Clinica molecolare (molecular medicine):come utilizzare le informazioni del genoma per studiare le patologie genetiche

Dissezione del fenotipo

(Fenomica)

(1) Esame obiettivo (specialistico)
(2) Consulenza Genetica (Genetica clinica, analisi del pedigree, valutazione componente genetica di un fenotipo, valutazione rischi empirici di ricorrenza, inquadramento genetico)
(3) Esami strumentali specifici (EMG, TAC, RMN, etc.)
(4) Esami biochimici (dosaggi enzimatici, dosaggi di metaboliti, ect)
(5) Esami di proteomica (analisi delle proteine, Western blotting, immunoistochimica,etc.)
(6) Valutazione interazione con fattori ambientali

Allestire un percorso di medicina molecolare

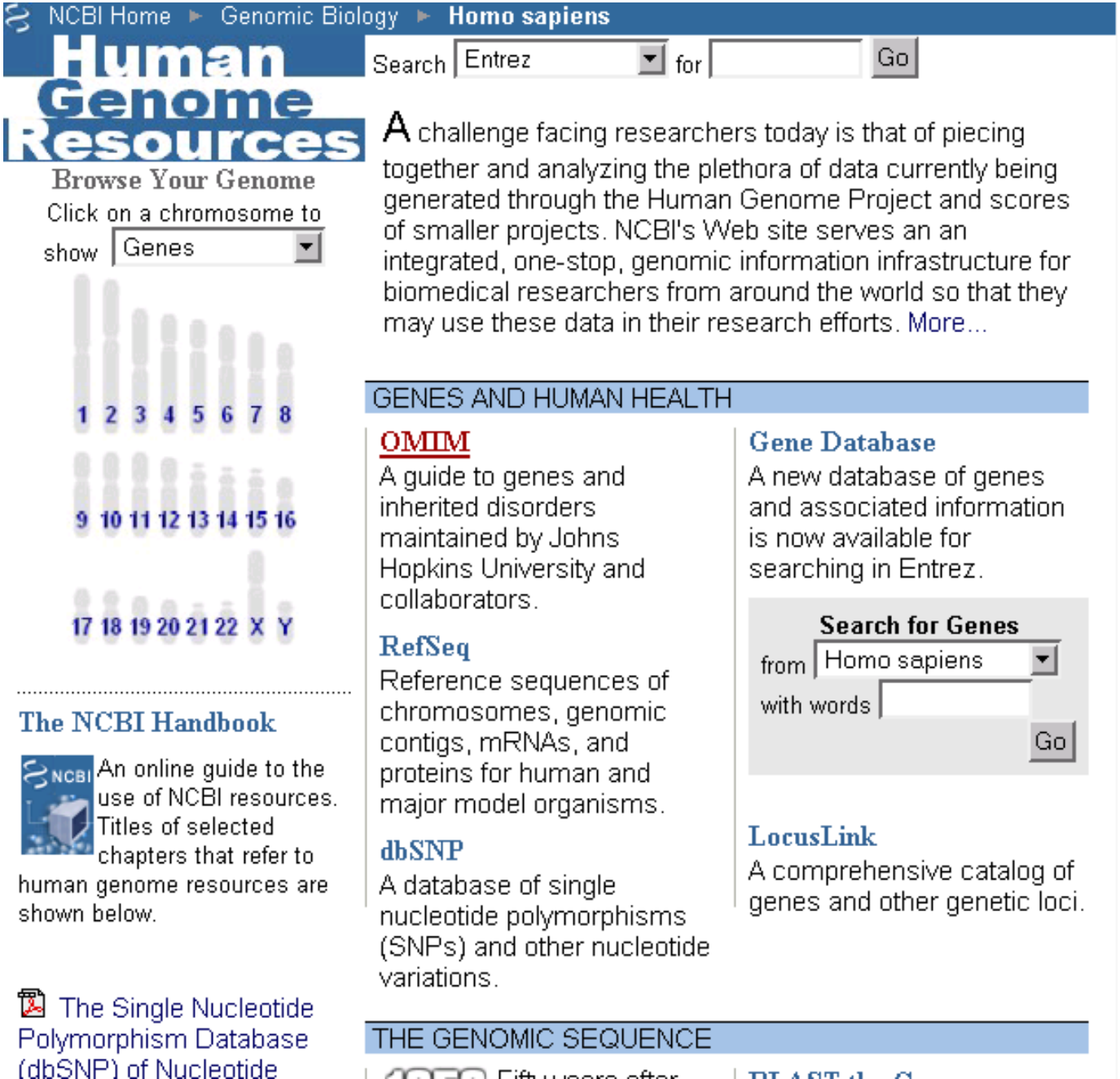
- FENOMICA

- ANALISI DI LINKAGE (albero informativo)
  - Ricerca marcatori appropriati e loro designing

