Genomic/Protein Databases

BIFX-550

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Discussion ?s

- Midterm
  - Biology/basics (C1)
  - Command-line (C2-3)
    - Linux; R; edirect
  - Databases (C4)
    - NCBI, Ensembl, UniProt
  - Pairwise-Sequence comparison (C5-6)
    - Theory
    - Matrices (PAM/BLOSUM)
    - Dynamic Programming
  - BLAST (C7)
    - Tool for sequence comparison
  - MSA (C8)
    - Multiple sequence comparison

March 7 to 15 break
Midterm: March 19

Discussion ?s

- Final Project
- Have you decided on a gene for the final project?
- Have you created an account for galaxy?

Discussion

- Explain how do you think Linux will be useful for your Bioinformatics career?
- Explain one case where the e-direct tool can be useful?
- Are you challenged by R?

Database (DB)

- Electronic filing system
  - Yellow book or telephone book

- DB contains
  - Data
    - organized
  - Fields, records, files with links
  - Collection of data (biological data)

Database

- Good database should let users
  - Search
  - Compare
  - Download relevant information in a meaningful format

Databases

- As soon as WWW was born, Computer devices became the storage medium of choice

- Margaret Dayhoff and Colleagues (1965)
  - Protein sequences (book form; till 1970s)
  - Eventually it gave rise to PIR

Databases

- Primary
  - Original Submission
  - Authors (control the data)
    - GenBank, SNP
- Secondary
  - Derived from primary
  - annotations
  - controlled by DB creators (NCBI ex.)
    - NCBI protein, Refseq, TPA, UniGene, Structure, Conserved Domain, RefSNP etc.

Goals for this talk

How do we store, group, extract (easily) Genomic/Protein data and also use them for analysis?

Two common approaches in Bioinformatics

- **Individual genes/mRNA/proteins**
  - HBB, Locus, Chromosomes, isoforms etc.
    - Promoters, Introns, exons
  - Where/when is it expressed (tissues)?
  - Protein (structure, homodimer etc.)
  - Relationship to diseases
  - Variation of expression (SNP etc.)

Two common approaches in Bioinformatics

- **Comparing genes**
  - Can we compare all the variants across all genes from a family?
    - Globin family
  - For a specific mutated gene, we might want to compare the expression (mRNA) of all the genes in a cell type
    - Microarray and RNAseq
  - Having identified some 100 genes, can we sequence them and compare them?
    - For an individual?

Genomic Databases

Basic Unit of size

Base Pairs	Unit (bp)	Abbr.	Ex. size
1	1 base pair	1 bp	
10^3	Killobase pair	1 kb	Coding region
10^6	1 megbase pair	1 Mb	Bacterial genome
10^9	1 gigabase pair	1 Gb	Human genome
10^{12}	1 terabase pair	1 Tb	
10^{15}	1 petabase pair	1 Pb	

Size of DNA

- 1 bp ~ 3.4 Angstrom ~ 3.4×10^{-9} m
  - 1 kilo bp = 1000 bp
  - 1 Mega bp = 1,000,000 bp
  - 1 Giga bp = 1,000,000,000 bp

3 billion bp in one copy of human genome.
Total length ~ 2 meters

- Total DNA length
  - One copy 3 billion bp * (total # of cells in a body)
  - $(0.34 \times 10^{-9}\text{m}) * (2 * 3{,}000{,}000{,}000) * 10^{13}$
  - $2 * 10^{13}$ m

- Length of human cell 10-100 micro m
  - 10^{-5} to 10^{-4}m

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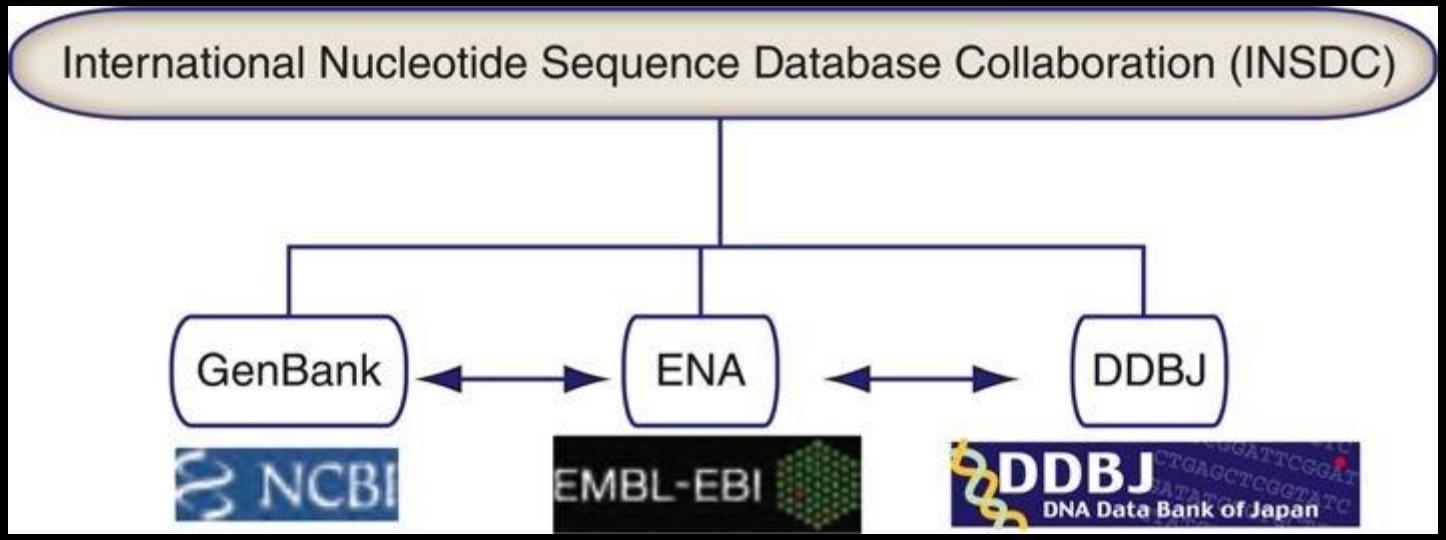
How much can I store?

- 3 Billion bp (a typical genome)
  - 3×10^9 byte
  - 3 x Gigabyte
  - 3 GB

Kilobyte	10^3
Megabyte	10^6
Gigabyte	10^9
Terabyte	10^{12}
Petabyte	10^{15}

Computers (work on bits, 1kilobyte = $2 \times 10^8 = 1024$)

Figures 2.1 Bioinformatics and Functional Genomics, (3rd Ed.) by Jonathan Pevsner



Data Sharing across three repositories and synced daily.

Let us focus on GenBank

GenBank

- Built and maintained at Los Alamos National Laboratory (LANL)
- 1990: Congressional Mandate moved to NCBI
  - Database: Literature scanning, typing
- 1993: Started direct data submission
- Mid 1990s: Collaborative efforts
  - DDBJ, EMBL, NCBI

GenBank

- Original submitted sequences
  - Primary database
- Nucletotide Sequences only
  - mRNA (with coding regions)
  - segments of genomic DNA (single or multiple genes)
  - Ribosomal RNA gene clusters
  - gene encodes a protein
    - CDs are added and eventually entered into protein db
- Redundant database

GenBank DNA-Level Data

- Divisions
- Main
  - mRNA or genomic sequence from the submitter
  - EST (Expressed Sequence Tags)
    - "short (usually <1000 bp), single-pass sequence reads from mRNA (**cDNA**)"
      - Post-splicing-after leaving nucleus…
  - GSS (Genomic Survey Sequences)
    - "most of the sequences are genomic in origin, rather than cDNA (mRNA)"
      - Pre splicing
  - Whole Genome Shotgun (WGS) Sequences
  - US Patent office (sequences from issued patents), other Sequencing centers etc…

NextGen

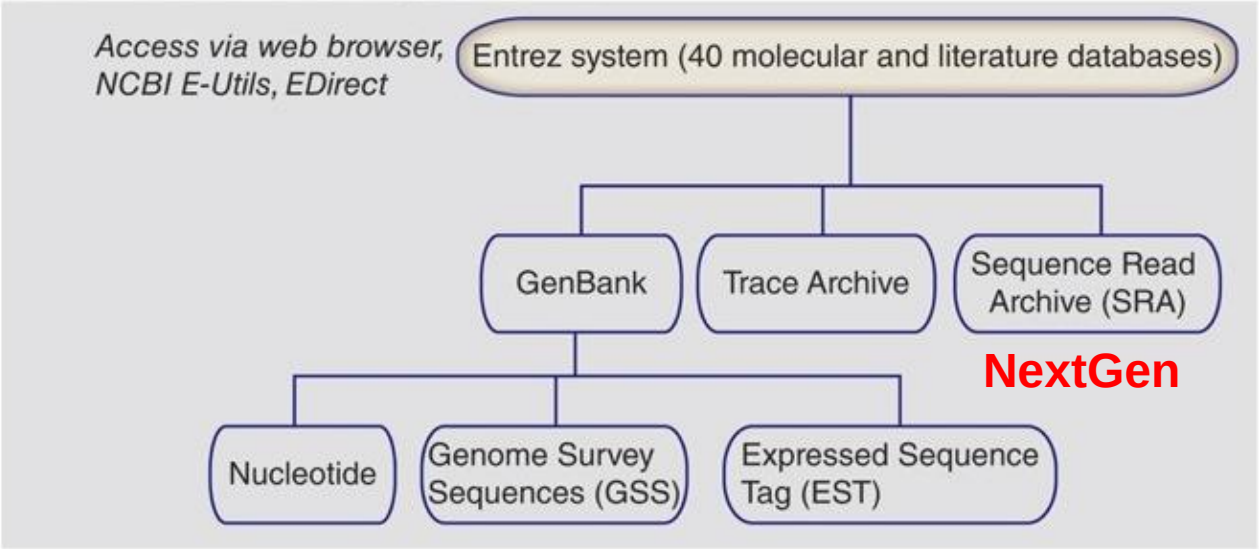
IonTorrent
Illumina
SOLiD
Helicos &
Complete
Genomics

Trace Archive

Seq. Data from
Gel/Capillary
Platforms ABI
3730

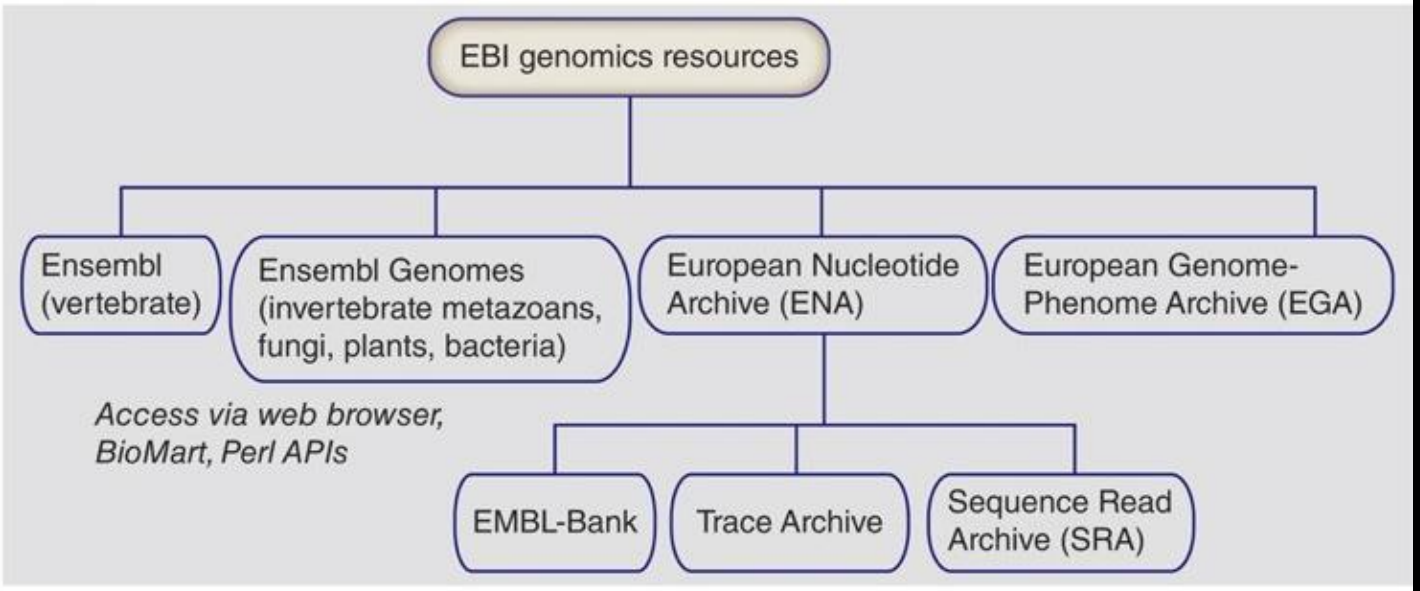
WG Shotgun

(a) National Center for Biotechnology Information



Figures 2.2 a & b Bioinformatics and Functional Genomics, (3rd Ed.) by Jonathan Pevsner

