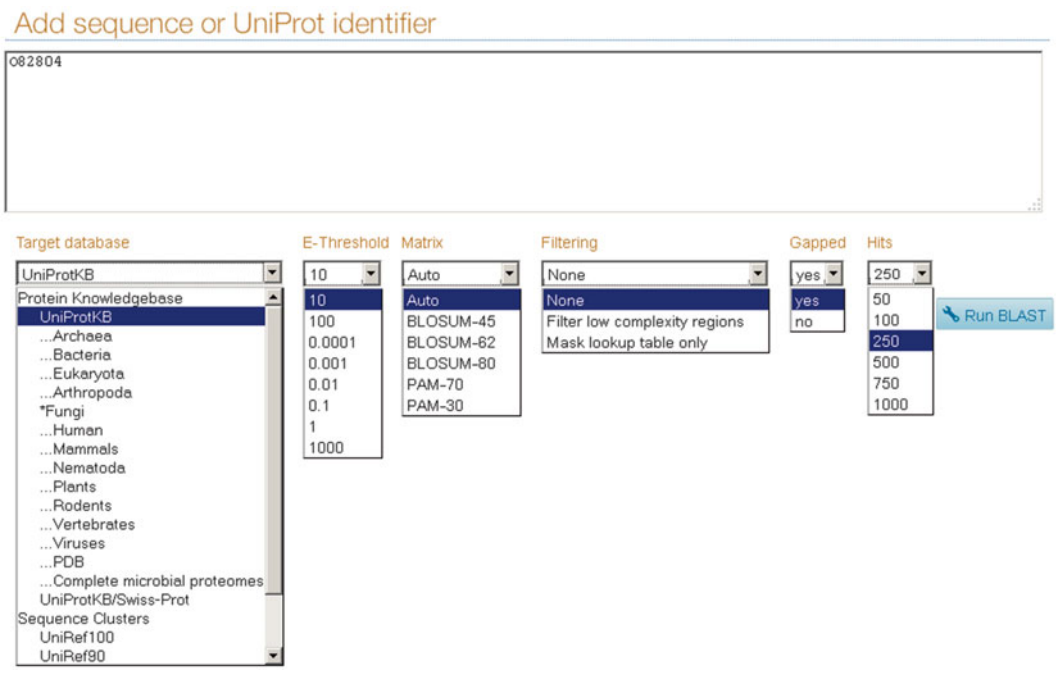


Fig. 7 The UniProtBLAST tool. View of the UniProt BLAST tool

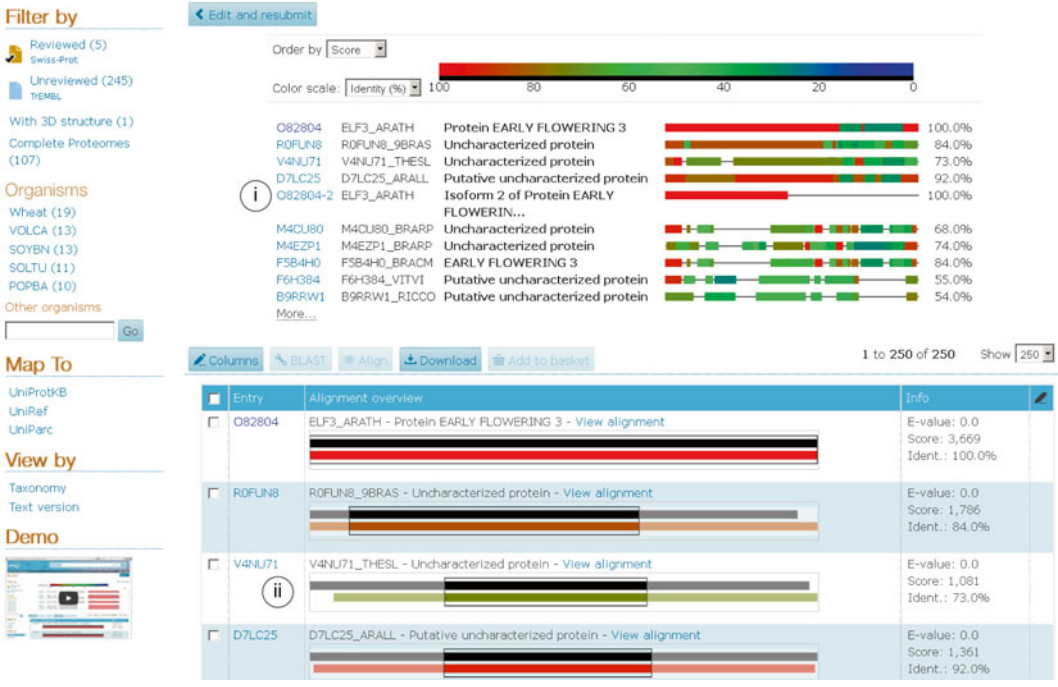


Fig. 8 BLAST result. Partial view of the result of the BLAST made on UniProtKB with O82804 entry as query

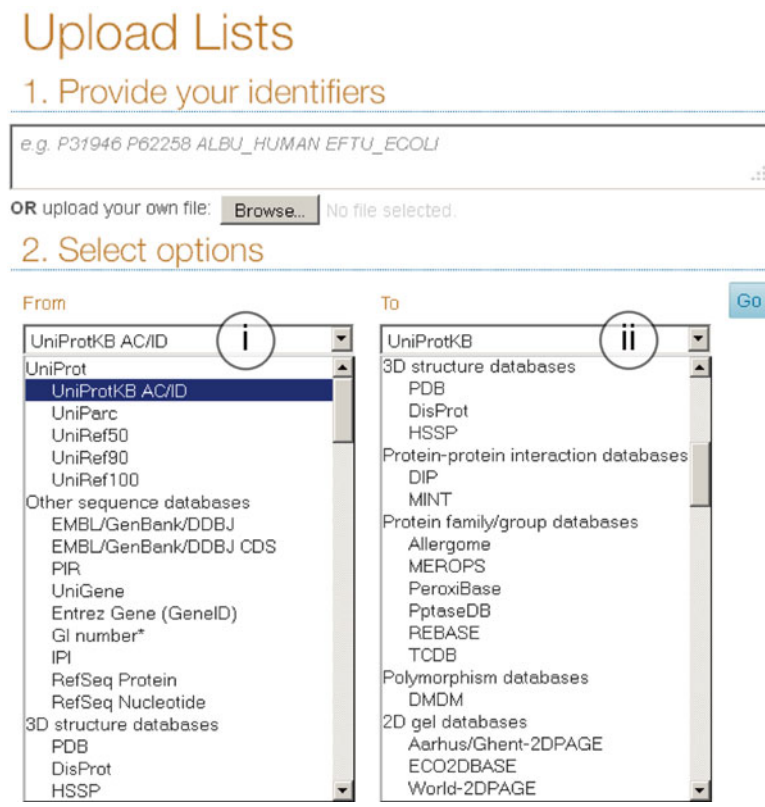


Fig. 9 The UniProt downloading tool. View of the UniProt downloading tool

www.uniprot.org/uploadlists/ (*see* Fig. 9). The user provides a list of accessions in any of the supported formats (*see* http://www.uniprot.org/help/uploadlists and Fig. 9 i) and can convert this list into any of the listed databases (*see* Fig. 9 ii). When the "from" database is "UniProtKB (AC/ID)" and the "to" database is "UniProt", the user can retrieve UniProtKB protein entries from a UniProtKB accession list.

5. UniProtKB entries are also present or cross-linked in several other biological databases and tools such as ExPASy (http://www.expasy.org/), the NCBI (http://www.ncbi.nlm.nih.gov/protein/) and TAIR (http://www.arabidopsis.org).

3.3 The Web View of a UniProtKB Entry

3.3.1 UniProt Banner

When accessing the UniProt website, some elements are always present at the top of the page: the UniProt logo to return to the home page, the search box (*see* Fig. 1-i), access to additional tools including BLAST, alignment and download, described elsewhere (*see* Fig. 1-ii), links to help (*see* **Note 13**), contact, and to the basket containing selected entries (*see* Fig. 1-iii).

3.3.2 Entry Header

The first block of each entry details (*see* Fig. 1-iv) accession numbers, status (*reviewed* for UniProtKB/Swiss-Prot and *unreviewed* for UniProtKB/TrEMBL), as well as protein and gene names and synonyms. The primary accession number (AC, e.g., O80452) of an entry (*see* **Note 14,** documentation available at http://www.uniprot.org/manual/accession_numbers) is stable and provides a unique identifier which allows unambiguous citation of the entry (*see* **Notes 15** and **16**). The entry name (ID, e.g., AMPD_ARATH) consists of up to 11 characters and takes the general form X_Y. Both X and Y represent mnemonic codes of up to 5 alphanumeric characters for both the protein name (X) and the species (Y) (documentation is available at http://www.uniprot.org/manual/entry_name). Entry names, corresponding to protein/gene name abbreviations, are subject to revision and therefore do not provide a stable means of identifying individual entries. Because entry names are prone to change, researchers who wish to cite entries in publications should always cite the primary accession number.