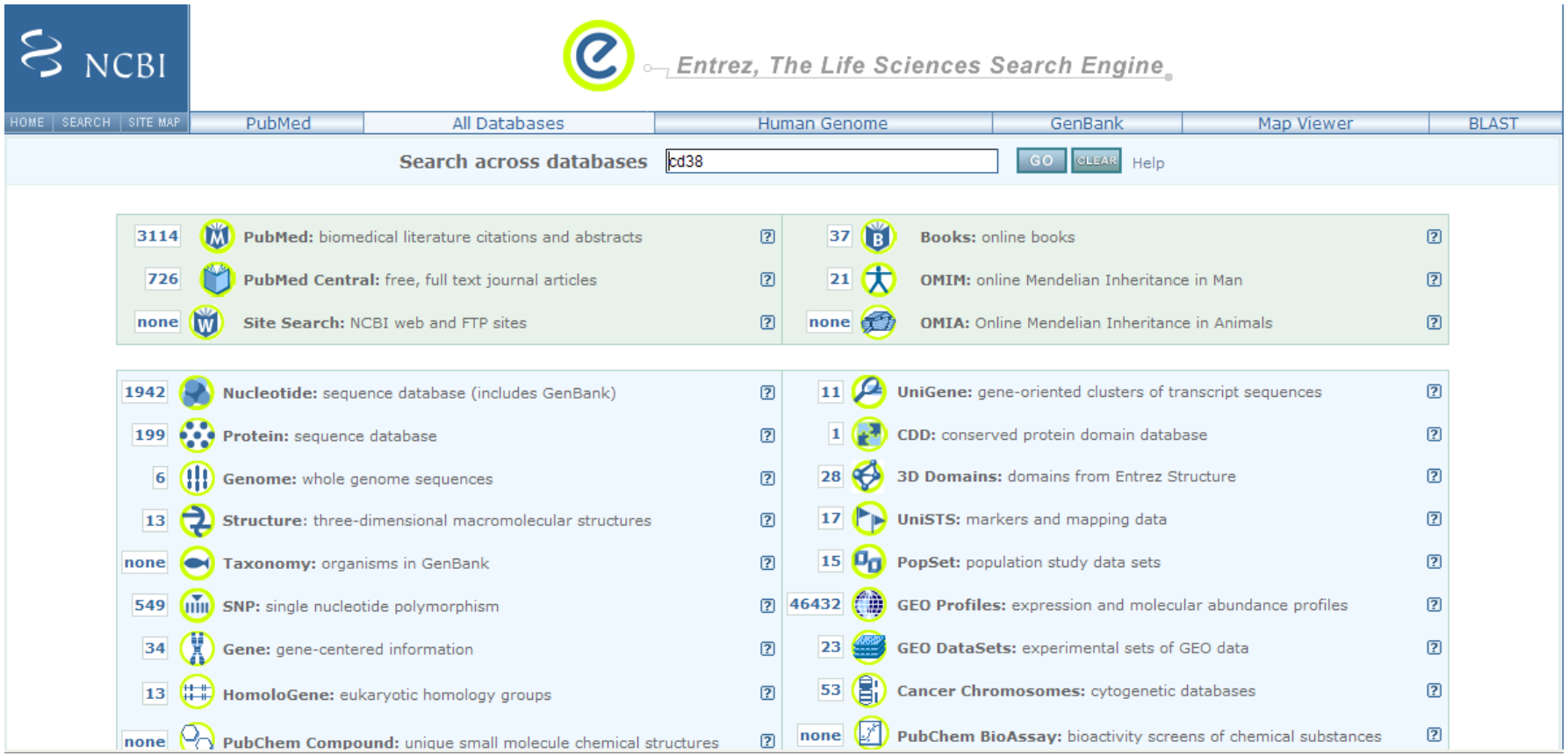
- ANALISI MOLECOLARE GENE CANDIDATO
  - Ricerca geni candidati (pubmed-OMIM-HGDB)
  - Valutazione anatomia genomica dei geni candidati
  - Valutazione espressione geni candidati
  - Sequenze annotate in HGMP
  - Gene Card
  - Strategie molecolari
  - Analisi dei dati molecolari (HGMP blast, HGDB, database specifici)
  - Validazione delle mutazioni identificate (ESE finder, etc)

La bioinformatica come tool per la analisi di geni malattia

http://www.ncbi.nlm.nih.gov/genome/guide/human/



http://www.ncbi.nlm.nih.gov/genome/guide/human/



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

National Center for Biotechnology Information

- OMIM: online mendelian inheritance in man

- Creato da Victor McKusick

- Continuamente aggiornato

- Punto chiave per acquisire informazione sui caratteri mendeliani umani, patologici e non

- A ogni carattere viene attribuito un numero a 6 cifre MIM

+143100
HUNTINGTON DISEASE; HD

GeneTests, Links

Alternative titles; symbols

HUNTINGTON CHOREA
HUNTINGTIN, INCLUDED; HD, INCLUDED
HTT, INCLUDED
IT15, INCLUDED

Gene map locus 4p16.3

TEXT

DESCRIPTION

Huntington disease (HD) is inherited as an autosomal dominant disease that gives rise to progressive, selective (localized) neural cell death associated with choreic movements and dementia. The disease is associated with increases in the length of a CAG triplet repeat present in a gene called 'huntingtin' located on chromosome 4p16.3.