(b) European Bioinformatics Institute



(c) DNA Database of Japan

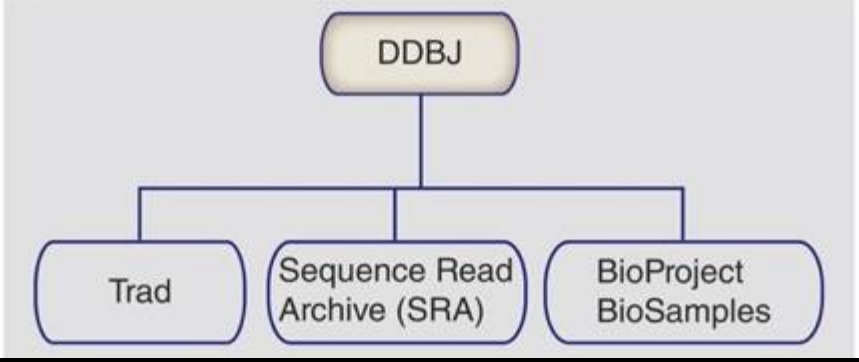


Figure2.2 c from Bioinformatics and Functional Genomics, (3rd Ed.) by Jonathan Pevsnsr

GenBank

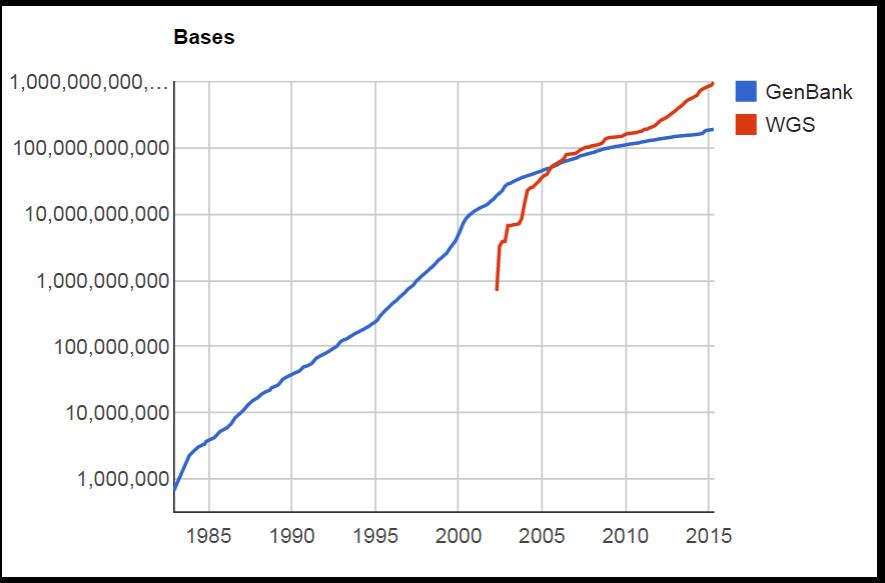
BASES

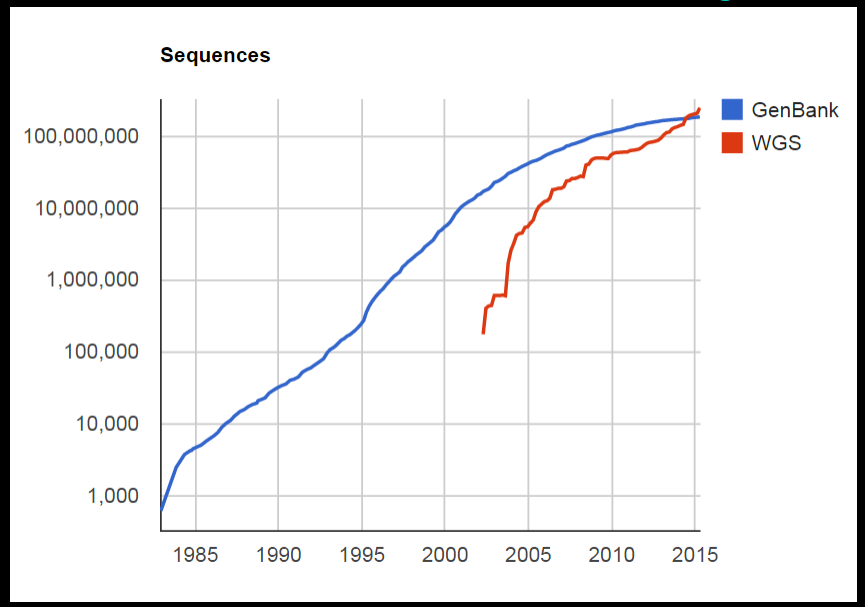
GenBank: ~211 B
WGS: ~ 1T 452 B

SEQUENCES

GenBank: ~193 M
WGS ~338 M

WGS: Whole Genome Shotgun





Figures from NCBI

Whole-Genome Shotgun (WGS) NOT PART OF GenBank

Commonly Analyzed Genomes in GenBank

Table 2.4 from Bioinformatics and Functional Genomics, (3rd Ed.) by Jonathan Pevsner

Table 2.4 Ten most sequenced organisms in GenBank.

Entries	Bases	Species	Common name
20,614,460	17,575,474,103	*Homo sapiens*	Human
9,724,856	9,993,232,725	*Mus musculus*	Mouse
2,193,460	6,525,559,108	*Rattus norvegicus*	Rat
2,203,159	5,391,699,711	*Bos taurus*	Cow
3,967,977	5,079,812,801	*Zea mays*	Maize
3,296,476	4,894,315,374	*Sus scrofa*	Pig
1,727,319	3,128,000,237	*Danio rerio*	Zebrafish
1,796,154	1,925,428,081	*Triticum aestivum*	Bread wheat
744,380	1,764,995,265	*Solanum lycopersicum*	Tomato
1,332,169	1,617,554,059	*Hordeum vulgare subsp. vulgare*	Barley

Source: GenBank, NCBI, ftp://ftp.ncbi.nih.gov/genbank/gbrel.txt (GenBank release 194.0).

Types of Data

Figures 2.4 from Bioinformatics and Functional Genomics, (3rd Ed.) by Jonathan Pevsner

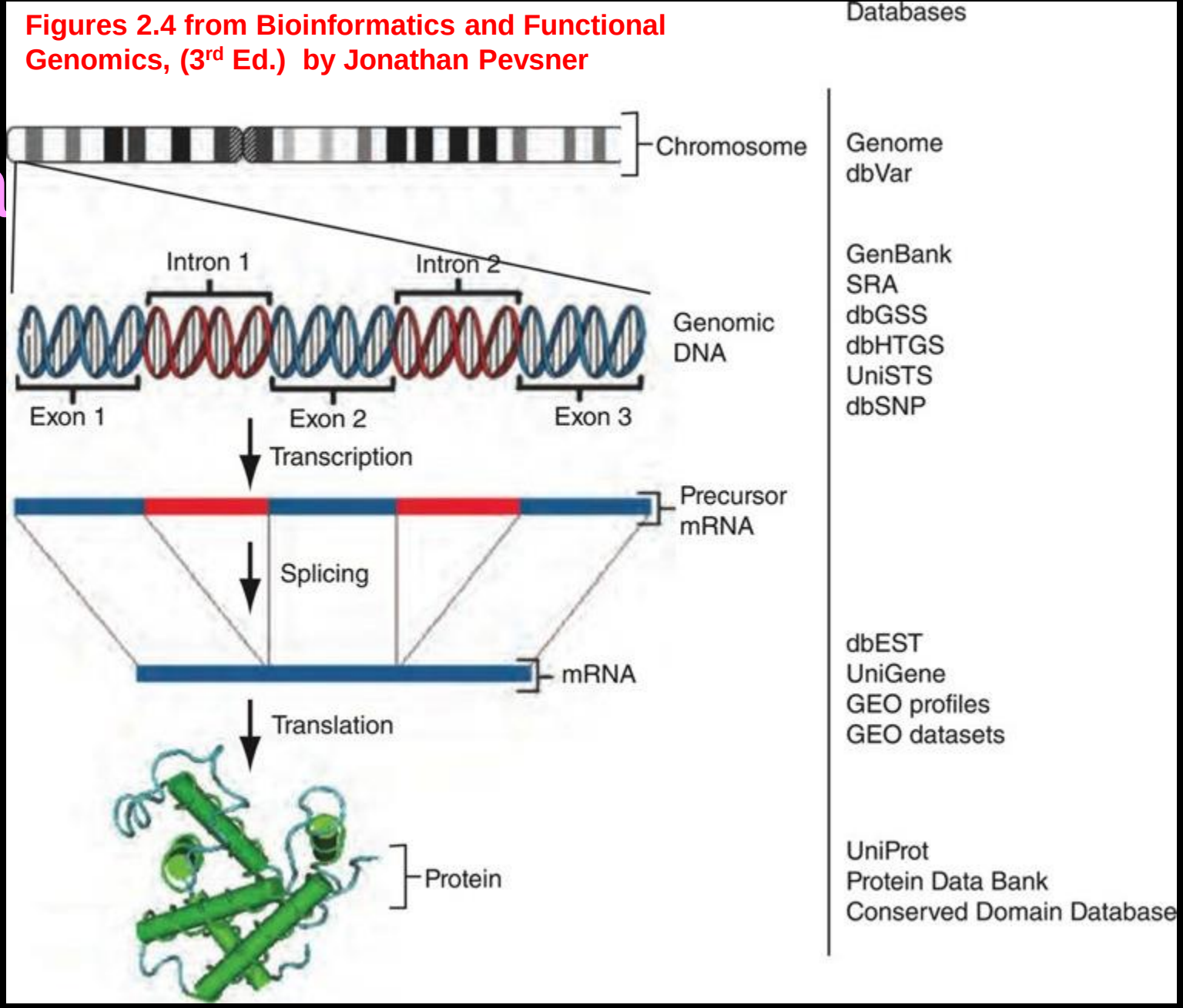


Figure2.4 from Bioinformatics and Functional Genomics, (3rd Ed.) by Jonathan Pevsnsr

Genomic Database in Detail

- DNA-Level
  (Sequence Tagged Sites (STSs)
- What is STS
  - ~500 bp genomic landmark sequences
  - Polymorphic; very useful for mapping
- What Organism?
  - Several hundred Organisms
- Where is it stored?
  - Probe DB

Search Probe using unists[“Properties”]

Unists used to be an STS db

https://www.ncbi.nlm.nih.gov/probe

www.ncbi.nlm.nih.gov/probe/?term=unists%5BProperties%5D

NCBI Resources How To

Probe | Probe | unists[Properties] | Search

Create alert Limits Advanced

Display Settings: Summary, 20 per page

Send to:

Filter your results:

All (546502)

Variation (0)

Silencing (16)

Expression (0)

Search results

Items: 1 to 20 of 546502

<< First < Prev Page 1 of 27326 Next > Last >>

1. STS probe **UniSTS**:486599
   Accession: Pr031817981 ID: 31817981
   Name: UniSTS:486599
   Type: STS

2. STS probe **UniSTS**:486598
   Accession: Pr031817980 ID: 31817980
   Name: UniSTS:486598
   Type: STS

3. STS probe **UniSTS**:486597
   Accession: Pr031817979 ID: 31817979

Results by taxon

Top Organisms [Tree]

Homo sapiens *(94951)*
Rattus norvegicus *(9276)*
Mus musculus *(4607)*
Bos taurus *(2587)*
Danio rerio *(2576)*
More...