3.3.3 Analysis Tabs

Direct access to BLAST, alignment, and download, tools described in Subheading 3.2, is available from the protein entry view (*see* Fig. 1-v). Entry can also be stored in the basket.

3.3.4 Contribution to Entry Annotation Tabs

Suggestions to update the content of the current entry can be sent via "comment" or "feedback" features (*see* Fig. 1-vi).

3.3.5 Entry's Section Navigation Panel

The content of a protein entry is organized in 15 topics. To navigate and switch between topics, a display menu containing direct links to the different blocks of the entry is always visible on the left side of the screen (*see* Fig. 1-vii). Check boxes in this menu permit to hide/display the corresponding section.

3.3.6 Entry Content View

In the main central area, the content of the current protein entry is displayed by thematic topics (*see* Fig. 1-viii). When a term is followed by "i" as exponent, this means that contextual information are available for this term.

Most of the information in this section is extracted from the literature. Some information is also based on unproven empirical biological evidence, determined by computer prediction, or propagated from homologous members of the family (for details about annotation procedures, *see* http://www.uniprot.org/faq/45). In these cases, non-experimental qualifiers are added (*see* http://www.uniprot.org/manual/non_experimental_qualifiers); the qualifiers are: "Potential" for computer predicted, logical or conclusive evidence (*see* **Note 17**, represented on the website as "Reviewed prediction" in Swiss-Prot and as "Predicted" in TrEMBL), "Probable" for non-direct experimental evidence (*see* **Note 18**,

represented on the website as "Inferred" in Swiss-Prot), and "By similarity" for experimental evidence in a close member of the family. Explanations of non-experimental qualifiers can be obtained by clicking on them in the entry.

Annotations are mainly distributed in four different types:

1. *General annotation*: provides general information about the protein, mostly biological knowledge, in different subsections (*see* http://www.uniprot.org/manual/general_annotation).
2. *Sequence feature*: information associated with specific residues of the current protein sequence (*see* http://www.uniprot.org/manual/sequence_annotation). Each sequence feature contains a "Feature key" (*see* **Note 19**), "Position(s)" indicates limits of the feature according to the amino acid residue positions of the displayed sequence (*see* **Note 20**), the "Length" of the feature is also given, a "Description" of the feature (*see* **Note 21**), a "Graphical view" to visualize the region in the consensus sequence, and, when available, "Feature identifier". UniProtKB/Swiss-Prot entries contain extensive annotation of all features that are predicted (and compatible with the protein function), experimentally proven, or determined by resolution of the protein structure.
3. *Cross-references*: used to point to information related to entries and found in data collections other than UniProtKB (*see* http://www.uniprot.org/help/cross_references_section).
4. *Ontologiesand controlled vocabularies*: a combination of controlled vocabularies and ontologies is used to summarize the functional implication of the current protein. The controlled vocabulary is developed by UniProtKB/Swiss-Prot (*see* http://www.uniprot.org/keywords/), and GO terms (GO, [10]), a formal representation of terms that can be used to describe biological function, process and component, are developed and curated by the GO consortium (*see* http://www.uniprot.org/help/gene_ontology). Some keywords are derived from automatic annotation in UniProtKB/TrEMBL entries, but the vast majority is added manually in UniProtKB/Swiss-Prot entries. They describe the main characteristics of the protein.

   The information contained in the entry is organized in a total of 15 topics, each accessible form the display panel. Depending of the information available in each entry, some sections might appear or not.

   The 15 sections used in UniProtKB and their respective subsections are listed below:

1. "Function": (*see* Fig. 10 and http://www.uniprot.org/help/function_section).
   Contains information pertinent to biological knowledge of the protein function.

Function

AMP deaminase plays a critical role in energy metabolism. Essential for the transition from zygote to embryo. 1 Publication

Catalytic activity

$AMP + H_2O = IMP + NH_3$. 1 Publication

Cofactor

Binds 1 zinc ion per subunit. 1 Publication

Enzyme regulation

Activated by ATP. Activated by sulfate ions (in vitro). Inhibited by phosphate ions. 1 Publication

Kinetics

K_M=6.7 mM for AMP (in the absence of ATP) 1 Publication

K_M=0.26 mM for AMP (in the presence of 1 mM ATP)

V_{max}=17 µmol/min/mg enzyme (in the absence of ATP)

V_{max}=375 µmol/min/mg enzyme (in the presence of 1 mM ATP)

Manual assertion based on experiment described in:

"Membrane association, mechanism of action, and structure of Arabidopsis embryonic factor 1 (FAC1)."
Han B.W., Bingman C.A., Mahnke D.K., Bannen R.M., Bednarek S.Y., Sabina R.L., Phillips G.N. Jr.
J. Biol. Chem. 281:14939-14947(2006) [PubMed] [Europe PMC] [Abstract]
Cited for: X-RAY CRYSTALLOGRAPHY (3.3 ANGSTROMS) OF 140-839 IN COMPLEX WITH COFORMYCIN 5'-PHOSPHATE;

Pathway

Purine metabolism; IMP biosynthesis via salvage pathway; IMP from AMP: step 1/1.

Sites

Feature key	Position(s)	Length	Description	Graphical view	Feature identifier
Metal binding	391	1	Zinc; catalytic		
Metal binding	393	1	Zinc; catalytic		
Binding site	393	1	Substrate		
Metal binding	659	1	Zinc; catalytic		
Binding site	662	1	Substrate		
Active site	681	1	Proton acceptor Inferred		
Metal binding	736	1	Zinc; catalytic		

Regions

Feature key	Position(s)	Length	Description	Graphical view	Feature identifier
Nucleotide binding	289 – 296	8	ATP Reviewed Prediction		

GO - Molecular function

AMP deaminase activity
Inferred from genetic interaction Ref.1 Source: TAIR

ATP binding
Inferred from electronic annotation Source: UniProtKB-KW

metal ion binding
Inferred from electronic annotation Source: UniProtKB-KW

Complete GO annotation...

Keywords - Molecular function

Hydrolase

Keywords - Biological process

Nucleotide metabolism

Keywords - Ligand

ATP-binding, Metal-binding, Nucleotide-binding, Zinc

Enzyme and pathway databases

SABIO-RK	O80452.
UniPathway	UPA00591; UER00663.

Fig. 10 Function section of a UniProtKB entry. View of the "function" section of the UniProtKB protein O80452

The different subsections of the function section are:

(a) General annotation dealing with function, catalytic activity, cofactor, enzyme regulation, biophysicochemical properties, and pathway

(b) Sequence features describing active site, metal binding, binding site, site, calcium binding, zinc finger, and DNA binding with a graphical view

(c) GO terms of the 'Molecular function' section

(d) Keywords of 'Molecular function', 'Biological process', and 'Ligand' subsections

(e) Cross-references that point to family, enzyme, and pathway databases

2. "Names & Taxonomy": (*see* Fig. 11 and http://www.uniprot.org/help/names_and_taxonomy_section).
This block describes protein names, gene names and taxonomy of the organism. The recommended protein name is given in the first row, followed by the alternative names used in the literature. In the case of an enzyme, the Enzyme Commission (EC) number is given as synonym. This EC number is an active link to the Enzyme database (http://www.expasy.org/enzyme/) [11], which contains detailed information about enzyme activity and lists all UniProtKB/Swiss-Prot entries having the same EC number. The second row of this block describes the gene encoding the protein in the following order: gene name, synonyms, ordered locus name when applicable (*see* **Note 22**) and ORF names used by the genomic sequencing projects, when available. Following the gene description, the organism name, the NCBI taxonomy identifier, and the summarized taxonomic hierarchy are actively linked to the UniProt taxonomy browser (http://www.uniprot.org/taxonomy/) which contains details on the organism and gives access to all UniProtKB entries of that organism (*see* **Note 23**).

3. "Subcellular location": (*see* Fig. 12 and http://www.uniprot.org/help/subcellular_location_section).
Contains information pertinent to biological knowledge of the protein localization and topology.