CLINICAL FEATURES

The classic signs of Huntington disease are progressive chorea, rigidity, and dementia, frequently associated with seizures. A characteristic atrophy of the caudate nucleus is seen radiographically. Typically, there is a prodromal phase of mild psychotic and behavioral symptoms which precedes frank chorea by up to 10 years. The results of a study by Shiwach and Norbury (1994) clashed with the conventional wisdom that psychiatric symptoms are a frequent presentation of Huntington disease before the development of neurologic symptoms. They performed a control study of 93 neurologically healthy individuals at risk for Huntington disease. The 20 asymptomatic heterozygotes showed no increased incidence of psychiatric disease of any sort when compared to the 33 normal homozygotes in the same group. However, the whole group of heterozygous and homozygous normal at-risk individuals showed a significantly greater number of psychiatric episodes than did their 43 spouses, suggesting stress from the uncertainty associated with belonging to a family segregating this disorder. Shiwach and Norbury (1994) concluded that neither depression nor psychiatric disorders are likely to be significant preneurologic indicators of heterozygous expression of the disease gene.

MIM +143100
Description
Clinical Features
Biochemical Features
Other Features
Inheritance
Mapping
Molecular Genetics
Pathogenesis
Diagnosis
Population Genetics
Clinical Management

NCBI OMIM Online Mendelian Inheritance in Man Johns Hopkins University

The OMIM Gene map presents the cytogenetic map location of disease genes and other expressed genes described in OMIM. See the OMIM Morbid Map for a list of disease genes organized by disease. For more refined maps of genes and DNA segments click on the **Location** to invoke NCBI Entrez Map Viewer.

Search for: Find Find Next (from the current location)

- Enter gene symbol, chromosomal location, or disorder keyword to search for, e.g. "CYP1", "5", "1pter", "Xq", or "alzheimer".
- You must capitalize X and Y to search for those chromosomes.

4p16.3, HD to 4p16.1, HMX1

<<Move Up Move Down>>

Location	Symbol	Title	MIM #	Disorder	Comments	Method	Mouse
4p16.3	HD, IT15	Huntingtin	143100	Huntington disease (3)	distal to D4S10	Fd	5(Hdh)
4p16.3	IDUA, IDA	Iduronidase, alpha-L-	252800	Mucopolysaccharidosis Ih, 607014 (3); Mucopolysaccharidosis Is,607016 (3); Mucopolysaccharidosis Ih/s, 607015 (3)		REa, A, S	5(Idua)
4p16.3	LETM1	Leucine zipper/EF-hand-containing transmembrane protein 1	604407			A	
4p16.3	LRPAP1, A2MRAP	Low density lipoprotein-related protein-associated protein 1 (alpha-2-macroglobulin receptor-associated protein 1)	104225		?involved in Wolf-Hirschhorn syndrome	A, REn	
4p16.3	MYL5	Myosin, light polypeptide-5, regulatory	160782			RE	
4p16.3	PDE6B, PDEB, CSNB3	Phosphodiesterase-6B, cGMP-specific, rod, beta	180072	Night blindness, congenital stationary, type 3, 163500 (3);Retinitis pigmentosa, autosomal recessive (3)		REa, A, Fd	5(Pdeb, rd)

NCBI OMIM Online Mendelian Inheritance in Man Johns Hopkins University

The OMIM Morbid Map presents the cytogenetic map location of disease genes described in OMIM. For a map organized by chromosome, see the OMIM Gene Map. For more refined maps of genes and DNA segments, use NCBI Entrez Map Viewer and the Genome Database.

Search for: huntington Find Find Next (from the current location)

- Enter gene symbol, chromosomal location, or disorder keyword to search for, e.g. "recessive", "CYP1","5", "1pter", or "Xq".
- You must capitalize X and Y to search for those chromosomes.

<<Move Up Move Down>>

Disorder	Symbol(s)	OMIM	Location
Huntington disease (3)	HD, IT15	143100	4p16.3
Huntington disease-like 1, 603218 (3)	PRNP, PRIP	176640	20pter-p12
Huntington disease-like 2, 606438 (3)	JPH3, JP3, HDL2	605268	16q24.3
Huntington disease-like 3 (2)	HDL3, HLN2	604802	4p15.3
Huntington disease-like-4, 607136 (3)	TBP, SCA17	600075	6q27
Huriez syndrome (2)	TYS, HRZ	181600	4q23
Hyalinosis, infantile systemic, 236490 (3)	ANTXR2, CMG2, JHF, ISH	608041	4q21
Hydatidiform mole, 231090 (3)	NALP7, NOD12, PYPAF3, HYDM	609661	19q13.4
Hydrocephalus due to aqueductal stenosis, 307000 (3)	L1CAM, CAML1, HSAS1	308840	Xq28
Hydrocephalus with Hirschsprung disease and cleft palate, 142623 (3)	L1CAM, CAML1, HSAS1	308840	Xq28
Hydrocephalus with congenital idiopathic intestinal pseudoobstruction, 307000 (3)	L1CAM, CAML1, HSAS1	308840	Xq28