High-Throughput Genomic Sequence (HTGS)

- What are HTGS sequences?
  - "unfinished" genomic data but made rapidly available for scientific study
- Where is the data coming from?
  - high-throughput sequencing centers using **traditional clone-based Sanger sequencing**.

https://www.ncbi.nlm.nih.gov/genbank/htgs/

RNA-Level Data

dbEST

- 200-800 nt long
- “Unedited, randomly selected single-pass sequence derived from cDNA libraries.”
  - Nagaraj et al, Brief Bioinform, 8,1,2007
- Low cost effort & not high quality
- Either the 5’ or 3’ end of cDNA clone will be sequenced

UniGene

- Related to EST db
- What is the goal of UniGene Project?
  - To group EST sequences into a gene oriented nr set.

Breakdown by Body Sites

	Hs.551506	
adipose tissue	0	0/12866
adrenal gland	0	0/32940
ascites	0	0/39834
bladder	0	0/29860
blood	0	0/122252
bone	0	0/71618
bone marrow	0	0/48737
brain	0	0/1092688
cervix	0	0/48486
connective tissue	0	0/149072
ear	0	0/16100
embryonic tissue	0	0/212896
esophagus	0	0/20154
eye	0	0/208840
heart	0	0/89524
intestine	25	6/231981
kidney	0	0/210778
larynx	0	0/23466
liver	0	0/205291
lung	0	0/334815
lymph	0	0/44302

UniGene

- More entries, more commonly (?) expressed
- Ideally the number of genes = number of UniGene Clusters
- Some genes have more than 1 entries

Breakdown by Health State

	Hs.551506	
adrenal tumor	0	0/12655
bladder carcinoma	0	0/17584
breast (mammary gland) tumor	0	0/93090
cervical tumor	0	0/34484
chondrosarcoma	0	0/82838
colorectal tumor	17	2/112517
esophageal tumor	0	0/17245
gastrointestinal tumor	0	0/118498
germ cell tumor	0	0/263230
glioma	0	0/107194
head and neck tumor	0	0/133826
kidney tumor	0	0/68872
leukemia	0	0/94479
liver tumor	0	0/96023
lung tumor	0	0/102765
lymphoma	0	0/72196
non-neoplasia	0	0/96623
normal	2	7/3328811
ovarian tumor	13	1/76185

UniGene

mRNA sequences (34)

BC046142.1	Homo sapiens breast cancer 1, early onset, mRNA (cDNA clone IMAGE:4342873)
NM_007294.3	Homo sapiens breast cancer 1, early onset (BRCA1), transcript variant 1, mRNA
NM_007297.3	Homo sapiens breast cancer 1, early onset (BRCA1), transcript variant 3, mRNA
NM_007298.3	Homo sapiens breast cancer 1, early onset (BRCA1), transcript variant 4, mRNA
NM_007299.3	Homo sapiens breast cancer 1, early onset (BRCA1), transcript variant 5, mRNA
NM_007300.3	Homo sapiens breast cancer 1, early onset (BRCA1), transcript variant 2, mRNA
BC062429.1	Homo sapiens breast cancer 1, early onset, mRNA (cDNA clone IMAGE:3686198), partial cds
BC072418.1	Homo sapiens breast cancer 1, early onset, mRNA (cDNA clone IMAGE:6181860), complete cds
AY354539.2	Homo sapiens IRIS mRNA, complete cds; alternatively spliced
AY751490.1	Homo sapiens breast and ovarian cancer susceptibility protein (BRCA1) mRNA, BRCA1-2201T/2430C/2731T/3232G/3667G/4427C/4956G allele, partial cds
BC085615.1	Homo sapiens breast cancer 1, early onset, mRNA (cDNA clone IMAGE:6042052), partial cds
BC106746.1	Homo sapiens breast cancer 1, early onset, mRNA (cDNA clone IMAGE:40017570), partial cds
BC106745.1	Homo sapiens breast cancer 1, early onset, mRNA (cDNA clone IMAGE:40017569), partial cds
BC114562.1	Homo sapiens cDNA clone IMAGE:40017575, containing frame-shift errors
BC114511.1	Homo sapiens breast cancer 1, early onset, mRNA (cDNA clone IMAGE:40017573)
BC115037.1	Homo sapiens breast cancer 1, early onset, mRNA (cDNA clone MGC:131629 IMAGE:7961446), complete cds
U14680.1	Homo sapiens breast and ovarian cancer susceptibility (BRCA1) mRNA, complete cds

BRCA1 UniGene

Collections of EST and mRNAs

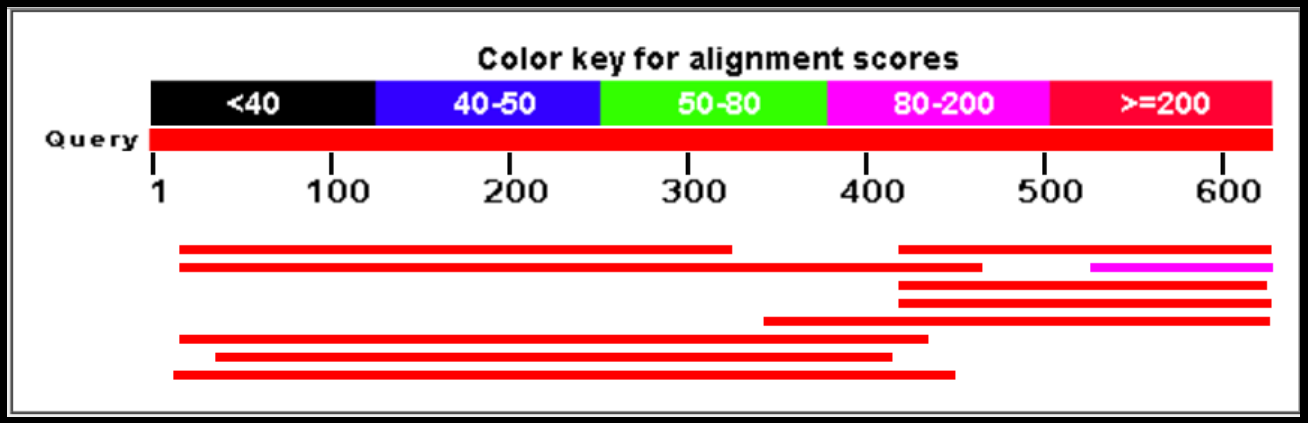
EST sequences (149)

AI016870.1	Clone IMAGE:1627848	mixed
AI040685.1	Clone IMAGE:1656659	mixed
BX102233.1	Clone IMAGp998C11519_;_IMAGE:241474	mixed
AI217721.1	Clone IMAGE:1844798	mixed
CB158976.1	Clone L18POOL1n1-32-H11	liver
CB108172.1	Clone L3SNU475-26-B03	liver
CB118225.1	Clone L3SNU475s1-13-B05	liver
CB136844.1	Clone L5HLK1-40-A10	liver
CB150491.1	Clone C1SNU17-30-H04	cervix
CB155501.1	Clone L12JSHC0s1-6-G05	liver
U25774.1	Clone 694:11	mammary gland
U25782.1	Clone 694:5	mammary gland
AI589028.1	Clone IMAGE:2154839	intestine
AI680547.1	Clone IMAGE:2266185	uterus
AI684595.1	Clone IMAGE:2302861	mixed
AI915085.1	Clone IMAGE:2216863	ovary
AL043576.1	Clone DKFZp434F0227	testis

ESTs mapped to HBB to create UniGene Cluster

HBB is Query

ESTs



Figures 2.5 from Bioinformatics and Functional Genomics, (3rd Ed.) by Jonathan Pevsner

Figures 2.5 from Bioinformatics and Functional Genomics, (3rd Ed.) by Jonathan Pevsner

(a)

UGID:914190 UniGene Hs.523443 *Homo sapiens* (human) HBB

Order cDNA clone, Links

Hemoglobin, beta (HBB)

Human protein-coding gene HBB. Represented by 2363 ESTs from 234 cDNA libraries. Corresponds to reference sequence NM_000518.4. [UniGene 914190 - Hs.523443]

SELECTED PROTEIN SIMILARITIES

Comparison of cluster transcripts with RefSeq proteins. The alignments can suggest function of the cluster.

	Best Hits and Hits from model organisms	Species	Id(%)	Len(aa)
XP_508242.1	PREDICTED: hemoglobin subunit beta isoform 2	*P. troglodytes*	100.0	146
NP_000509.1	HBB gene product	*H. sapiens*	100.0	146
NP_001188320.1	hemoglobin subunit beta-1-like	*M. musculus*	83.7	146
NP_001091375.1	uncharacterized protein LOC100037217	*X. laevis*	61.9	146
NP_571095.1	ba1 gene product	*D. rerio*	52.7	147
	Other hits (2 of 21) [Show all]	Species	Id(%)	Len(aa)
NP_001157900.1	HBB gene product	*M. mulatta*	95.9	146
NP_001162318.1	HBB gene product	*P. anubis*	95.2	146

GENE EXPRESSION

Tissues and development stages from this gene's sequences survey gene expression. Links to other NCBI expression resources.

EST Profile: Approximate expression patterns inferred from EST sources. [Show more entries with profiles like this]

GEO Profiles: Experimental gene expression data (Gene Expression Omnibus).

cDNA Sources: blood; mixed; muscle; placenta; bone marrow; lung; brain; spleen; pancreas; connective tissue; pharynx; eye; ovary; uterus; liver; bone; heart; prostate; mammary gland; kidney; uncharacterized tissue; skin; adipose tissue; intestine; stomach; umbilical cord; adrenal gland; nerve; vascular; thymus; testis; embryonic tissue; pituitary gland; parathyroid; ganglia; thyroid; lymph node; pineal gland; ear

Figures 2.5 from Bioinformatics and Functional Genomics, (3rd Ed.) by Jonathan Pevsner

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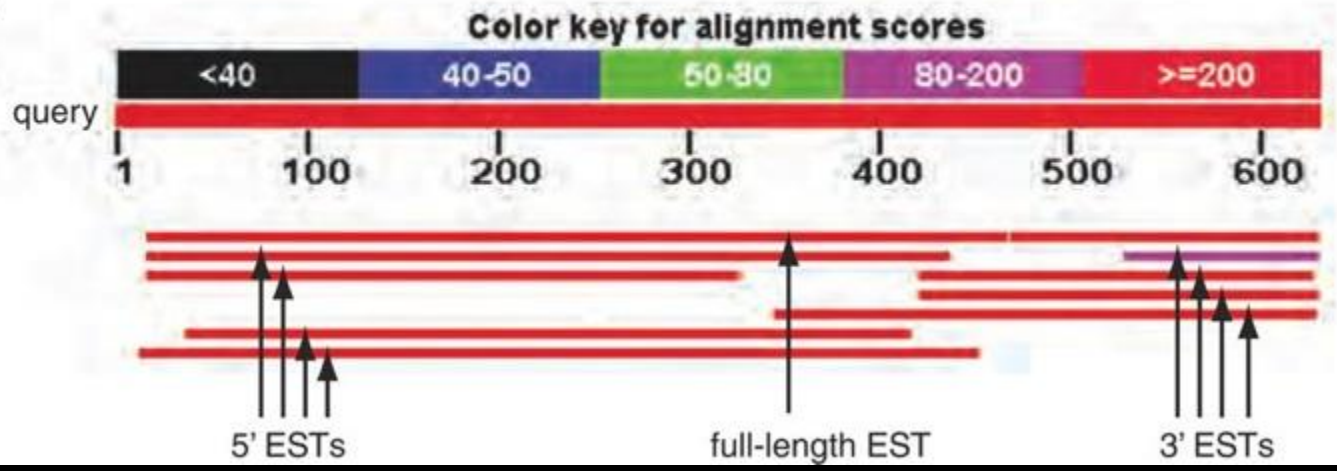