The different subsections of the subcellular location section are:

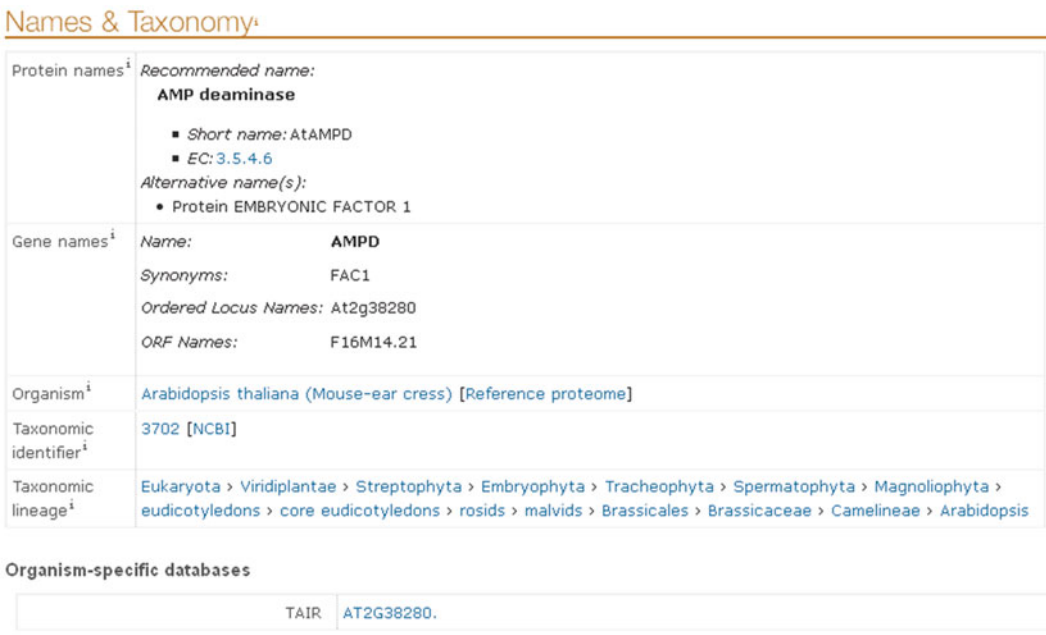
(a) General annotation dealing with subcellular location

(b) Sequence features describing transmembrane and topological domain with a graphical view

(c) GO terms of the 'Cellular component' section

(d) Keywords of the 'Cellular component' section

4. "Pathology & Biotech": (*see* Fig. 13 and http://www.uniprot.org/help/pathology_and_biotech_section).



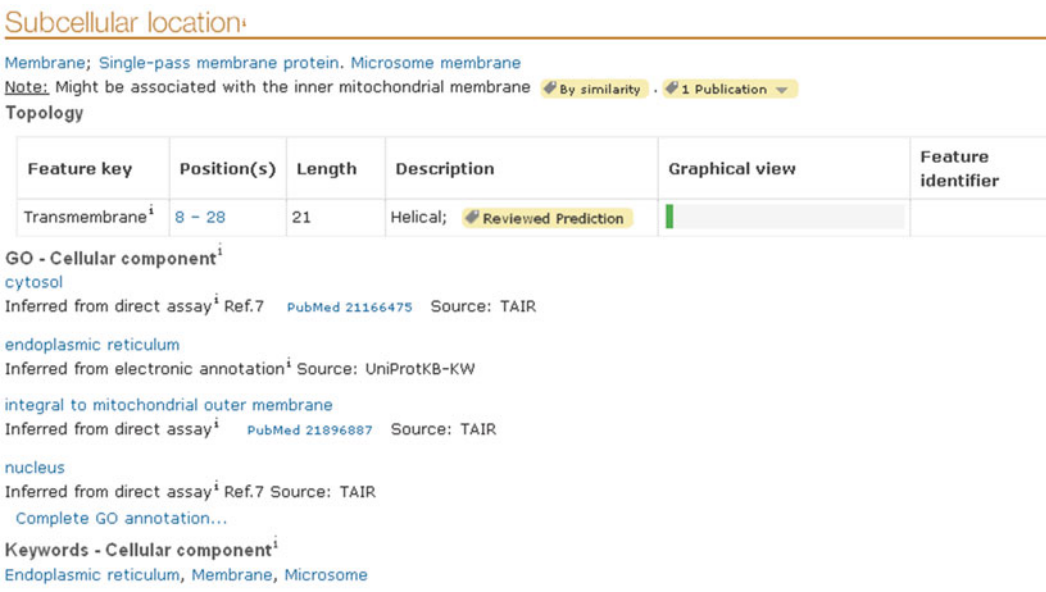
Names & Taxonomy

Protein names	*Recommended name:* **AMP deaminase** ▪ *Short name:* AtAMPD ▪ *EC:* 3.5.4.6 *Alternative name(s):* • Protein EMBRYONIC FACTOR 1
Gene names	*Name:* **AMPD** *Synonyms:* FAC1 *Ordered Locus Names:* At2g38280 *ORF Names:* F16M14.21
Organism	Arabidopsis thaliana (Mouse-ear cress) [Reference proteome]
Taxonomic identifier	3702 [NCBI]
Taxonomic lineage	Eukaryota › Viridiplantae › Streptophyta › Embryophyta › Tracheophyta › Spermatophyta › Magnoliophyta › eudicotyledons › core eudicotyledons › rosids › malvids › Brassicales › Brassicaceae › Camelineae › Arabidopsis

Organism-specific databases

TAIR	AT2G38280.

Fig. 11 Names & taxonomy section of a UniProtKB entry. View of the "names and taxonomy" section of the UniProtKB protein O80452



Subcellular location

Membrane; Single-pass membrane protein. Microsome membrane
Note: Might be associated with the inner mitochondrial membrane By similarity . 1 Publication

Topology

Feature key	Position(s)	Length	Description	Graphical view	Feature identifier
Transmembrane	8 – 28	21	Helical; Reviewed Prediction		

GO - Cellular component

cytosol
Inferred from direct assay Ref.7 PubMed 21166475 Source: TAIR

endoplasmic reticulum
Inferred from electronic annotation Source: UniProtKB-KW

integral to mitochondrial outer membrane
Inferred from direct assay PubMed 21896887 Source: TAIR

nucleus
Inferred from direct assay Ref.7 Source: TAIR

Complete GO annotation...

Keywords - Cellular component

Endoplasmic reticulum, Membrane, Microsome

Fig. 12 Subcellular location section of a UniProtKB entry. View of the "subcellular location" section of the UniProtKB protein O80452

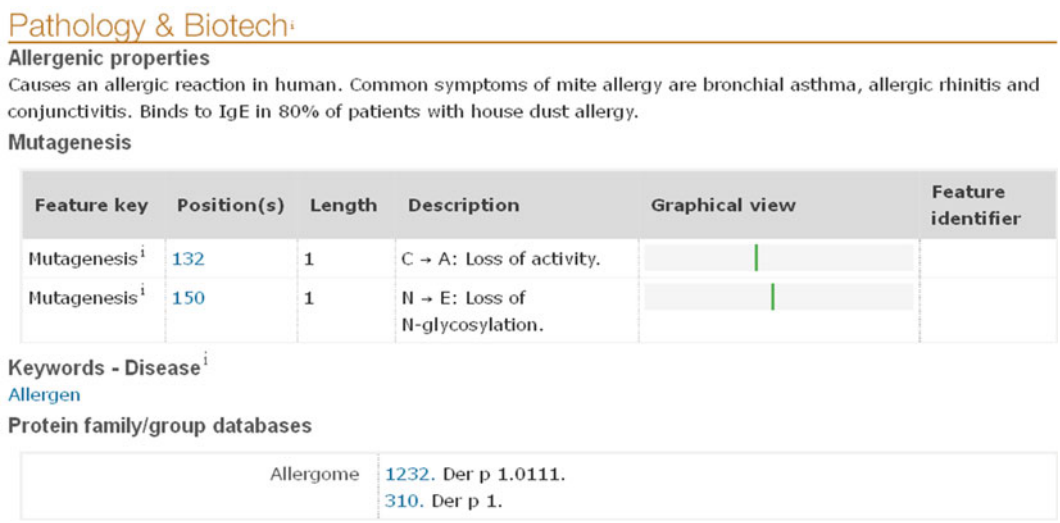


Fig. 13 Pathology & biotech section of a UniProtKB entry. View of the "pathology and biotech" section of the UniProtKB protein P08176

Contains information pertinent to biological knowledge of disease(s) and phenotype(s) associated with the deficiency of the protein.