NCBI OMIM Online Mendelian Inheritance in Man Johns Hopkins University

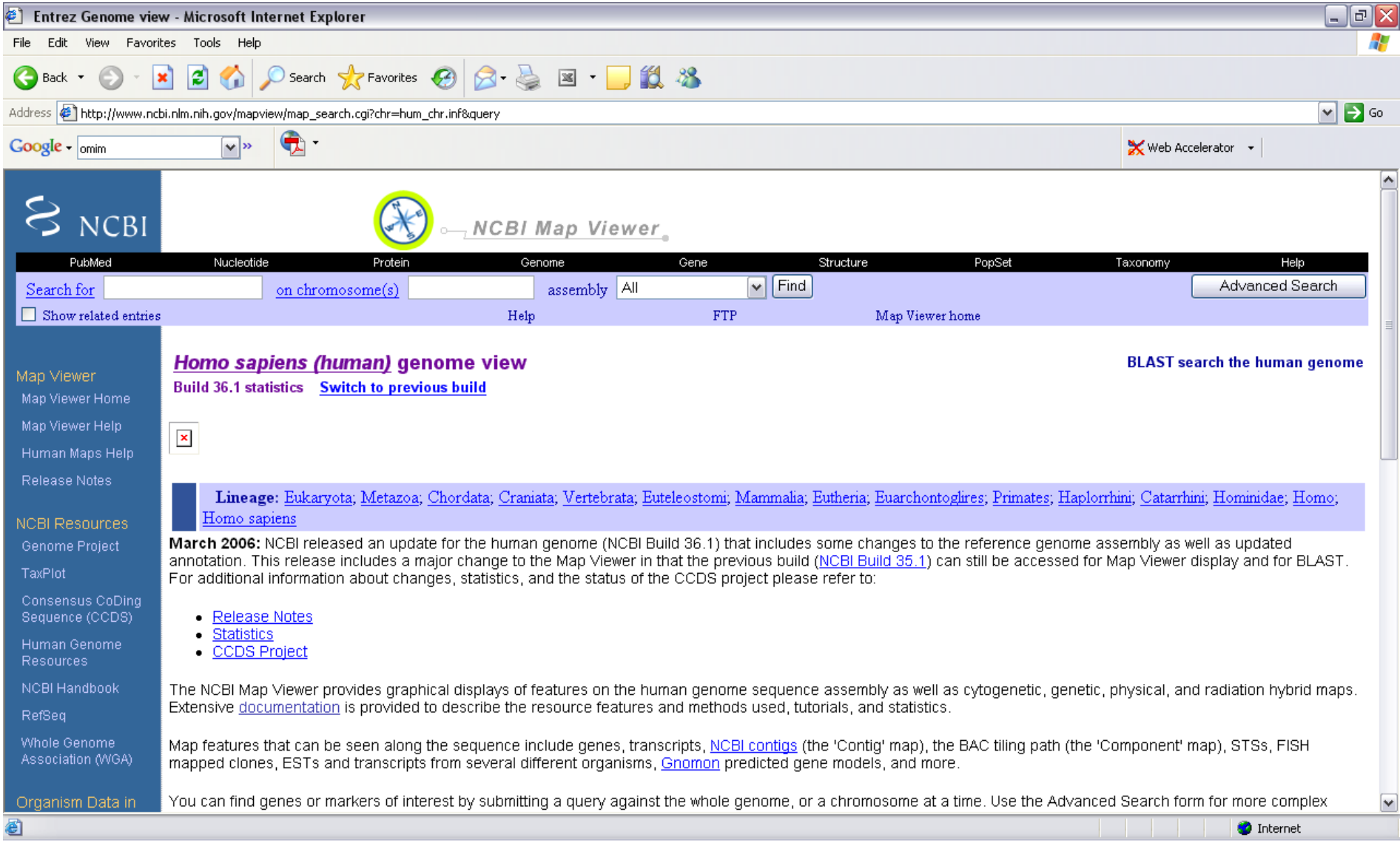
The OMIM Morbid Map presents the cytogenetic map location of disease genes described in OMIM. For a map organized by chromosome, see the OMIM Gene Map. For more refined maps of genes and DNA segments, use NCBI Entrez Map Viewer and the Genome Database.