Protein Database

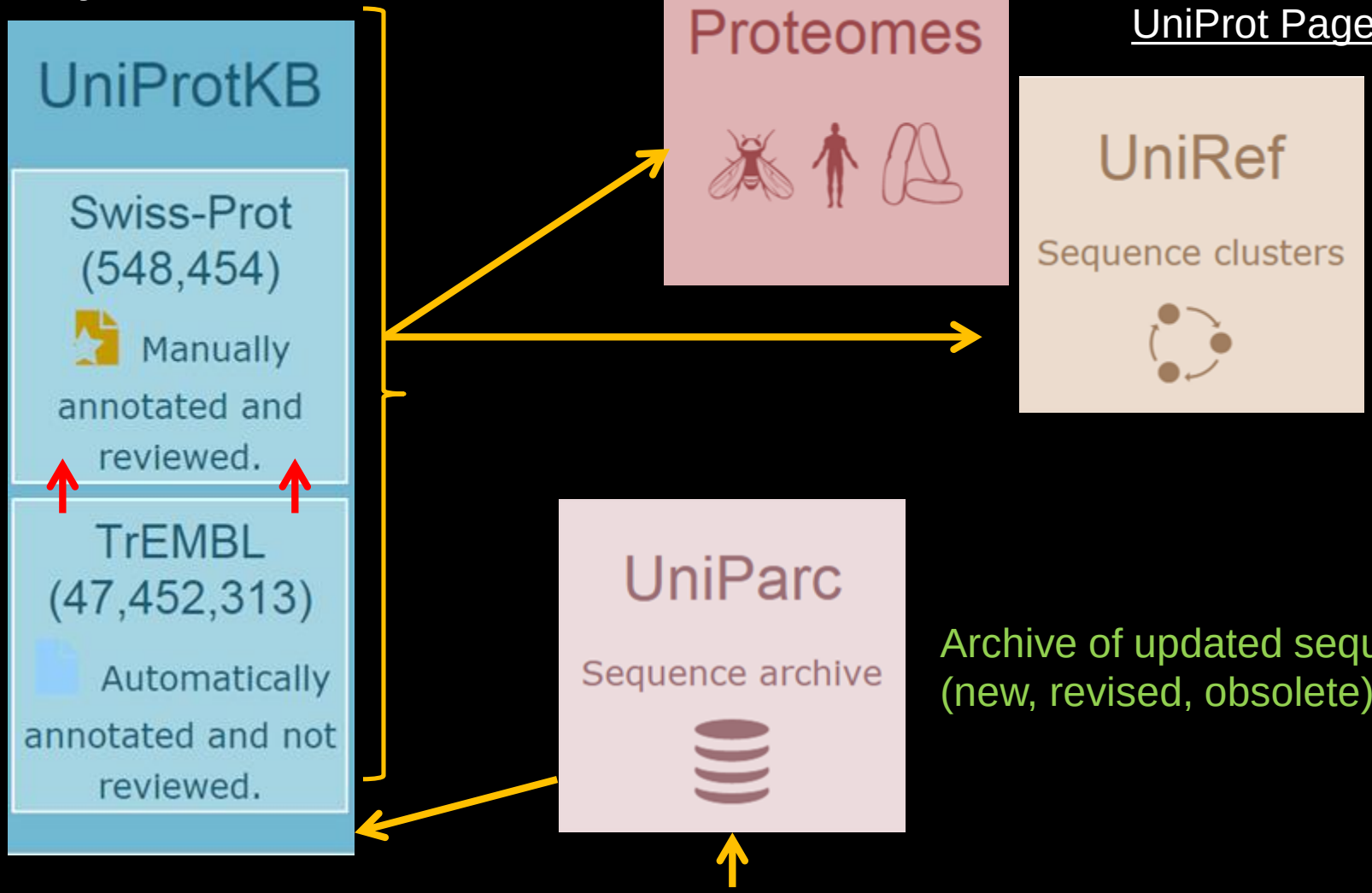
UniProt

Why?

- Protein function is key to many research areas
  - Medicine, Drug discovery, Biotechnology etc.
- Data generation in unprecedented amounts especially after NextGen sequencing methods
- UniProt acts as an Universal Protein Resource
  - Consolidating all the experimental, inferred information in one site

Early of 2015

Pictures from UniProt Page



Archive of updated sequences (new, revised, obsolete)-nr

External:
EMBL/GenBank/DDBJ (plus metagenomics sequences)
Ensembl (VEGA), PDB, RefSeq + Others

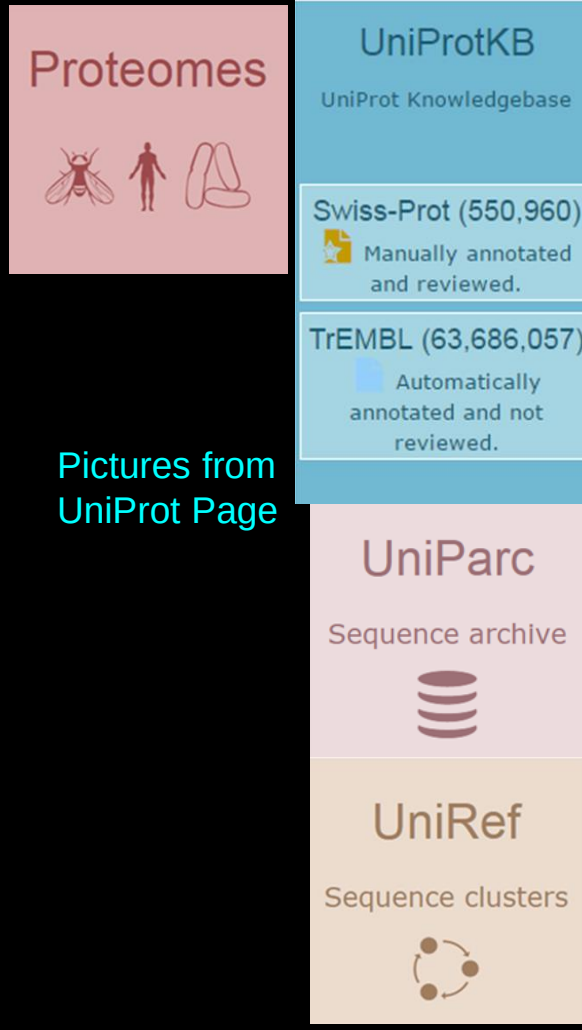
UniProt

www.uniprot.org

- Universal Protein Resource
- Protein data only
- Collaborative effort:
  - EMBL-EBI, SIB and PIR
    - **E**uropean **B**ioinformatics **I**nstitute, the **S**wiss **I**nstitute of **B**ioinformatics and the **P**rotein **I**nformation **R**esource.
- Cross-references to other 150 DBs

Datasets of UniProt

- UniProtKB/TrEMBL
  - Swiss-Prot
    - 550,690 (05/2016)
    - manually annotated
  - TrEMBL
    - 63,686,057 (05/2016)
    - automatic not reviewed
    - Extra information drug binding etc.
- UniParc (Sequence Archive)

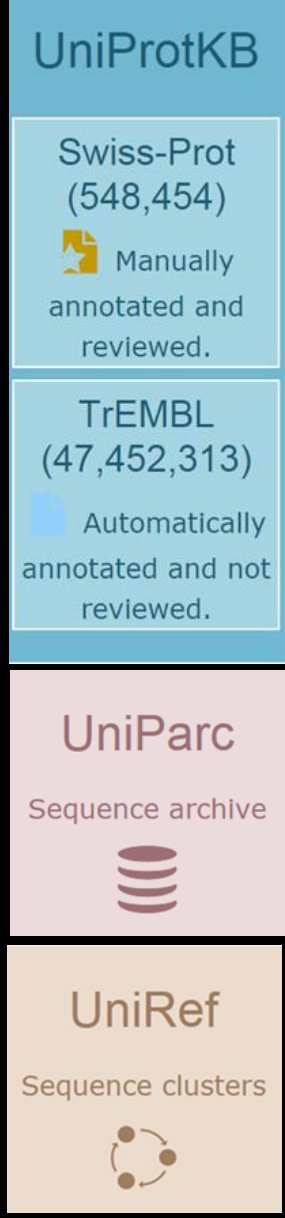


Pictures from UniProt Page

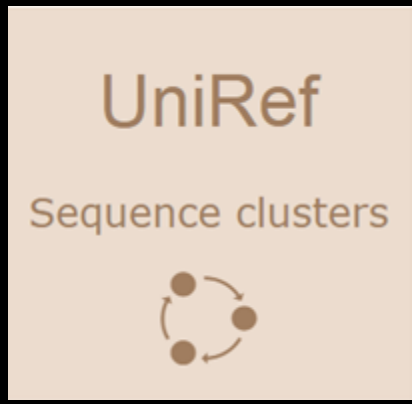
Datasets of UniProt

- UniParc: Sequence archive
  - Non-redundant; Each sequence stored once-gets unique ID
- Proteomes

Pictures from UniProt Page



- **UniRef100, UniRef90 ….**
  - Combines all identical sequences from all organisms into a single entry
    - Lists all merged entries with links



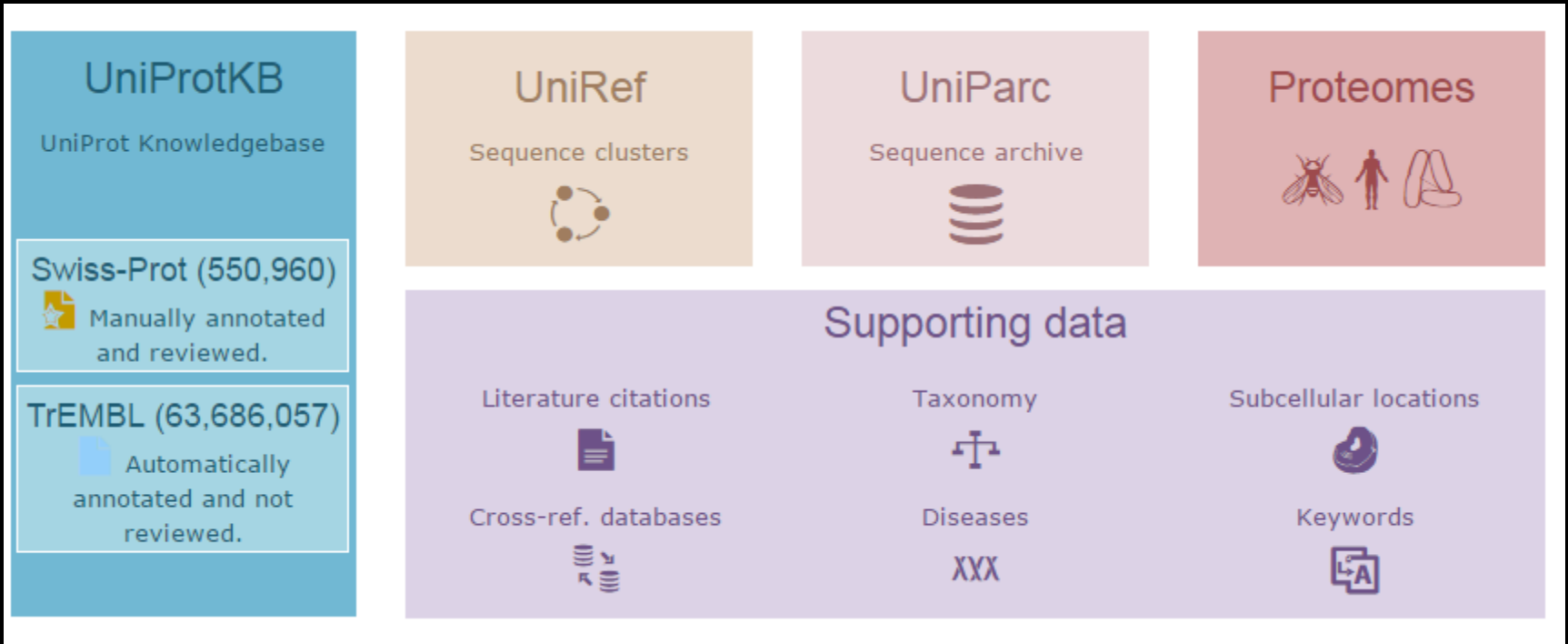
Picture from UniProt Page

UniRef100_P09848		Cluster: Lactase-phlorizin hydrolase	1	P09848	Homo sapiens (Human)	1,927	100%
UniRef90_P09848		Cluster: Lactase-phlorizin hydrolase	23	P09848 UPI0006250A0D UPI00029DB8E7 F6RJ72 F6V0B1 G7NB02 A0A0D9RUU4 G3RPU6 G7PN30 +13	Homo sapiens (Human) Aotus nancymaae (Ma's night monkey) Gorilla gorilla gorilla (Western lowland gorilla) Callithrix jacchus (White-tufted-ear	1,927	90%