The different subsections of the Pathology & Biotech section are:

(a) General annotation dealing with involvement in disease, natural variant, allergenic properties, biotechnological use, toxic dose, and pharmaceutical use

(b) Sequence features describing disruption phenotype and mutagenesis with a graphical view

(c) Keywords of the 'Disease' section

(d) Cross-references that point to organism-specific databases

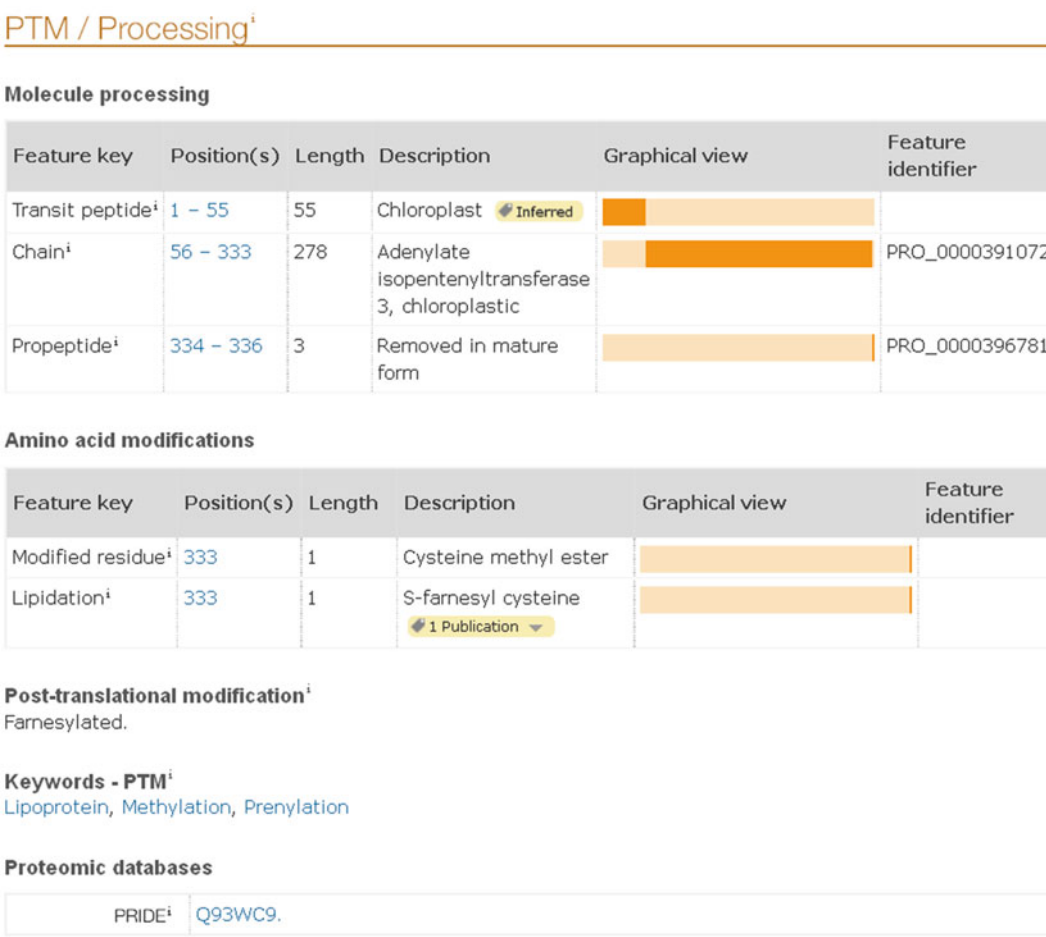
5. "Post translational modification (PTMs) / Processing": (*see* Fig. 14 nd http://www.uniprot.org/help/ptm_processing_section).

Contains information pertinent to biological knowledge of the protein posttranslational modifications.

The different subsections of the PTM / processing section are:

(a) Sequence features describing initiator methionine, signal, pro-peptide, transit peptide, chain, peptide, modified residue, lipidation, glycosylation, disulfide bond, and cross-link with a graphical view

(b) General annotation dealing with posttranslational modification



PTM / Processing

Molecule processing

Feature key	Position(s)	Length	Description	Graphical view	Feature identifier
Transit peptide	1 – 55	55	Chloroplast Inferred		
Chain	56 – 333	278	Adenylate isopentenyltransferase 3, chloroplastic		PRO_0000391072
Propeptide	334 – 336	3	Removed in mature form		PRO_0000396781

Amino acid modifications

Feature key	Position(s)	Length	Description	Graphical view	Feature identifier
Modified residue	333	1	Cysteine methyl ester		
Lipidation	333	1	S-farnesyl cysteine 1 Publication		

Post-translational modification
Farnesylated.

Keywords - PTM
Lipoprotein, Methylation, Prenylation

Proteomic databases

PRIDE	Q93WC9.

Fig. 14 PTM/processing section of a UniProtKB entry. View of the "PTM/processing" section of the UniProtKB protein Q93WC9

(c) Keywords of the 'PTM' section

(d) Cross-references that point to proteomics and PTM databases

6. "Expression": (*see* Fig. 15 and http://www.uniprot.org/help/expression_section).
   Contains information pertinent to biological knowledge of the protein expression.
   The different subsections of the expression section are:

   (a) General annotation dealing with tissue specificity, developmental stage and induction

   (b) Keywords of the 'Developmental stage' section

   (c) Cross-references that point to gene expression databases

7. "Interaction": (*see* Fig. 16 and http://www.uniprot.org/help/interaction_section).

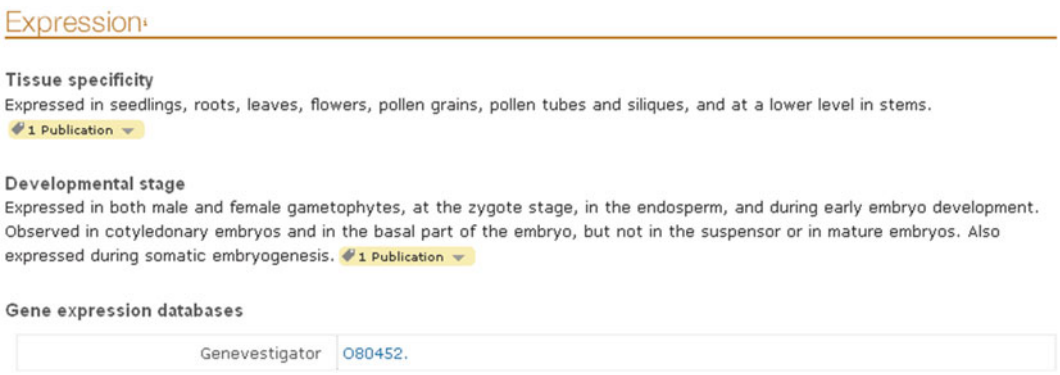


Fig. 15 Expression section of a UniProtKB entry. View of the "expression" section of the UniProtKB protein O80452

Fig. 16 Interaction section of a UniProtKB entry. View of the "interaction" section of the UniProtKB protein O80452

Contains information pertinent to biological knowledge of the protein interactions.

The different subsections of the interaction section are:

(a) General annotation dealing with subunit structure

(b) Specific annotation describing binary interactions

(c) Cross-references that point to protein–protein interaction databases

8. "Structure": (*see* Fig. 17 and http://www.uniprot.org/help/structure_section).
Contains information pertinent to biological knowledge of the protein structure.

The different subsections of the structure section are:

(a) Sequence features describing turn, beta strand and helix with a graphical view (when available)

(b) Cross-references that point to 3D structure databases

9. "Family & Domains": (*see* Fig. 18 and http://www.uniprot.org/help/family_and_domains_section).

Fig. 17 Structure section of a UniProtKB entry. View of the "structure" section of the UniProtKB protein O80452

Contains information pertinent to biological knowledge of the protein family and domains

The different subsections of the Family & Domains section are:

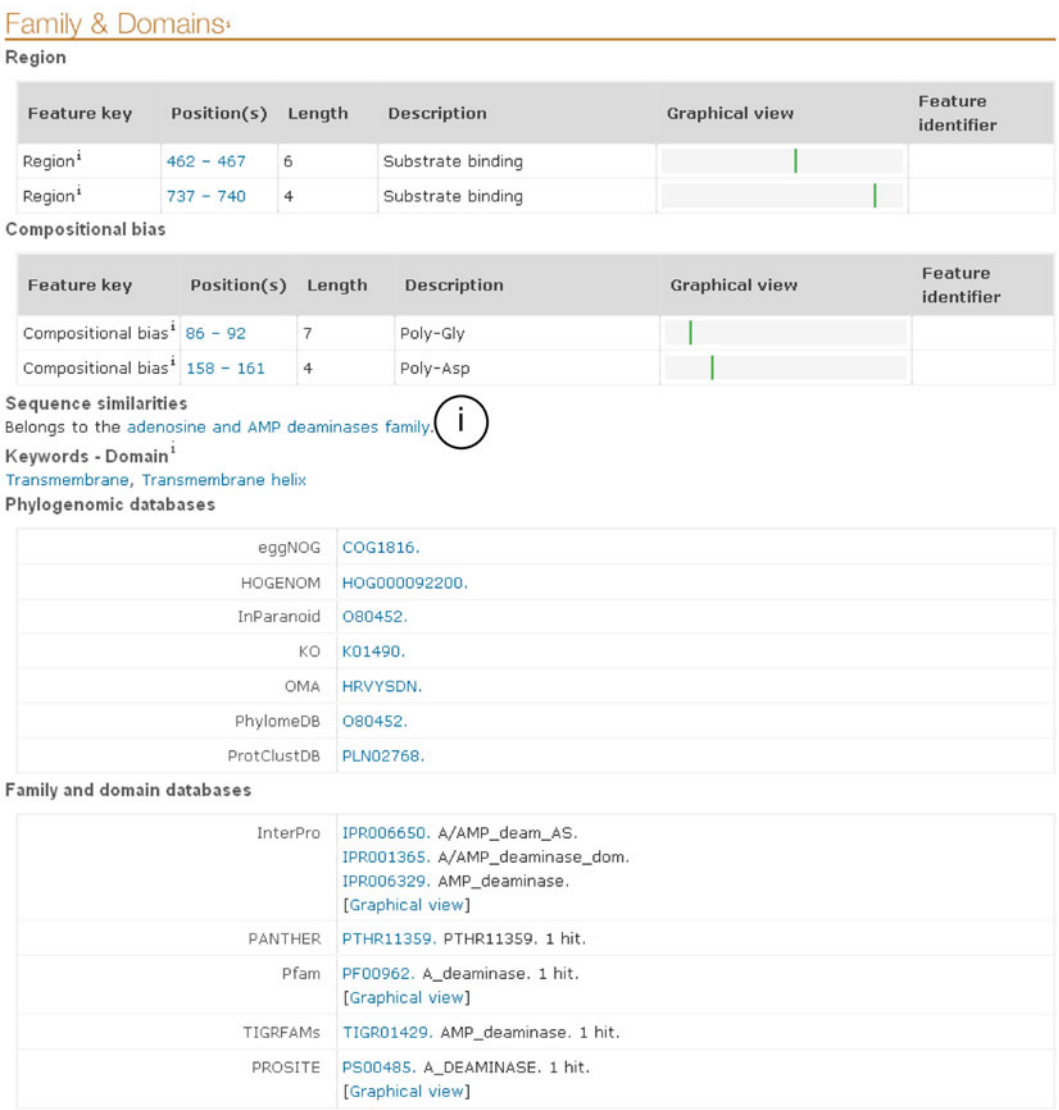
(a) Sequence features describing domain, repeat, compositional bias, region, coiled coil, motif, and domain with a graphical view with a graphical view

(b) General annotation dealing with sequence similarities; a comment describing to which family the protein may belong may be included. It is linked to a UniProt query that lists all UniProtKB entries belonging to the same family (*see* **Note 24** and Fig. 18 i). In the case of transporter families, the transport classification (TC) number is present when available, and a cross-link to the transport classification database (http://www.tcdb.org) is also included.

(c) Keywords of the 'Domain' section

(d) Cross-references that point to phylogenomic and family and domain databases

10. "Sequence": (*see* Fig. 19 and http://www.uniprot.org/help/sequences_section).
Contains general metadata determined for the given sequence, such as sequence length, molecular weight, and CRC64 checksum (64 bit Cyclic Redundancy Check value) [12] (*see* **Note 25**). Each subsection contains information pertinent to biological knowledge of the protein sequence. On the right side of all sequences, a quick access to the FASTA format (http://en.wikipedia.org/wiki/FASTA_format) of the sequence and to sequence/proteomic tools is present (*see* Fig. 19 i).



Family & Domains

Region

Feature key	Position(s)	Length	Description	Graphical view	Feature identifier
Region	462 – 467	6	Substrate binding		
Region	737 – 740	4	Substrate binding		

Compositional bias

Feature key	Position(s)	Length	Description	Graphical view	Feature identifier
Compositional bias	86 – 92	7	Poly-Gly		
Compositional bias	158 – 161	4	Poly-Asp		

Sequence similarities

Belongs to the adenosine and AMP deaminases family.

Keywords - Domain

Transmembrane, Transmembrane helix

Phylogenomic databases

eggNOG	COG1816.
HOGENOM	HOG000092200.
InParanoid	O80452.
KO	K01490.
OMA	HRVYSDN.
PhylomeDB	O80452.
ProtClustDB	PLN02768.

Family and domain databases

InterPro	IPR006650. A/AMP_deam_AS. IPR001365. A/AMP_deaminase_dom. IPR006329. AMP_deaminase. [Graphical view]
PANTHER	PTHR11359. PTHR11359. 1 hit.
Pfam	PF00962. A_deaminase. 1 hit. [Graphical view]
TIGRFAMs	TIGR01429. AMP_deaminase. 1 hit.
PROSITE	PS00485. A_DEAMINASE. 1 hit. [Graphical view]

Fig. 18 Family & domains section of a UniProtKB entry. View of the "family and domains" section of the UniProtKB protein O80452

The different subsections of the sequence section are:

(a) The sequence status, either complete or fragment(s)

(b) Sequence processing when accurate; details about this processing are described in the "PTM/Processing" section

(c) The canonical protein sequence

(d) Alternative products with sequence and additional related information, when existing. The alternative products subsection describes the proteins which may be produced by

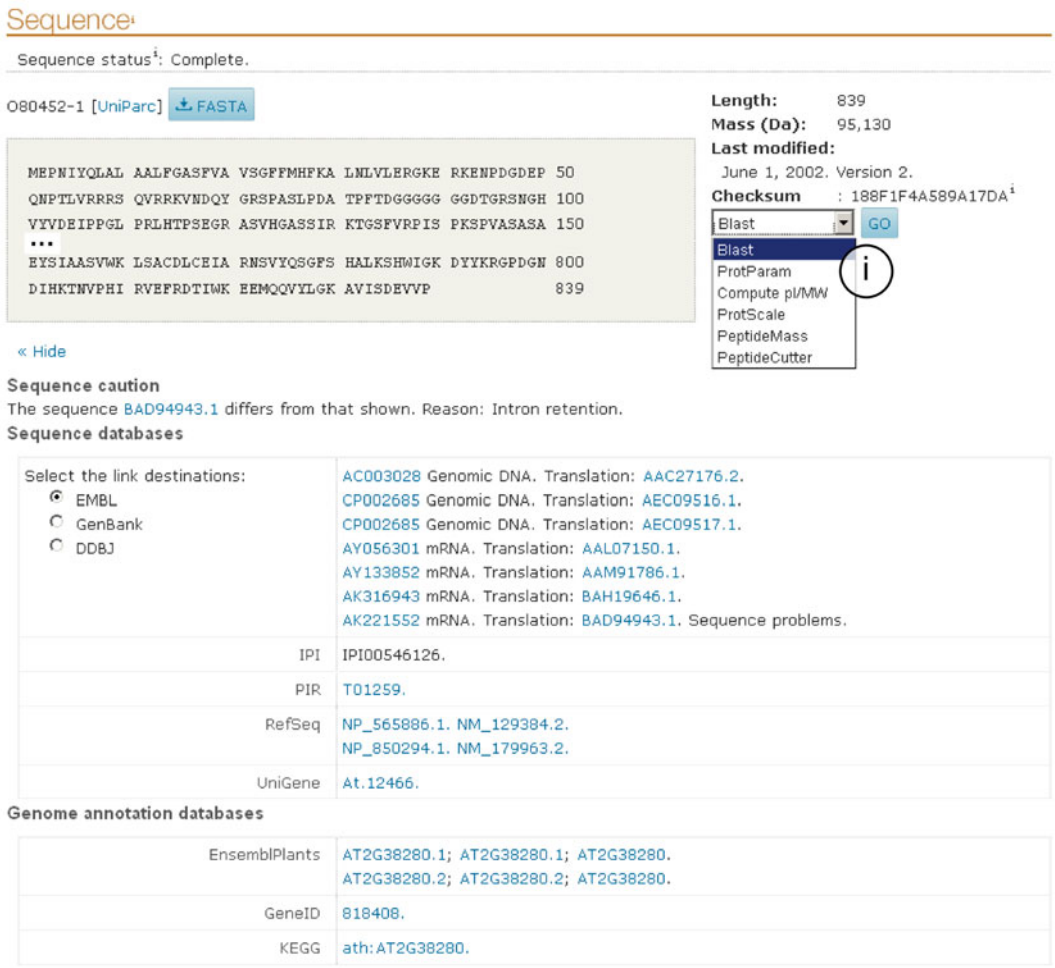


Fig. 19 Sequence section of a UniProtKB entry. View of the "sequence" section of the UniProtKB protein O80452

alternative splicing or promoter usage. Modifications of the canonical sequence necessary to produce the alternative product sequence are described in the sequence features subsection (*see* Fig. 20).