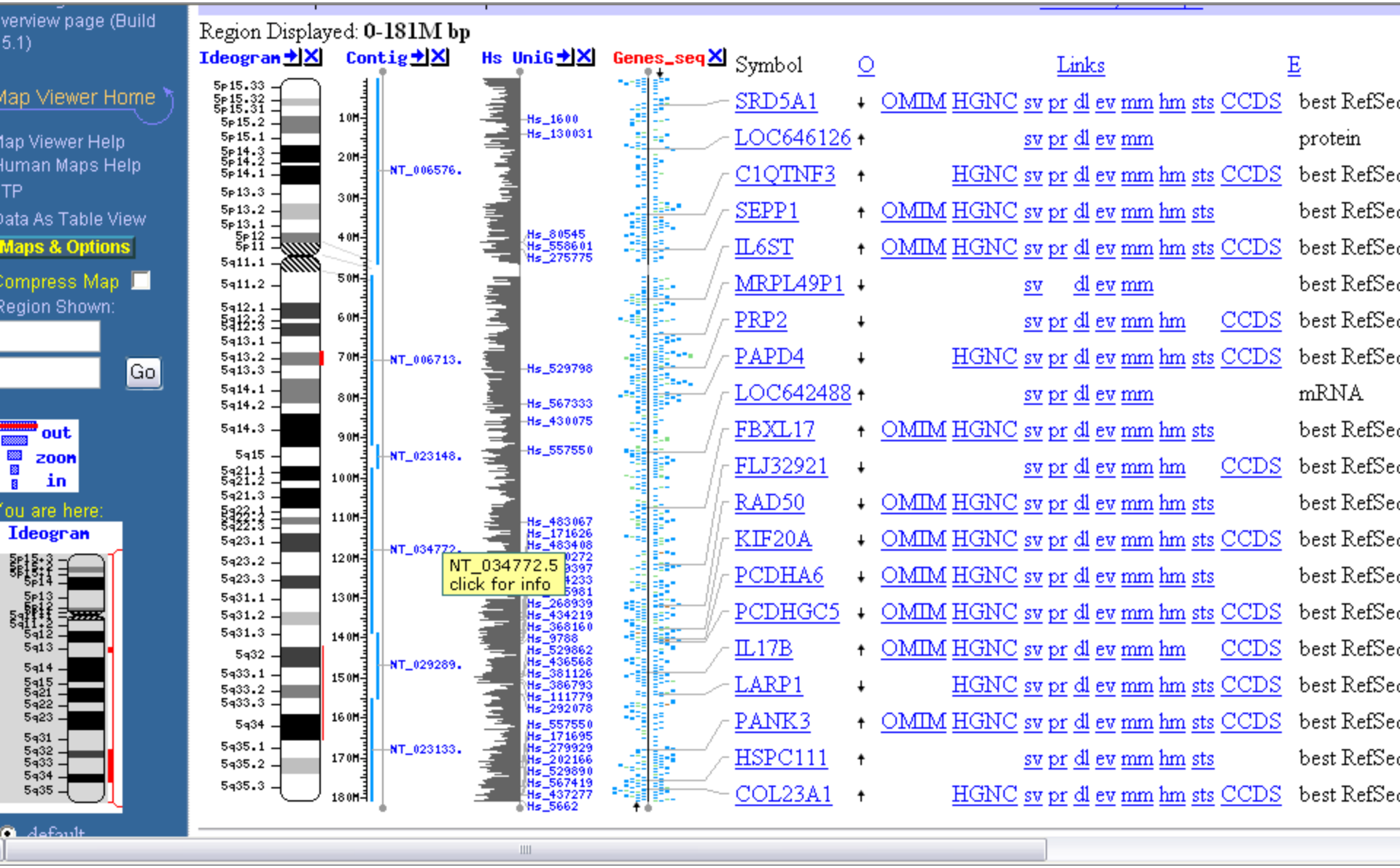
Search for: obesity Find Find Next (from the current location)

- Enter gene symbol, chromosomal location, or disorder keyword to search for, e.g. "recessive", "CYP1","5", "1pter", or "Xq".
- You must capitalize X and Y to search for those chromosomes.

<<Move Up Move Down>>

Disorder	Symbol(s)	OMIM	Location
{Obesity, susceptibility to}, 601665 (3)	ADRB2	109690	5q32-q34
{Obesity, susceptibility to}, 601665 (3)	ADRB3	109691	8p12-p11.2
{Obesity, susceptibility to}, 601665 (3)	CART	602606	5q13.2
{Obesity, susceptibility to}, 601665 (3)	ENPP1, PDNP1, NPPS, M6S1, PCA1	173335	6q22-q23
{Obesity, susceptibility to}, 601665 (3)	GHRL	605353	3p26-p25
{Obesity, susceptibility to}, 601665 (3)	UCP1	113730	4q31
{Obesity, susceptibility to}, 601665 (3)	UCP2	601693	11q13
{Obesity/hyperinsulinism, susceptibility to} (2)	OQTL	602025	20q13.11-q13.2
{Obsessive-compulsive disorder 1}, 164230 (3)	SLC6A4, HTT, OCD1	182138	17q11.1-q12
{Obsessive-compulsive disorder, protection against}, 164230 (3)	BDNF	113505	11p13
{Obsessive-compulsive disorder, susceptibility to}, 164230 (3)	HTR2A	182135	13q14-q21