UniRef

- "***UniRef90*** *is built by clustering UniRef100 sequences such that each cluster is composed of sequences that have at least 90% sequence identity to the longest sequence (the seed sequence) of the cluster.*" Taken from EBI website

- **"UniRef50 is built by clustering UniRef90 seed sequences that have at least 50% sequence identity to the longest sequence in the cluster."** Taken from EBI website


UniProtKB
UniProt Knowledgebase
Swiss-Prot (550,960)
Manually annotated and reviewed.
TrEMBL (63,686,057)
Automatically annotated and not reviewed.
UniRef
Sequence clusters
UniParc
Sequence archive
Proteomes
Supporting data
Literature citations
Taxonomy
Subcellular locations
Cross-ref. databases
Diseases
XXX
Keywords

UniProt Consortium
Nucleic Acids Research, 2015, Vol. 43, Database issue D204-12

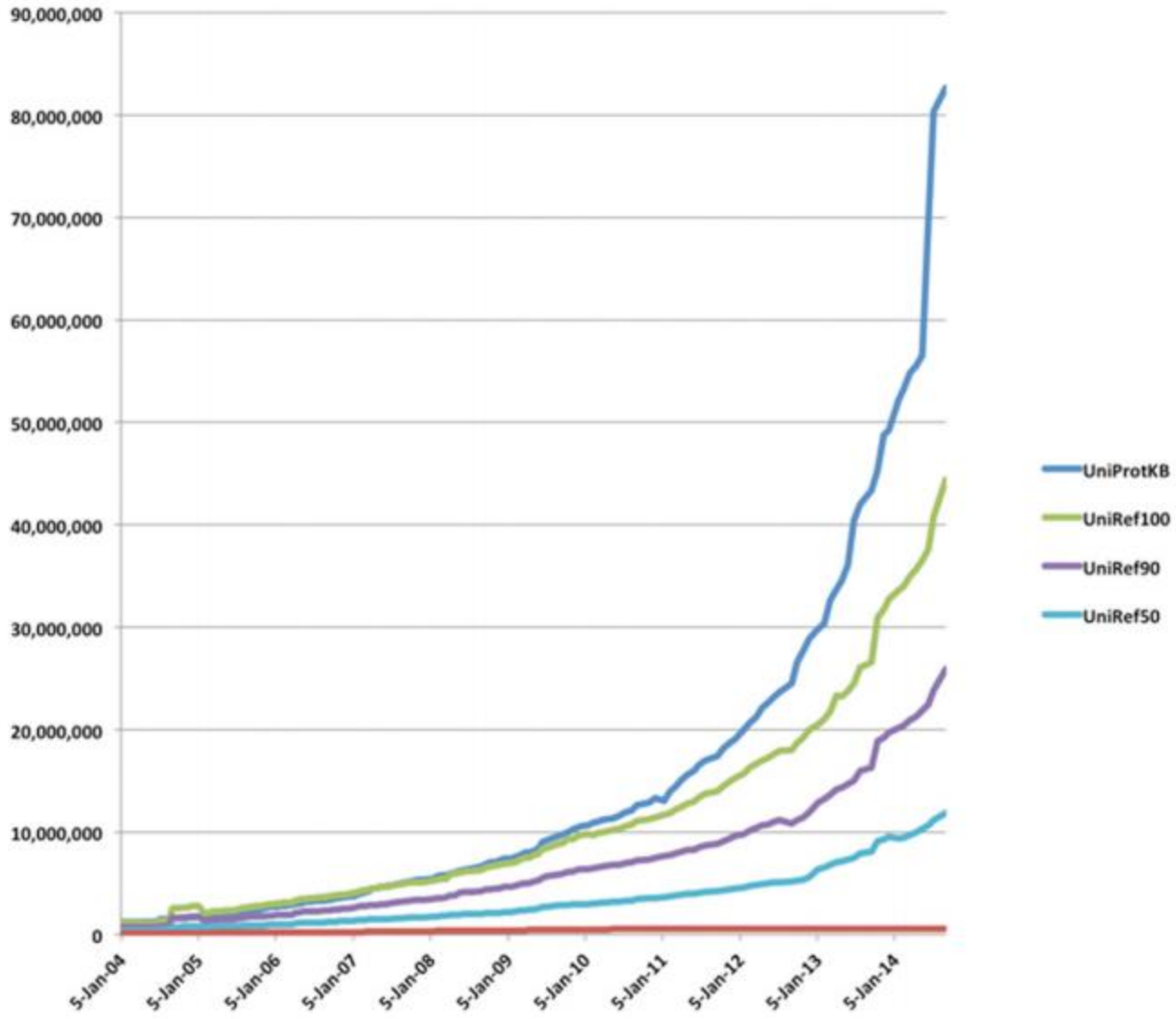
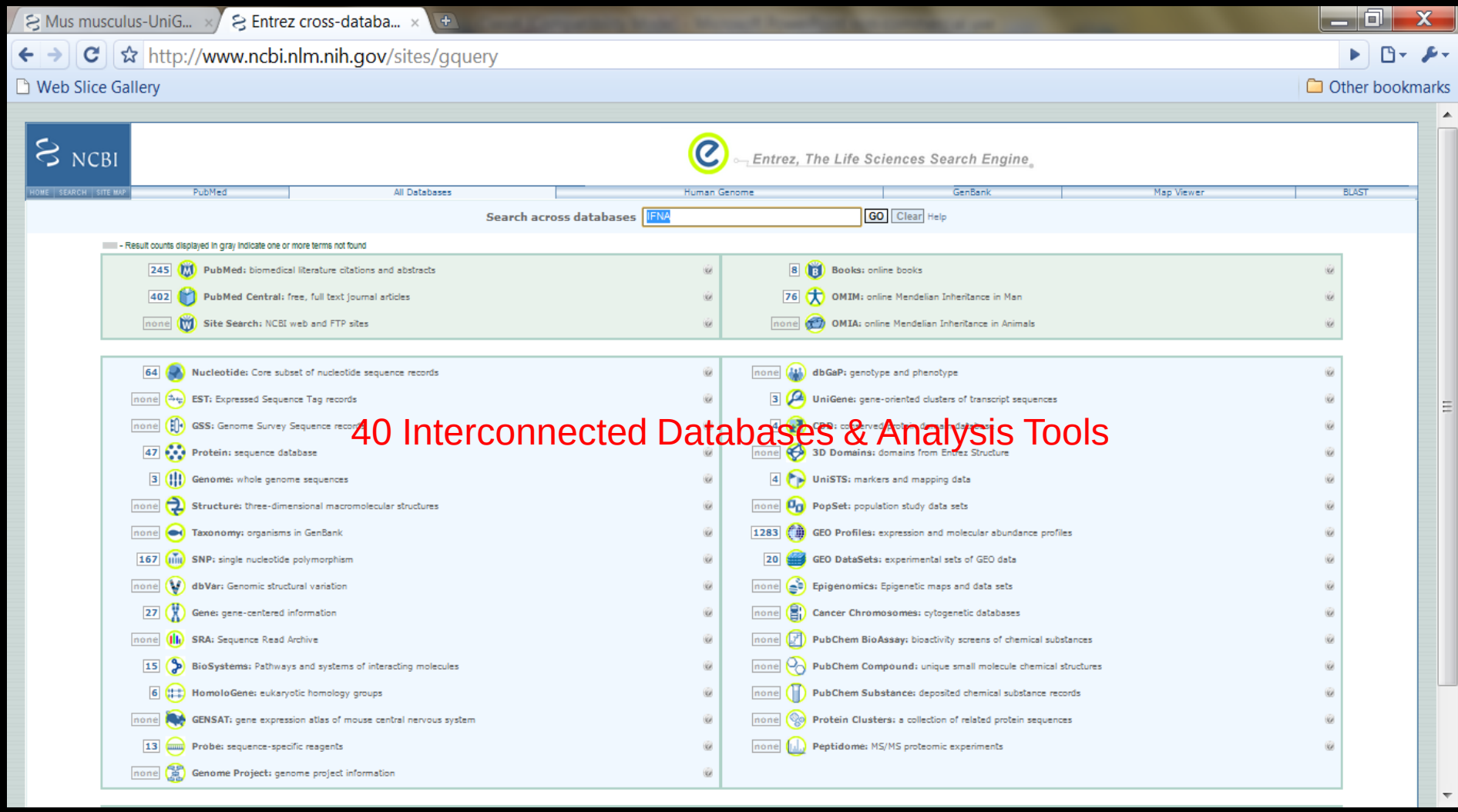


Figure 1. Growth of UniProt and UniRef databases.

40 DBs together contain 1.3 Billion recprds; NAR 2015, V43, DB issue D6

NCBI Entrez



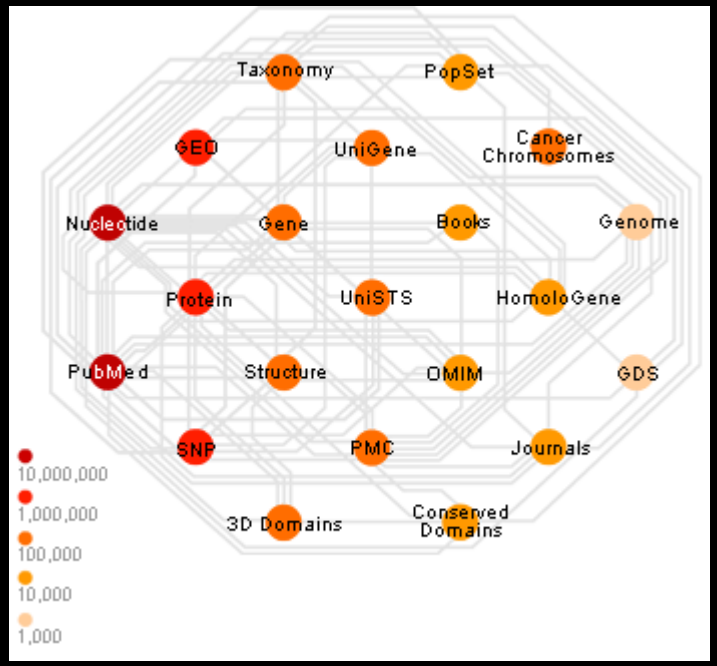
40 Interconnected Databases & Analysis Tools

NCBI Resources How To

Search NCBI databases

Lactose intolerance | Search

Results found in 21 databases for "Lactose intolerance"



Literature

Books	275	books and reports
MeSH	2	ontology used for PubMed indexing
NLM Catalog	50	books, journals and more in the NLM Collections
PubMed	3,263	scientific & medical abstracts/citations
PubMed Central	2,601	full-text journal articles

Health

ClinVar	0	human variations of clinical significance
dbGaP	17	genotype/phenotype interaction studies
GTR	14	genetic testing registry
MedGen	17	medical genetics literature and links
OMIM	7	online mendelian inheritance in man
PubMed Health	84	clinical effectiveness, disease and drug reports

Genomes

Assembly	0	genome assembly information
BioProject	5	biological projects providing data to NCBI
BioSample	3	descriptions of biological source materials
Clone	0	genomic and cDNA clones
dbVar	0	genome structural variation studies
Epigenomics	0	epigenomic studies and display tools
Genome	6	genome sequencing projects by organism
GSS	0	genome survey sequences
Nucleotide	16	DNA and RNA sequences
Probe	0	sequence-based probes and primers
SNP	0	short genetic variations
SRA	2	high-throughput DNA and RNA sequence read archive
Taxonomy	0	taxonomic classification and nomenclature catalog