(e) General annotation dealing with sequence caution, caution, polymorphism, RNA editing and mass spectrometry

(f) Sequence features describing natural variant, alternative sequence, sequence uncertainty, sequence conflict, non-adjacent residues, non-terminal residue, and non-standard residue with a graphical view

(g) Keywords of the 'Coding sequence diversity' section

(h) Cross-references that point to sequence, genome annotation databases and polymorphism databases

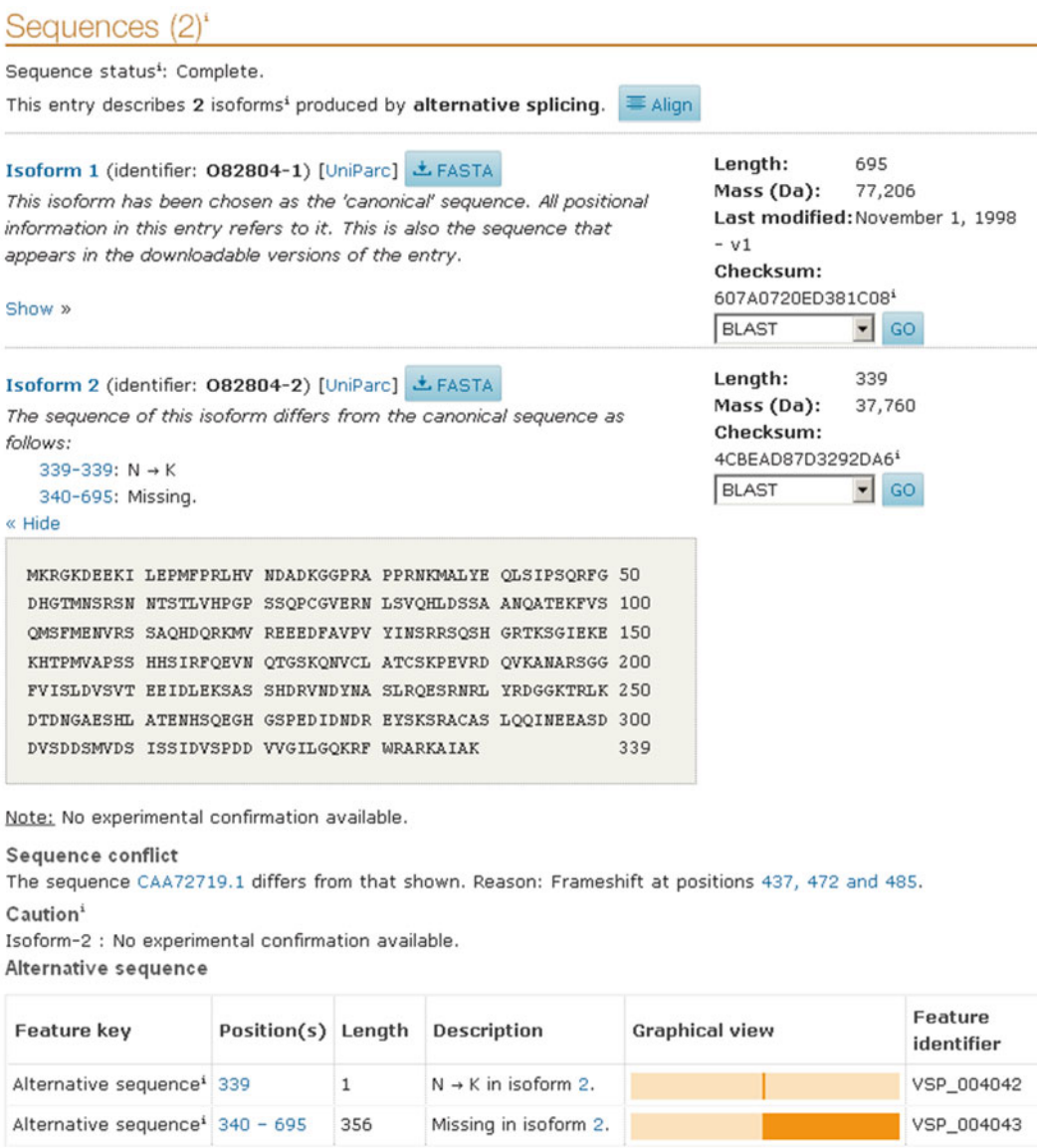


Fig. 20 Sequence section of a UniProtKB entry containing alternative products. View of the "sequence" section of the UniProtKB protein O82804; only details concerning the alternative splicing are shown

11. "Cross-references": (*see* Fig. 21 and http://www.uniprot.org/help/cross_references_section).
    The cross-references section is divided into subsections organized by themes. This section links the protein to several other databases that contain information relevant to that protein. Many of these cross-links are automatically added to UniProtKB/TrEMBL entries, but some are manually created in UniProtKB/Swiss-Prot entries (*see* **Note 19**). Each row of this block corresponds to a single database, the name of which

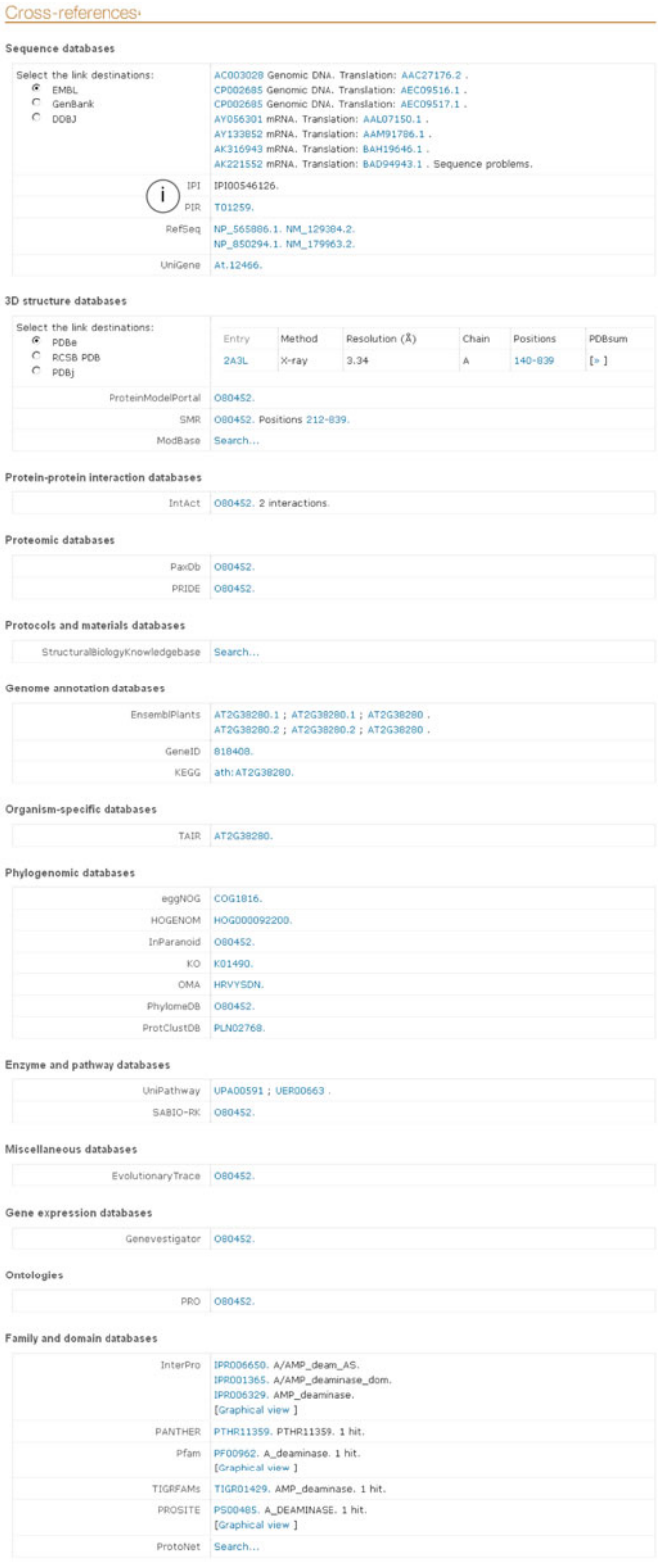


Fig. 21 Cross-references section of a UniProtKB entry. View of the "cross-references" section of the UniProtKB protein O80452

Table 1
Plant-specific cross-references present in UniProtKB

Database name and URL and goals	DR line format
GeneFarm [13] http://genoplante-info.infobiogen.fr/Genefarm/ Structural and functional annotation of *Arabidopsis thaliana* gene and protein families (*see* http://www.uniprot.org/database/DB-0032).	**DR GeneFarm;** GeneID; FamilyID. *In UniProtKB/Swiss-Protonly*
Gramene; a comparative mapping resource for grains [14] http://www.gramene.org/ Curated, open-source, Web-accessible data resource for comparative genome analysis in the grasses (*see* http://www.uniprot.org/database/DB-0039).	**DR Gramene;** UniProtKB_AC; -. *In UniProtKB/Swiss-Protand UniProtKB/TrEMBL*
MaizeGenetics/GenomicsDatabase(MaizeGDB) [15] http://www.maizegdb.org/ Central repository for public maize information (*see* http://www.uniprot.org/database/DB-0058).	**DR MaizeDB;** ProteinID; -. *In UniProtKB/Swiss-Protonly*
The Arabidopsis Information Resource (TAIR) [16] http://www.arabidopsis.org/index.jsp Searchable relational database on Arabidopsis thaliana, which includes many different molecular data types and provides a comprehensive resource for the scientific community (*see* http://www.uniprot.org/database/DB-0102).	**DR TAIR;** Order_locus_name; -. *In UniProtKB/Swiss-Protand UniProtKB/TrEMBL*

is indicated in the first column (*see* Fig. 21 i). A link to the relevant data in the cross-linked database is present in next columns. Plant specific databases that are currently cross-linked in UniProtKB entries are listed in Table 1. They have been chosen because of their content, their stability and their frequent updates. All of them give additional information about the protein and are linked back to UniProtKB.