Entrez Genome view - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query
Go
Google omim
Web Accelerator
NCBI
NCBI Map Viewer
PubMed Nucleotide Protein Genome Gene Structure PopSet Taxonomy Help
Search for
on chromosome(s)
assembly All
Find
Advanced Search
Show related entries
Help FTP Map Viewer home
Map Viewer
Map Viewer Home
Map Viewer Help
Human Maps Help
Release Notes
NCBI Resources
Genome Project
TaxPlot
Consensus CoDing Sequence (CCDS)
Human Genome Resources
NCBI Handbook
RefSeq
Whole Genome Association (WGA)
Organism Data in
Homo sapiens (human) genome view
Build 36.1 statistics
Switch to previous build
BLAST search the human genome
Lineage: Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo; Homo sapiens
March 2006: NCBI released an update for the human genome (NCBI Build 36.1) that includes some changes to the reference genome assembly as well as updated annotation. This release includes a major change to the Map Viewer in that the previous build (NCBI Build 35.1) can still be accessed for Map Viewer display and for BLAST. For additional information about changes, statistics, and the status of the CCDS project please refer to:
Release Notes
Statistics
CCDS Project
The NCBI Map Viewer provides graphical displays of features on the human genome sequence assembly as well as cytogenetic, genetic, physical, and radiation hybrid maps. Extensive documentation is provided to describe the resource features and methods used, tutorials, and statistics.
Map features that can be seen along the sequence include genes, transcripts, NCBI contigs (the 'Contig' map), the BAC tiling path (the 'Component' map), STSs, FISH mapped clones, ESTs and transcripts from several different organisms, Gnomon predicted gene models, and more.
You can find genes or markers of interest by submitting a query against the whole genome, or a chromosome at a time. Use the Advanced Search form for more complex
Internet

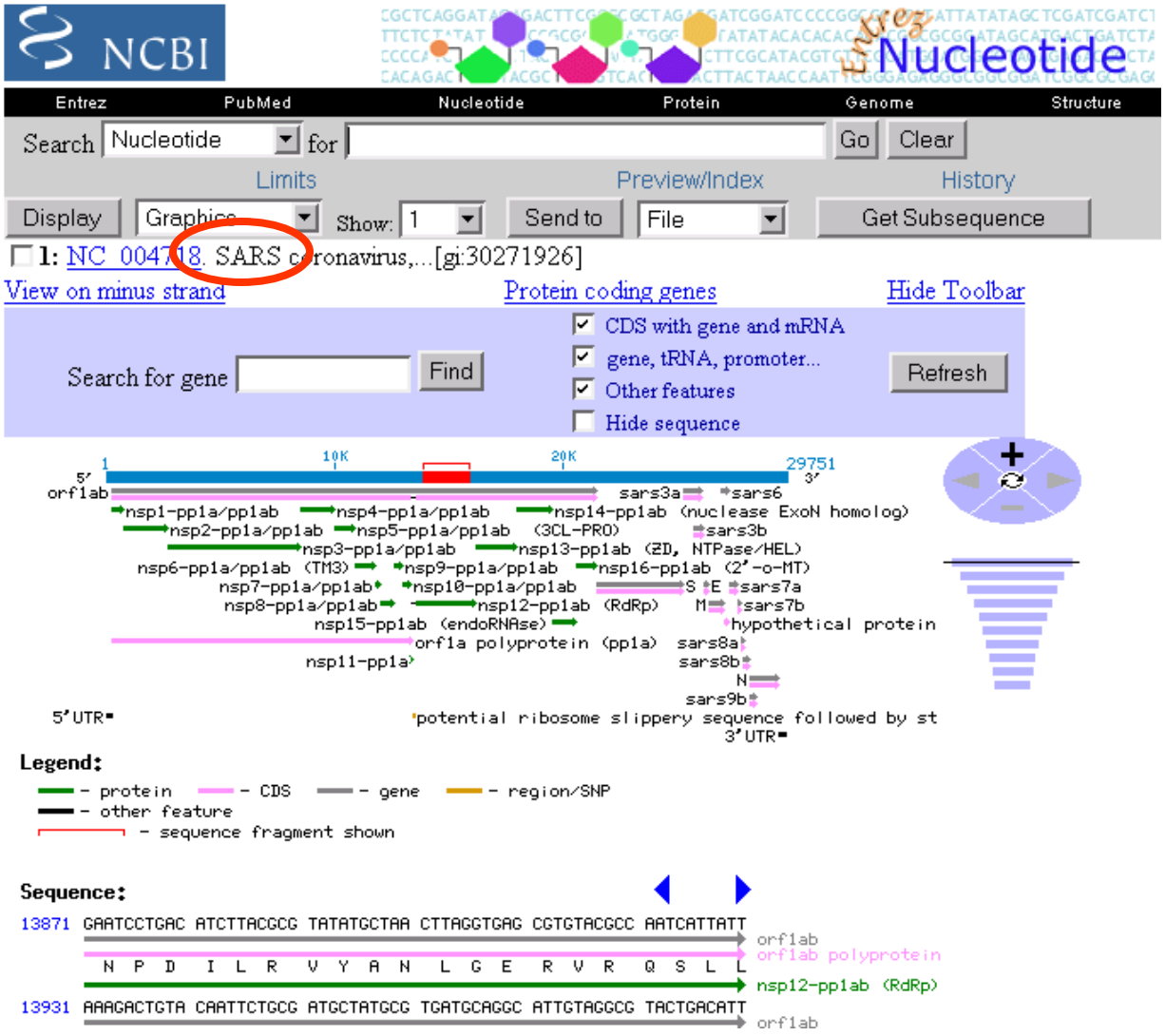

verview page (Build 5.1)
Map Viewer Home
Map Viewer Help
Human Maps Help
TP
Data As Table View
Maps & Options
Compress Map
Region Shown:
Go
out
zoom
in
You are here:
Ideogram
default
Region Displayed: 0-181M bp
Ideogram
Contig
Hs UniG
Genes_seq
NT_034772.5
click for info
Symbol
O
Links
E
SRD5A1
LOC646126
C1QTNF3
SEPP1
IL6ST
MRPL49P1
PRP2
PAPD4
LOC642488
FBXL17
FLJ32921
RAD50
KIF20A
PCDHA6
PCDHGC5
IL17B
LARP1
PANK3
HSPC111
COL23A1
best RefSeq
protein
mRNA