Genes

EST	0	expressed sequence tag sequences
Gene	4	collected information about gene loci
GEO DataSets	0	functional genomics studies
GEO Profiles	0	gene expression and molecular abundance profiles
HomoloGene	0	homologous gene sets for selected organisms
PopSet	0	sequence sets from phylogenetic and population studies
UniGene	21	clusters of expressed transcripts

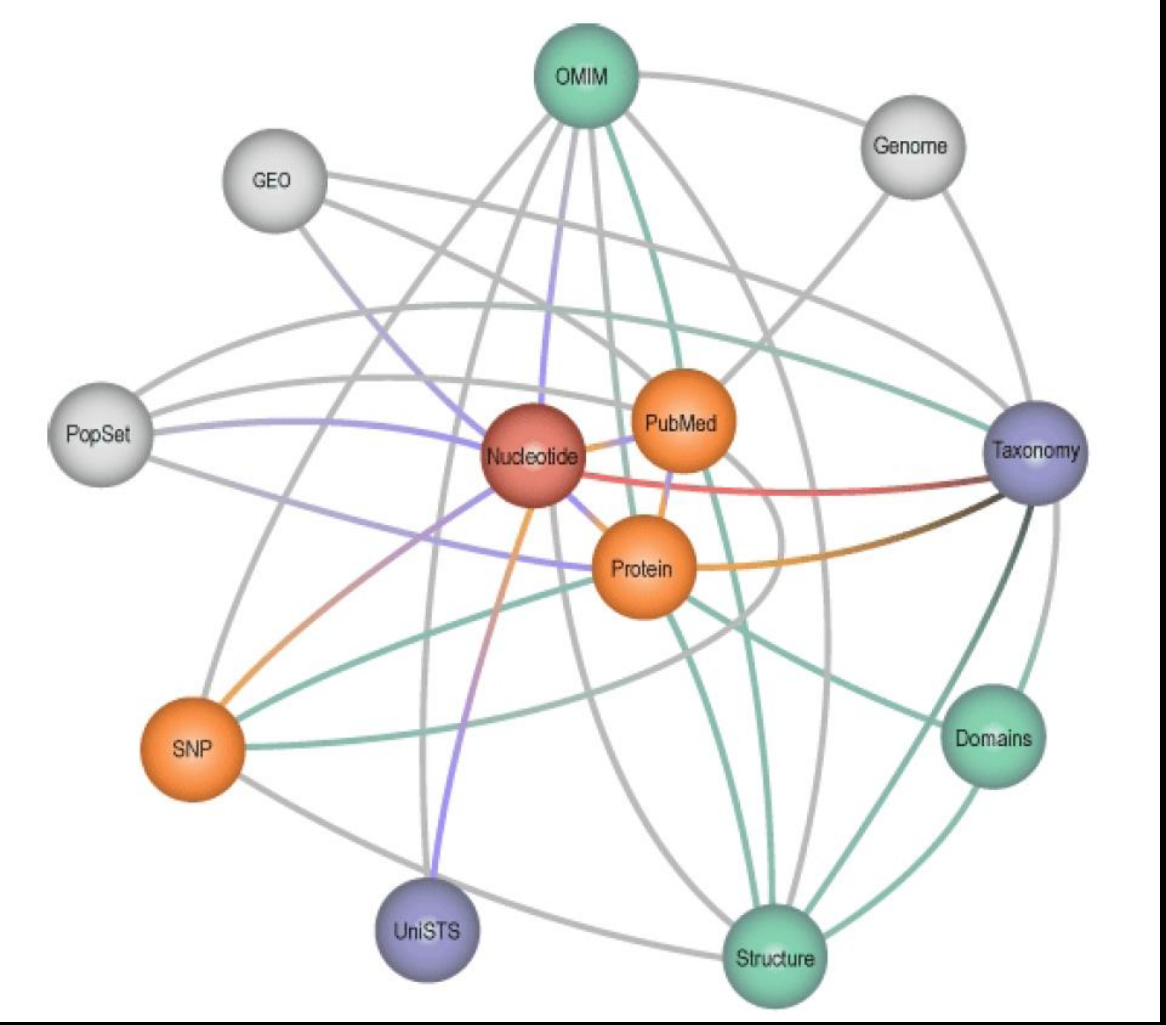
Proteins

Conserved Domains	0	conserved protein domains
Protein	3	protein sequences
Protein Clusters	294	sequence similarity-based protein clusters
Structure	0	experimentally-determined biomolecular structures

Chemicals

BioSystems	1	molecular pathways with links to genes, proteins and chemicals
PubChem BioAssay	0	bioactivity screening studies
PubChem Compound	0	chemical information with structures, information and links
PubChem Substance	6	deposited substance and chemical information

Links in NCBI taken from
http://www.nlm.nih.gov/bsd/disted/pubmedtutorial/060_010.html


OMIM
Genome
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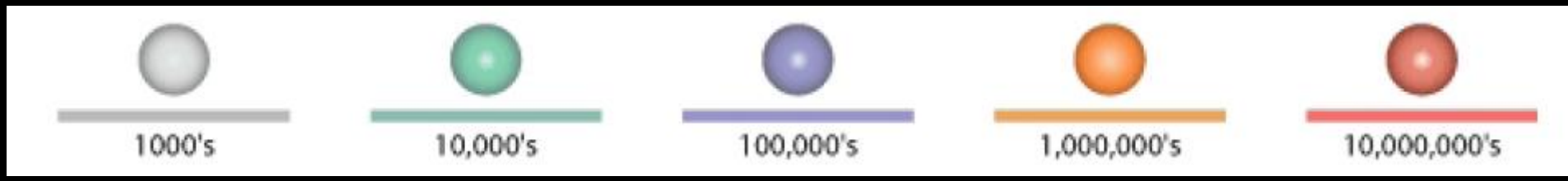
PopSet
PubMed
Nucleotide
Taxonomy
Protein
SNP
Domains
UniSTS
Structure


1000's
10,000's
100,000's
1,000,000's
10,000,000's

NCBI Entrez-LinkOut

http://www.ncbi.nlm.nih.gov/pubmed/20575042

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FULL TEXT ONLINE InterScience

Am J Hematol. 2010 Jul;85(7):525-8.

The assessment of human organic cation transporter 1 (hOCT1) mRNA expression in patients with chronic myelogenous leukemia is affected by the proportion of different cells types in the analyzed cell population.

Racil Z, Razga F, Buresova L, Jurcek T, Dvorakova D, Zackova D, Timilsina S, Cetkovsky P, Mayer J.

PMID: 20575042 [PubMed - in process]

Publication Types

LinkOut - more resources

Related citations

Effective dasatinib uptake may occur without human organic cation transporter 1 [Blood. 2008]

Functional characterization of an organic cation transporter (hOCT1 [J Pharmacol Exp Ther. 1998]

Expression and pharmacological profile of the human organic cation trans [Br J Pharmacol. 2002]

Review Pharmacologic markers and predictors of responses to imatinib the [Leuk Lymphoma. 2008]

Links to resources such as full text articles and biological data

Full Text Sources:

John Wiley & Sons, Inc.
EBSCO
OhioLINK Electronic Journal Center
Swets Information Services

Data entry in Entrez has LinkOuts to enrich info

Ex from NCBI Nucleotide DB

http://www.ncbi.nlm.nih.gov/nuccore/NM_153187

Linkout (External references)

Mus musculus-UniG... | Homo sapiens solut...

http://www.ncbi.nlm.nih.gov/nuccore/N

Web Slice Gallery

NCBI Resources How To

Nucleotide
Alphabet of Life

Search: Nucleotide Limits Advanced search Help

Display Settings: GenBank

Homo sapiens solute carrier family 22 (organic cation transpo

NCBI Reference Sequence: NM_153187.1

Comment Features Sequence

```
LOCUS       NM_153187               1808 bp    mRNA    linear   PRI 05-JUL-2010
DEFINITION  Homo sapiens solute carrier family 22 (organic cation transporter),
            member 1 (SLC22A1), transcript variant 2, mRNA.
ACCESSION   NM_153187
VERSION     NM_153187.1  GI:23510409
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini;
            Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 1808)
  AUTHORS   Galetti,M., Alfieri,R.R., Cavazzoni,A., La Monica,S., Bonelli,M.,
            Fumarola,C., Mozzoni,P., De Palma,G., Andreoli,R., Mutti,A.,
            Mor,M., Tiseo,M., Ardizzoni,A. and Petronini,P.G.
  TITLE     Functional characterization of gefitinib uptake in non-small cell
            lung cancer cell lines
  JOURNAL   Biochem. Pharmacol. 80 (2), 179-187 (2010)
   PUBMED   20363215
  REMARK    GeneRIF: Gefitinib may exert an inhibitory effect on the
            intracellular accumulation of drugs transported by hOCT1 and hOCT2.
REFERENCE   2  (bases 1 to 1808)
  AUTHORS   Rzeoz,A., Marin,D., Reid,A.G., Gerrard,G., Milojkovic,D.,
            May,P.C., de Lavallade,H., Garland,P., Rezvani,K., Apperley,J.F.,
            Goldman,J.M., Foroni,L. and Khorashad,J.S.
  TITLE     hOCT1 transcript levels and single nucleotide polymorphisms as
            predictive factors for response to imatinib in chronic myeloid
            leukemia
  JOURNAL   Leukemia 24 (6), 1243-1245 (2010)
   PUBMED   20445576
  REMARK    GeneRIF: Observational study of gene-disease association,
            gene-environment interaction, and pharmacogenomic / toxicogenomic.
            (HuGE Navigator)
REFERENCE   3  (bases 1 to 1808)
  AUTHORS   Sallinen,R., Kaunisto,M.A., Forsblom,C., Thomas,M., Fagerudd,J.,
            Pettersson-Fernholm,K., Groop,P.H. and Wessman,M.
  CONSRTM   Finnish Diabetic Nephropathy Study Group
  TITLE     Association of the SLC22A1, SLC22A2, and SLC22A3 genes encoding
            organic cation transporters with diabetic nephropathy and
            hypertension
  JOURNAL   Ann. Med. 42 (4), 296-304 (2010)
   PUBMED   20429798
  REMARK    GeneRIF: Observational study of gene-disease association. (HuGE
            Navigator)
REFERENCE   4  (bases 1 to 1808)
```

LinkOut to external resources

BioGPS [BioGPS]

Order full-length cDNA clone [GeneCopoeia Inc.]

antibody [ExactAntigen/Labome]

antibody review [ExactAntigen/Labome]

cDNA clone [ExactAntigen/Labome]

others [ExactAntigen/Labome]

protein and peptide [ExactAntigen/Labome]

siRNA and shRNA [ExactAntigen/Labome]

Genotyping Assays [TaqMan® probe and primer sets...]

Gene Expression Assays [TaqMan® probe and primer sets...]

imaGenes [imaGenes]

Silencer® Select siRNAs

Other bookmarks

out 1 of 1

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Analyze this sequence
Run BLAST
Pick Primers

Articles about the SLC22A1 gene
hOCT1 transcript levels and single nucleotide polymorphisms as predictive factors fc [Leukemia. 2010]
Association of the SLC22A1, SLC22A2, and SLC22A3 genes encoding organic cation transp [Ann Med. 2010]
L-Type Voltage-Dependent Calcium Channel Alpha Subunit 1C is a Novel Cand [Nephron Clin Pract. 2010]
See all...

Reference sequence information
RefSeq alternative splicing
See the other reference mRNA sequence splice variant for the SLC22A1 gene (NM_003057.2).
RefSeq protein product
See the reference protein sequence for solute carrier family 22 member 1 isoform b (NP_694857.1).

More about the SLC22A1 gene
Polyspecific organic cation transporters in the liver, kidney, intestine, and other organs are critical for elimination of many endogenous s...
Also Known As: hOCT1, OCT1, oct1_ods

Homologs of the SLC22A1 gene
The SLC22A1 gene is conserved in chimpanzee, dog, cow, mouse, and rat.