The different subsections of the cross-references section are:

(a) **2D gel databases**

(b) **3D structure databases**; Cross-references to the PDB database (http://www.rcsb.org/pdb/) are present when protein structures are available. PDB cross-links contain information about the crystallographic method, the number of chains, and the range of residues present in the structure.

(c) **Enzyme and pathway databases**

(d) **Family and domain databases**

(e) **Gene expression databases**

(f) **Genomeannotationdatabases**

(g) **Ontologies**

(h) **Organism-specific databases**

(i) **Phylogenomic databases**

(j) **Polymorphism databases**

(k) **Proteomic databases**

(l) **Protein-protein interaction databases**

(m) **Protein family/group databases**

(n) **PTM databases**

(o) **Sequence databases**; Cross-references to the EMBL database (http://www.embl-heidelberg.de/) are displayed in the same order as the corresponding references associated with a sequence submission. EMBL cross-links contain a nucleic acid sequence ID, a protein sequence ID and a molecule type to indicate the origin of the sequence (e.g., mRNA or Genomic_DNA) (*see* **Note 26**). When no coding sequence to translate the nucleic acid sequence into the protein sequence was provided by the submitters to the EMBL, the flag "No translation available" is present to replace the lacking protein sequence ID. When the sequence displayed in UniProt differs from the original EMBL sequence, a flag "Sequence problems" is added and the differences between the two sequences are summarized in the "Sequence" section.

(p) **Other**

12. "Publications": (*see* Fig. 22 and http://www.uniprot.org/help/publications_section). This block lists all references used for the annotation of the protein entry. The first references are usually associated with sequence submission, followed by references providing other information concerning the function and structure of the protein. Each reference is numbered and contains title, authors, and conventional citation information for the reference, including cross-links to PubMed and digital object identifier (DOI), thus allowing retrieval of the electronic version of the article. In addition, an indication of what information was extracted from the article, strain and tissues used is also mentioned when available. In the case of references associated with a sequence submission, the sequenced molecule type is mentioned and, if relevant, the corresponding isoform is indicated. Each author name is linked to a UniProtKB query that retrieves all entries where that author is cited.

13. "Entry information": (*see* Fig. 23a and http://www.uniprot.org/help/entry_information_section). In addition to the

Publications

« Hide 'large scale' publications

Download

1. **"EMBRYONIC FACTOR 1 encodes an AMP deaminase and is essential for the zygote to embryo transition in Arabidopsis."**
Xu J., Zhang H.-Y., Xie C.-H., Xue H.-W., Dijkhuis P., Liu C.-M.
Plant J. 42:743-756(2005) [PubMed] [Europe PMC] [Abstract]
Cited for: NUCLEOTIDE SEQUENCE [GENOMIC DNA], MUTAGENESIS OF ASP-598, FUNCTION, TISSUE SPECIFICITY, DEVELOPMENTAL STAGE.
Strain: cv. Landsberg erecta.

2. **"Sequence and analysis of chromosome 2 of the plant Arabidopsis thaliana."**
Lin X., Kaul S., Rounsley S.D., Shea T.P., Benito M.-I., Town C.D., Fujii C.Y., Mason T.M., Bowman C.L., Barnstead M.E., Feldblyum T.V., Buell C.R., Ketchum K.A., Lee J.J., Ronning C.M., Koo H.L., Moffat K.S., Cronin L.A. Venter J.C.
Nature 402:761-768(1999) [PubMed] [Europe PMC] [Abstract]
Cited for: NUCLEOTIDE SEQUENCE [LARGE SCALE GENOMIC DNA].
Strain: cv. Columbia.

3. The Arabidopsis Information Resource (TAIR)
Submitted (APR-2011) to the EMBL/GenBank/DDBJ databases
Cited for: GENOME REANNOTATION.
Strain: cv. Columbia.

...

8. **"Toward an interaction map of the two-component signaling pathway of Arabidopsis thaliana."**
Dortay H., Gruhn N., Pfeifer A., Schwerdtner M., Schmuelling T., Heyl A.
J. Proteome Res. 7:3649-3660(2008) [PubMed] [Europe PMC] [Abstract]
Cited for: INTERACTION WITH AHK4.

...

10. **"Crystallization and preliminary X-ray crystallographic analysis of adenosine 5'-monophosphate deaminase (AMPD) from Arabidopsis thaliana in complex with coformycin 5'-phosphate."**
Han B.W., Bingman C.A., Mahnke D.K., Sabina R.L., Phillips G.N. Jr.
Acta Crystallogr. F 61:740-742(2005) [PubMed] [Europe PMC] [Abstract]
Cited for: CRYSTALLIZATION, X-RAY CRYSTALLOGRAPHY (3.3 ANGSTROMS) OF 140-839 IN COMPLEX WITH COFORMYCIN 5'-PHOSPHATE AND ZINC IONS.

11. **"Membrane association, mechanism of action, and structure of Arabidopsis embryonic factor 1 (FAC1)."**
Han B.W., Bingman C.A., Mahnke D.K., Bannen R.M., Bednarek S.Y., Sabina R.L., Phillips G.N. Jr.
J. Biol. Chem. 281:14939-14947(2006) [PubMed] [Europe PMC] [Abstract]
Cited for: X-RAY CRYSTALLOGRAPHY (3.3 ANGSTROMS) OF 140-839 IN COMPLEX WITH COFORMYCIN 5'-PHOSPHATE; PHOSPHATE AND ZINC IONS, CATALYTIC ACTIVITY, SUBUNIT, COFACTOR, SUBCELLULAR LOCATION, ENZYME REGULATION, BIOPHYSICOCHEMICAL PROPERTIES.

Fig. 22 Publications section of a UniProtKB entry. View of the "publications" section of the UniProtKB protein O80452

primary accession number, a protein entry may contain one or more secondary accession numbers, which follow the primary accession number. These are usually accession numbers of UniProtKB/TrEMBL entries that have been merged into a single UniProtKB/Swiss-Prot entry. The history of the current protein entry give the date when the entry was first created, the date of last modification of the sequence and the date of last modification of annotation, respectively. The corresponding releases are also indicated. A quick access to this history is also available beneath the entry remote control (*see* Fig. 1 ix).