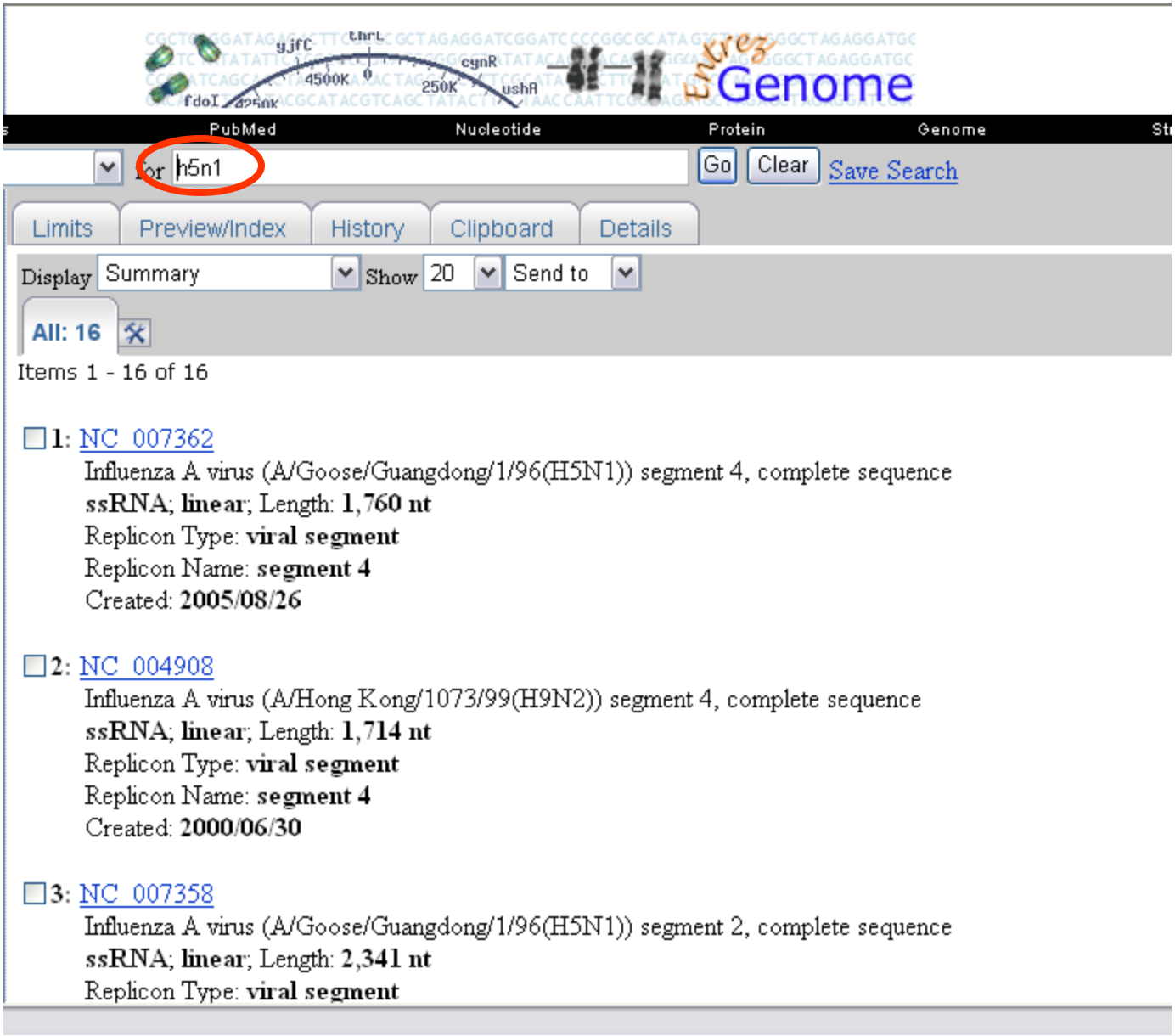
How is genomics impacting on the practice of medicine?