LinkOut to external resources
BioGPS [BioGPS]

Taxonomy

- Organizational group identification is very important in biology/bioinformatics
- This is how we identify homologs and use this to identify function etc.
- How are the organisms identified?
  - Sequence data (not just this)
  - Mainly morphological studies

1995

Haemophilus influenza

Bacterium

Ranks:	higher taxa	genus	species	lower taxa	total
Archaea	174	157	592	0	923
Bacteria	1623	3031	15425	862	20941
Eukaryota	22080	74508	341109	25095	462792
Fungi	1606	5131	33542	1165	41444
Metazoa	15808	51185	171613	12563	251169
Viridiplantae	2952	15180	125741	11072	154945
Viruses	667	495	2371	0	3533
All taxa	24577	78198	359523	25957	488255

Source NCBI Taxonomy

2016 March

Database that includes 400,000 different Organisms and about >10^{18} bases (quintillion)

PubMed

- Biomedical research literature Database- since 1996
- NCBI (National Center for Biotechnology Information)
  - Belongs to National Library of Medicine (NLM) at the NIH
- Medline the source of PubMed Data
  - Scientific Citations going back to 1960s

PubMed

- 28 M references (as of 08/2018)
  - 24 M (05/2015)
- Includes
  - MEDLINE indexed journals
  - Journals deposited in PMC (archives full-text Journal articles) and/or publishers
  - NCBI Bookshelf

http://www.ncbi.nlm.nih.gov/pubmed

- Well linked to other Entrez Db
- Articles also linked to each other
  - MeSH

The assessment of human organic cation transporter... [Am J Hematol. 2010] - PubMed result - Windows Internet Explorer

http://www.ncbi.nlm.nih.gov/pubmed/20575042

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The assessment of human organic cati...

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Am J Hematol. 2010 Jul;85(7):525-8.

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Publication Types

LinkOut - more resources

Related citations

Effective dasatinib uptake may occur without human organic cation transporter 1 (hOCT1): ir [Blood. 2008]

Functional characterization of an organic cation transporter (hOCT1) in [J Pharmacol Exp Ther. 1998]

Expression and pharmacological profile of the human organic cation transporters h([Br J Pharmacol. 2002]

Review Pharmacologic markers and predictors of responses to imatinib therap [Leuk Lymphoma. 2008]

Review Chronic myelogenous leukemia. [Curr Opin Hematol. 1996]

See reviews...

See all...

Internet | Protected Mode: On | 100%

http://www.ncbi.nlm.nih.gov/books

NCBI Bookshelf

- Biomedical Books collection
  - accessible from Entrez
  - collaboration with publishers and authors
- Before placing books in Book Shelf
  - NCBI converts all book contents to XML
  - figures to GIF and JPEG formats
  - XML files are stored in a DB
    - user requests, XML -> HTML on the fly using Cascading Style Sheets and Extensible Stylesheet Language Transformation (XSLT)

Bookshelf

- Accessbile via Entrez
  - Available from Pubmed
    - well connected

European Database

- EMBnet (European Molecular Biology network)
  - Important nodes of EMBnet: EMBI, European Bioinformatics Institute, MIPS (The Munich Information center for Protein Sequences) etc.
    - EMBL: Collaborative project between GenBank (NCBI, Bethesda and DNA Databank of Japan (DDBJ)-Head-Quarters in Germany
    - EBI (outstation of EMBL, UK): Develops, Distributes EMBL nucleotide's sequences. Collaborates with UniProt for protein DBs- Shares and distributes the data between groups on daily basis.

Ensembl (website 2000)

- Joint effort between EBI, EMBL and Wellcome Trust Sanger Institute (WTSI)

- Goal: annotate the genome, integrate the annotation with other DBs and make it available on the web

Why Genome Browswers?

MLEICLKLVGCKSKKGLSSSSSCYLEEALQRPVASDFEPQGLSEAARWNSKENLLAGPSENDPNLFVALY
DFVASGDNTLSITKGEKLRVLGYNHNGEWCEAQTKNGQGWVPSNYITPVNSLEKHSWYHGPVSRNAAEYL
LSSGINGSFLVRESESSPGQRSISLRYEGRVYHYRINTASDGKLYVSSESRFNTLAELVHHHSTVADGLI
TTLHYPAPKRNKPTVYGVSPNYDKWEMERTDITMKHKLGGGQYGEVYEGVWKKYSLTVAVKTLKEDTMEV
EEFLKEAAVMKEIKHPNLVQLLGVCTREPPFYIITEFMTYGNLLDYLRECNRQEVNAVVLLYMATQISSA
MEYLEKKNFIHRDLAARNCLVGENHLVKVADFGLSRLMTGDTYTAHAGAKFPIKWTAPESLAYNKFSIKS
DVWAFGVLLWEIATYGMSPYPGIDLSQVYELLEKDYRMERPEGCPEKVYELMRACWQWNPSDRPSFAEIH
QAFETMFQESSISDEVEKELGKQGVRGAVSTLLQAPELPTKTRTSRRAAEHRDTTDVPEMPHSKGQGESD
PLDHEPAVSPLLPRKERGPPEGGLNEDERLLPKDKKTNLFSALIKKKKKTAPTPPKRSSSFREMDGQPER
RGAGEEEGRDISNGALAFTPLDTADPAKSPKPSNGAGVPNGALRESGGSGFRSPHLWKKSSTLTSSRLAT
GEEEGGGSSSKRFLRSCSASCVPHGAKDTEWRSVTLPRDLQSTGRQFDSSTFGGHKSEKPALPRKRAGEN
RSDQVTRGTVTPPPRLVKKNEEAADEVFKDIMESSPGSSPPNLTPKPLRRQVTVAPASGLPHKEEAGKGS
ALGTPAAAEPVTPTSKAGSGAPGGTSKGPAEESRVRRHKHSSESPGRDKGKLSRLKPAPPPPPAASAGKA
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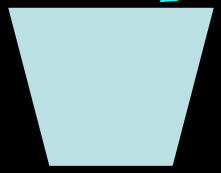
VPSTLPSASSALAGDQPSSTAFIPLISTRVSLRKTRQPPERIASGAITKGVVLDSTEALCLAISRNSEQM
ASHSAVLEAGKNLYTFCVSYVDSIQQMRNKFAFREAINKLENNLRELQICPATAGSGPAATQDFSKLLSS
VKEISDIVQR



NCBI
National Center for Biotechnology Information

UCSC

Ensembl

Genome Builds or Assembly

- What is a “genome build” for an organism?
  - It refers to the assembly (manual + curated) in which the sequence is collected, arranged and annotated in terms of chromosome
- What is the latest version?
  - GRCh38
- How often a build is released?
  - Once in few years. But patches are released often.

Patches?

- https://www.ncbi.nlm.nih.gov/grc/help/patches/

Current version GRCh38.

Assembly

This site provides a data set based on the December 2013 *Homo sapiens* high coverage assembly GRCh38 from the Genome Reference Consortium. This assembly is used by UCSC to create their hg38 database. The data set consists of gene models built from the genewise alignments of the human proteome as well as from alignments of human cDNAs using the cDNA2genome model of exonerate.

This release of the assembly has the following properties:

- contig length total 3.4 Gb.
- chromosome length total 3.1 Gb (excluding haplotypes).

giga = G = 1000^3

It also includes 261 alt loci scaffolds, mainly in the LRC/KIR complex on chromosome 19 (35 alternate sequence representations) and the MHC region on chromosome 6 (7 alternate sequence representations).

Genome Reference Consortium

The Wellcome Trust Sanger Institute

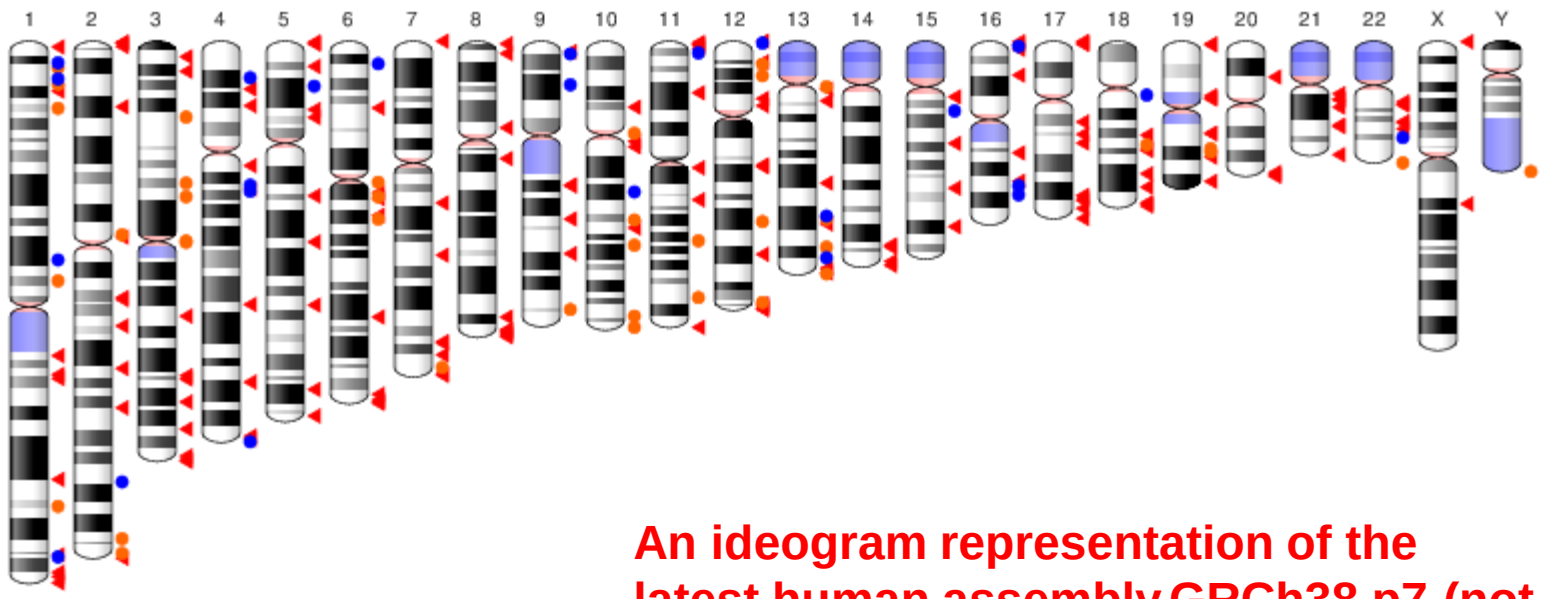
The Genome Institute at Washington University

The European Bioinformatics Institute

The National Center for Biotechnology Information

Previous version
2009: GRCh37 or hg18
2013: GRCh38 or hg38

Assembly



An ideogram representation of the latest human assembly,GRCh38.p7 (not showing unplaced or unlocalized sequences).

Figure from Genome Reference Consortium

Assembly

- **Reads:**
  NextGen (HTS)
  (stored in SRA: Sequence Read Archive)

- **Contigs:**
  Whole Genome Sequencing
  Made up of Reads
- **Scaffolds:**
  Consists of Contigs and gaps

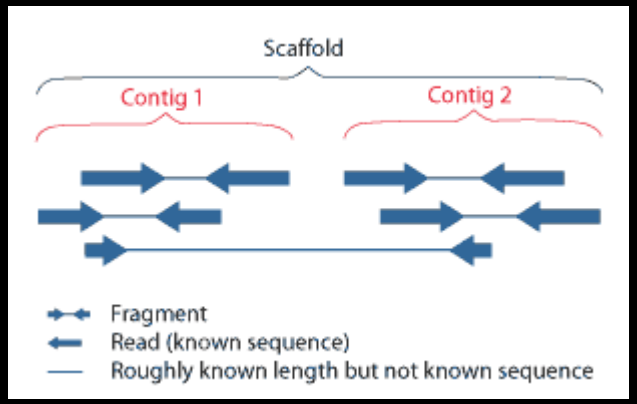


Figure from
http://genome.jgi.doe.gov/help/scaffolds.html

GRCh??