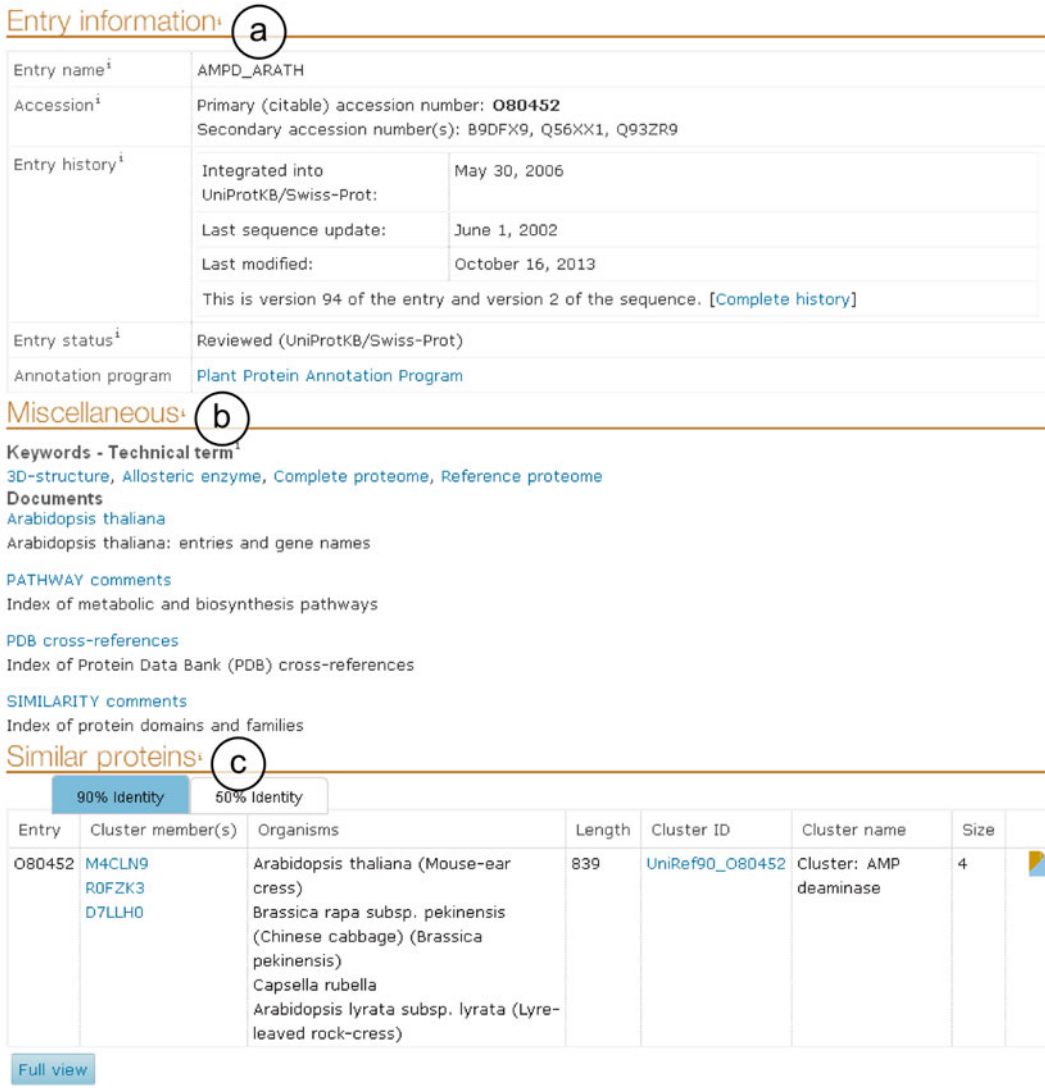


Fig. 23 Entry information, miscellaneous and similar proteins sections of a UniProtKB entry. View of the "information, miscellaneous and similar proteins" sections of the UniProtKB protein O80452

14. "Miscellaneous": (*see* Fig. 23b and http://www.uniprot.org/help/miscellaneous_section). Links to relevant documents (*see* **Note 2**) and keywords of the 'Technical term' section are listed.
15. "Similar proteins": (*see* Fig. 23c and http://www.uniprot.org/help/similar_proteins_section). This section provides links to UniRef100, UniRef90, and UniRef50, corresponding to protein sequences sharing 100 %, 90 %, or 50 % identity, respectively. UniRef are sequence clusters, used to speed up sequence similarity searches (*see* **Note 4**).

4 Notes

1. The SIB (Switzerland, Geneva), in collaboration with the EBI (UK, Hinxton) and PIR (USA, Georgetown University Medical Center and National Biomedical Research Foundation), develop the UniProt protein resource that contain a Protein knowledgebase (UniProtKB), Sequence clusters (UniRef), and a sequence archive (UniParc).
2. For more information, *see* http://www.uniprot.org/docs and http://www.expasy.org/sprot/userman.html. UniProt propose also demonstration videos on its YouTube channel: https://www.youtube.com/channel/UCkCR5RJZCZZoVTQzTYY92aw.
3. For more information, *see* http://www.uniprot.org/manual/non_experimental_qualifiers.
4. The UniRef reference clusters combine closely related sequences into a single record on order to speed sequence similarity searches. The UniRef100 database combines identical sequences and subfragments of the UniProt Knowledgebase (from any species) and selected UniParc records into a single UniRef entry (http://www.uniprot.org/help/uniref). UniRef90 and UniRef50 yield a database size reduction of approximately 40 % and 65 %, respectively, providing for significantly faster sequence searches.
5. UniProtKB proteomes are listed at http://www.uniprot.org/taxonomy/complete-proteomes. Each protein of a reference organism has the keyword "Reference proteome" (*see* http://www.uniprot.org/keywords/KW-1185).
6. UniProt is currently hosted by a unified UniProt website http://www.uniprot.org/.
7. Major releases usually introduce important format changes. They are distinguishable from other releases by a new primary number followed by ".0".
8. To download a local version of UniProtKB, use the web page ftp://ftp.uniprot.org/pub.
9. When a gene encodes different isoforms and/or when different protein sequences for the same gene of a given species (given cultivar/strain/isolate) are available, they are merged into a single UniProtKB entry (e.g., Jasmonic acid-amido synthetase JAR1, entry **Q9SKE2**).
10. Other tools and databases developed by the EBI and PIR are available at http://www.ebi.ac.uk/services/ [17] and http://pir.georgetown.edu/, respectively.
11. For users of the Mozilla Web browser (http://www.mozilla.org/), the biobar navigation bar, dedicated to search into various

biological databases, is available at https://addons.mozilla.org/en-US/firefox/addon/biobar/. An ExPASy navigation bar is available at http://expasybar.mozdev.org, it allows searches to be performed in several databases hosted by ExPASy.

12. A complete documentation about BLAST parameters is available on the UniProt website at this address: http://www.uniprot.org/help/sequence-searches.
13. Your feedback is highly important and allows us to continuously improve our knowledgebase according to your needs.
14. UniProtKB accessions (AC) contain six characters and respect one of these regular expressions **[A-N,R-Z][0-9][A-Z][A-Z,0-9][A-Z,0-9][0-9]** or **[O,P,Q][0-9][A-Z,0-9][A-Z,0-9][A-Z,0-9][0-9]** (e.g., O80452). To face the fast increasing amount of new protein entries, an additional accession format extended to 10 alphanumerical characters for entries integrated after all 6 characters accessions will be used, possibly in 2014. The format of this new format will be **[A-N,R-Z][0-9][A-Z][A-Z,0-9][A-Z,0-9][0-9][A-Z][A-Z,0-9][A-Z,0-9][0-9]**. Both 6 and 10 characters accessions will coexist. All accessions are stable in time and should be used for UniProtKB protein citation.
15. It can also (but rarely) happen that the primary accession number becomes a secondary accession number (e.g., when an entry is split in two entries).
16. An accession number uniquely identifies an entry. If an entry is deleted, its AC will never be attributed to another entry.
17. A typical example is the annotation of N-glycosylation sites in the entries of non-cytoplasmic domains or proteins.
18. A typical example is the annotation of nuclear subcellular location in the entries of active transcription factors in eukaryotic organisms.
19. Exhaustive information about all cross-references present into UniProtKB (more than 140 in 2014) is available at http://www.uniprot.org/database/ and http://www.uniprot.org/docs/dbxref.
20. Amino-acid residue numbering begins at the N-terminus of the precursor protein (the displayed sequence).
21. The description of the feature may contain a non-experimental qualifier (*see* http://www.uniprot.org/manual/non_experimental_qualifiers).
22. In the case of *Arabidopsis thaliana* and *Oryza sativa* (and in other organisms following the same standards), we use the following nomenclature according to the standard defined for *A. thaliana*: [first letter of the genius name]-[first letter of the

species name]-[chromosome number]-[g, for gene]-[locus number] (e.g., At1g15690, Os03g16440).

23. Currently, Oryza sativa has three different taxonomy identifiers in UniProtKB/TrEMBL: **39947** for japonica cultivars, **39946** for indica cultivars, and **4530** for unspecified rice cultivars. In UniProtKB/Swiss-Prot, when possible, cultivars are specified for each reference related to a sequence deposition.
24. The family classification is exclusively based on sequence similarities, not on functions.
25. The algorithm to compute the CRC64 is described in the ISO 3309 standard [12].
26. Additional qualifiers may be present: ALT_SEQ, ALT_INIT, ALT_TERM, or ALT_FRAME. These are used in the case of discrepancies between the EMBL derived CDS and the displayed protein sequence. These may be due to gross differences in the predicted CDS sequence (arising from the failure to correctly predict all exons for a given gene for instance), incorrect selection of the initiating methionine, and termination of the sequence or frameshifts, respectively. For more details, see the documentation (http://www.uniprot.org/help/sequence_caution).

Acknowledgments

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References

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2. Bairoch A, Boeckmann B, Ferro S, Gasteiger E (2004) Swiss-Prot: juggling between evolution and stability. Brief Bioinform 5:39–55
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