- GRCh38 (24 Dec 2013)
  - Mosaic
- GRCh37
  - Build 37 is derived from 13 anonymous people (volunteers from Buffalo, NY)

Build#	Year	NCBI	UCSC
35	2004	NCBI35	hg17
36	2006	NCBI36	hg18
37	2009	GRCh37	hg19
38	2013	GRCh38	hg38

Which Assembly to use?

http://lh3.github.io/2017/11/13/which-human-reference-genome-to-use

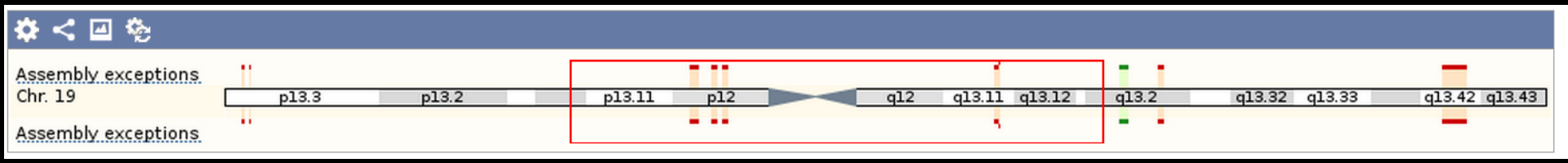
Annotations in Ensembl

- Automatic pipeline (Genome-wide at once)
  - Ab initio
  - Experimental data
    - ESTs, RNAseq, cNDA and sequence DBs along with their alignments from other DBs (NCBI etc.)
- Manual Curation (few species; Gene-by-gene)
  - Havana effort
  - Genome-wide: Human, Rat and Zebra Fish
  - Genes: Chimp, Dog and few others

Assembly Information

Gaps between contigs

Centromere region of Chromosome 19



Repeats make sequencing difficult

The other important browser

- UCSC
  - The University of California, Santa Cruz
  - http://genome.ucsc.edu

Other data sources

- UCSC Genome browser
- FlyBase (fruit fly genes & genomes)
- WormBase (nematode biology)
- SGD (Saccharomyces (budding Yeast) Genome
- RNA-central (meta database that combines data from different resources)
- TAIR (Arabidopsis (model for higher plant)
- EcoCyc (E.coli genes)

Journal of Nucleic Acid Research (NAR)

Each year publishes about databases. You should check it out.

Sequence IDs

ACCESSION vs ID

6,274 bp linear mRNA

Accession: NM_002299.2 GI: 32481205

Current status: live

I	II	Version	Gi	Update Date
●	○	2	32481205	Mar 15, 2015 03:11 PM
○	●	2	32481205	Sep 6, 2014 06:40 AM
○	○	2	32481205	May 3, 2014 03:52 PM
○	○	2	32481205	Mar 12, 2014 03:26 PM
○	○	2	32481205	Feb 26, 2014 01:29 AM
○	○	2	32481205	Feb 23, 2014 03:02 PM
○	○	2	32481205	Feb 1, 2014 03:16 PM
○	○	2	32481205	Nov 17, 2013 02:35 PM
○	○	2	32481205	Nov 3, 2013 02:18 PM
○	○	2	32481205	Oct 27, 2013 02:58 PM
○	○	2	32481205	Sep 14, 2013 02:52 PM
○	○	2	32481205	Jul 29, 2013 12:50 AM
○	○	2	32481205	Jun 24, 2013 12:45 AM
○	○	2	32481205	Sep 6, 2003 06:39 PM
○	○	2	32481205	Jul 9, 2003 10:58 AM
○	○	1	4504966	Apr 7, 2003 11:50 AM
○	○	1	4504966	Nov 5, 2002 10:29 AM
○	○	1	4504966	Aug 27, 2002 03:25 PM
○	○	1	4504966	Oct 31, 2000 06:51 PM
○	○	1	4504966	Jan 6, 2000 11:52 AM
○	○	1	4504966	Mar 24, 1999 05:15 PM

ACCESSION (STABLE)

Shared across all three collaborating patners (GenBank, DDBJ and ENA)

LCT:

Accession: NM_002299.2 **GI: 32481205**
GI is the sequence Identifier **DO NOT USE**

ANY changes to the sequence will result in a new ID

Only changes to the sequence will result in the integer extension change

NM_002299.1 GI: 4504966
NM_002299.2 GI: 32481205

RefSeq

- Derived and curated database of DNA, RNA, protein sequences
  - "*Provide a best representative seq. for each normal (nonmutated) transcript and for each normal protein product*" Pevsner Book Quote
  - Annotated, no-redundancy
  - Updated by NCBI not by submitter
  - "REFSEQ PROVIDES ONLY ONE EXAMPLE OF EACH NATURAL MOLECULE"

RefSeq and GenBank

GenBank	RefSeq
Uncurated	Curated
Submission by Authors	NCBI makes an entry from existing data
Author only can revise	NCBI modifies the entry as new data emerge
Multiple records for same loci	Usually single records were made for each molecule of major organisms
Records might contradict each other	Usually one record entry
No limit to species included	Limited to model organisms
Exchanged DDBJ & EMBL	Not exchanged and exclusive NCBI
Proteins identified and linked	Proteins and transcripts identified and linked
Via NCBI Nucleotide databases	Via Nucleotide & Protein databases

RefSeq

- Reference Genomic Sequence
  - NG_123456
- Chromosome
  - NC_123456 or AC_123456
- Contig Assembly
  - NT_123456
- WGS Supercontig (NW_123456)

RefSeq

- curated
  - mRNA, NM_123456
  - Protein, NP_123456
  - non-coding RNA, NR_123456
- Predicted
  - mRNA, XM_123456
  - protein, XP_123456
  - non-coding RNA, XR_123456
- Will model mRNA (XM) same as (NM)?
  - XM/XP same as NM/NP?

Issue with RefSeq

- RefSeq
  - **NM_002299.3 → NP_002290.2**
  - **If you miss the version and if there is a variation that will be missed as well.**
- **Locus Refernce Genome (LRG)**
  - **"*Define Genomic sequences as reference standards for genes, representing a standard allele*" , Pevsner, book reference**

Usefullness of LRG

- rs72651646 COLA1A Variant
- GRCh37-17:g.48268823C>T
- GRCh37-17:g.50191462C>T
- LRG
  - Genomic: LRG_1:g.15178G>A
  - Transcript: LRG_1t1:c.2156G>A
  - Protein: LRG_1p1:p.Gly719Asp

Never Change

Vertebrate Genome Annotation Project (VEGA)

ene: LCT ENSG00000115850

scription	lactase [Source:HGNC Symbol;Acc:HGNC:6530]
nonyms	LAC, LPH1, LPH
cation	Chromosome 2: 135,787,840-135,837,180 reverse strand. GRCh38:CM000664.2
out this gene	This gene has 2 transcripts (splice variants), 78 orthologues, 4 paralogues, is a member of 1 Ensembl protein family and is associated with 2 phenotypes.
anscripts	Hide transcript table

Show/hide columns (1 hidden) Filter

ame	Transcript ID	bp	Protein	Biotype	CCDS	UniProt	RefSeq	Flags
CT-001	ENST00000264162	6279	1927aa	Protein coding	CCDS2178	P09848	NM_002299 NP_002290	TSL:1 GENCODE basic APPRIS P1
CT-002	ENST00000452974	3508	1003aa	Nonsense mediated decay	-	H0Y4E4	-	CDS 5' incomplete TSL:1

Comparing CCDS set and RefSeq with Ensembl Transcripts

Note the transcript, CCDS2178.1 is displayed in CCDS track.

CCDS: Consensus CoDing Sequence and agreed upon by all the four Genome Groups: Ensembl, Havana, NCBI and UCSC and is also the same as LCT-001 transcript

Communication Problem

- Gene
  - Approved Name: RB1
  - Previous Names; OSR, “osteosarcoma”
  - Synonyms/a.k.a: PPP1R130, “prepro-retinoblastoma-associated protein”, protein phosphatase 1”, regulatory subunit 130, RB, OSRC, pp110, p105-Rb

Communication Problem

- Protein
  - Ensembl: RB1-001, RB1-002, RB1-003, RB1-004,RB1-005,RB1-006
  - RB1-002 or NST00000267163
- Example

UniProt	NCBI	TrEMBL	Ensembl	EnsemblName
P06400-1,	NP_000312,	A0A024RDV3,	ENSP00000267163	RB1-002

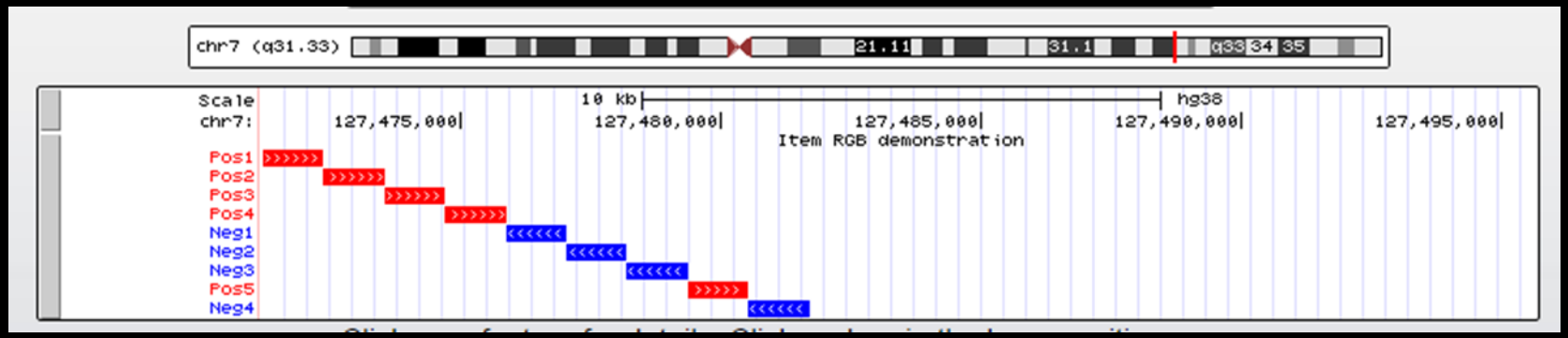
All mean the same protein 4840 bp and 928 aa

Commonly Used Formats

- VCF, fasta, FastQ (discuss later)
- BED (NextGen Data)
  - Contains experimental information
    - DNA/RNA-seq etc
  - Chromosome
    - Start and end position
  - Plus optional information

BED sample format

```
browser position chr7:127471196-127495720
browser hide all
track name="ItemRGBDemo" description="Item RGB demonstration" visibility=2
itemRgb="On"
chr7 127471196 127472363 Pos1 0 + 127471196 127472363 255,0,0
chr7 127472363 127473530 Pos2 0 + 127472363 127473530 255,0,0
chr7 127473530 127474697 Pos3 0 + 127473530 127474697 255,0,0
chr7 127474697 127475864 Pos4 0 + 127474697 127475864 255,0,0
chr7 127475864 127477031 Neg1 0 - 127475864 127477031 0,0,255
chr7 127477031 127478198 Neg2 0 - 127477031 127478198 0,0,255
chr7 127478198 127479365 Neg3 0 - 127478198 127479365 0,0,255
chr7 127479365 127480532 Pos5 0 + 127479365 127480532 255,0,0
chr7 127480532 127481699 Neg4 0 - 127480532 127481699 0,0,255
```



From UCSC

Let us explore the Gene

- In-class demonstration
- NCBI and Ensembl
  - Gene: Human Lactase
- Students will attempt the same process using HBB (book example)

NCBI E-Direct

- Most Linux commands were covered in the last class
  - Strongly encourage you to try them on your system
  - Edirect examples from the book
    - Windows users: Use Cygwin
    - Mac Users: Use terminal window

To do

- Self-Quiz
  - In some versions of the book there is a typo in quiz [2-1]
    - last choice label have to be **e** and not **d**
- Problems/Computer Lab for this week
  - 2-1, 2-2, 2-4, 2-5
  - Optional: 2-9, 2-10

Thanks

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