…(genomics) catalogues only the birth of the genomic era and thus no more captures in detail the ultimate effect of genomic medicine than does the examination of a newborn foretell what the mature adult will be like…

ricadute immediate

1) Identificazione rapida di patogeni di recente scoperta (SARS)




Entrez Genome
PubMed
Nucleotide
Protein
Genome
for h5n1
Go
Clear
Save Search
Limits
Preview/Index
History
Clipboard
Details
Display Summary
Show 20
Send to
All: 16
Items 1 - 16 of 16
1: NC_007362
Influenza A virus (A/Goose/Guangdong/1/96(H5N1)) segment 4, complete sequence
ssRNA; linear; Length: 1,760 nt
Replicon Type: viral segment
Replicon Name: segment 4
Created: 2005/08/26
2: NC_004908
Influenza A virus (A/Hong Kong/1073/99(H9N2)) segment 4, complete sequence
ssRNA; linear; Length: 1,714 nt
Replicon Type: viral segment
Replicon Name: segment 4
Created: 2000/06/30
3: NC_007358
Influenza A virus (A/Goose/Guangdong/1/96(H5N1)) segment 2, complete sequence
ssRNA; linear; Length: 2,341 nt
Replicon Type: viral segment

NAVIGARE NEI GENE DATABASE

Organismi Modello

L'obbiettivo primario della biologia è lo studio e la comprensione degli organismi viventi. E' però praticamente impossibile studiarli tutti perchè ci sono milioni e milioni di specie diverse. E' quindi importante trovare degli organismi rappresentativi dei vari gruppi, che fungano da modello per l'intero gruppo e che siano i più semplici possibili.
Su questo principio molto semplice si basa il concetto degli organismi modello

Nei procarioti **Escherichia coli** rappresenta il batterio più studiato, anche se *Haemophilus influenzae* fu il primo batterio ad essere sequenziato nel 1995

Il lievito **Saccharomyces cerevisiae** (sequenziato nel 1996) permette di studiare diversi aspetti doi biologia cellulare e della biologia di tutti gli organismi eucarioti

Arabidopsis thaliana (sequenziata nel 2000) è l'organismo modello per le piante; si tratta di una piccola crucifera che non ha alcuna applicazione pratica, ma rappresenta un ottimo organismo modello.

Caenorabditis elegans (sequenziato nel 1998) è un nematode è un animale, quindi il suo programma genetico è in grado di gestire i problemi del differenziamento delle cellule animali e dello sviluppo embrionale.

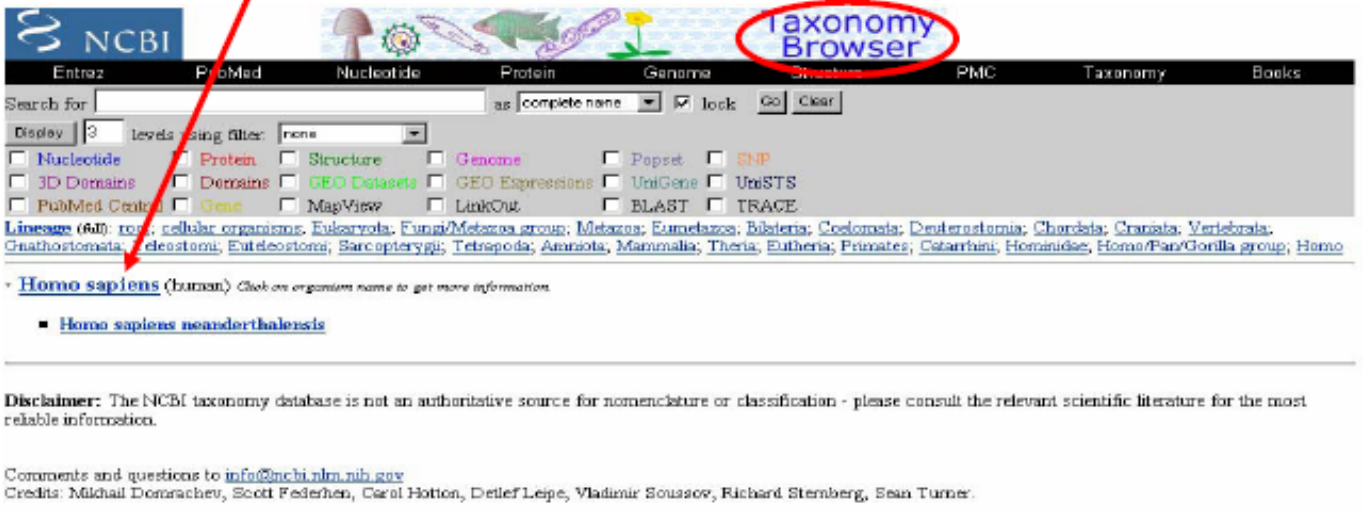
Drosophila melanogaster (sequenziata nel 2000) è un organismo modello molto utilizzato; oltre ad essere un modello di semplice animale, rappresenta anche un modello per tutti gli insetti.

I due pesci **Zebrafish** e **Fugu** rappresentano due ottimi modelli per lo studio dei vertebrati. Infine il **topo e l'uomo** sono i principali modelli per lo studio dei mammiferi.

LINK A TAXONOMY

- **Vediamo più in dettaglio alcuni dei campi ed in particolare i link agli altri database integrati in ENTREZ**

```
LOCUS       NM_003673                963 bp    mRNA    linear   PRI 20-DEC-2003
DEFINITION  Homo sapiens titin-cap (telethonin) (TCAP), mRNA.
ACCESSION   NM_003673
VERSION     NM_003673.2  GI:19924299
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
```



LINK AL GENE

Vediamo ora più in dettaglio la parte di record relativa al gene

```
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```

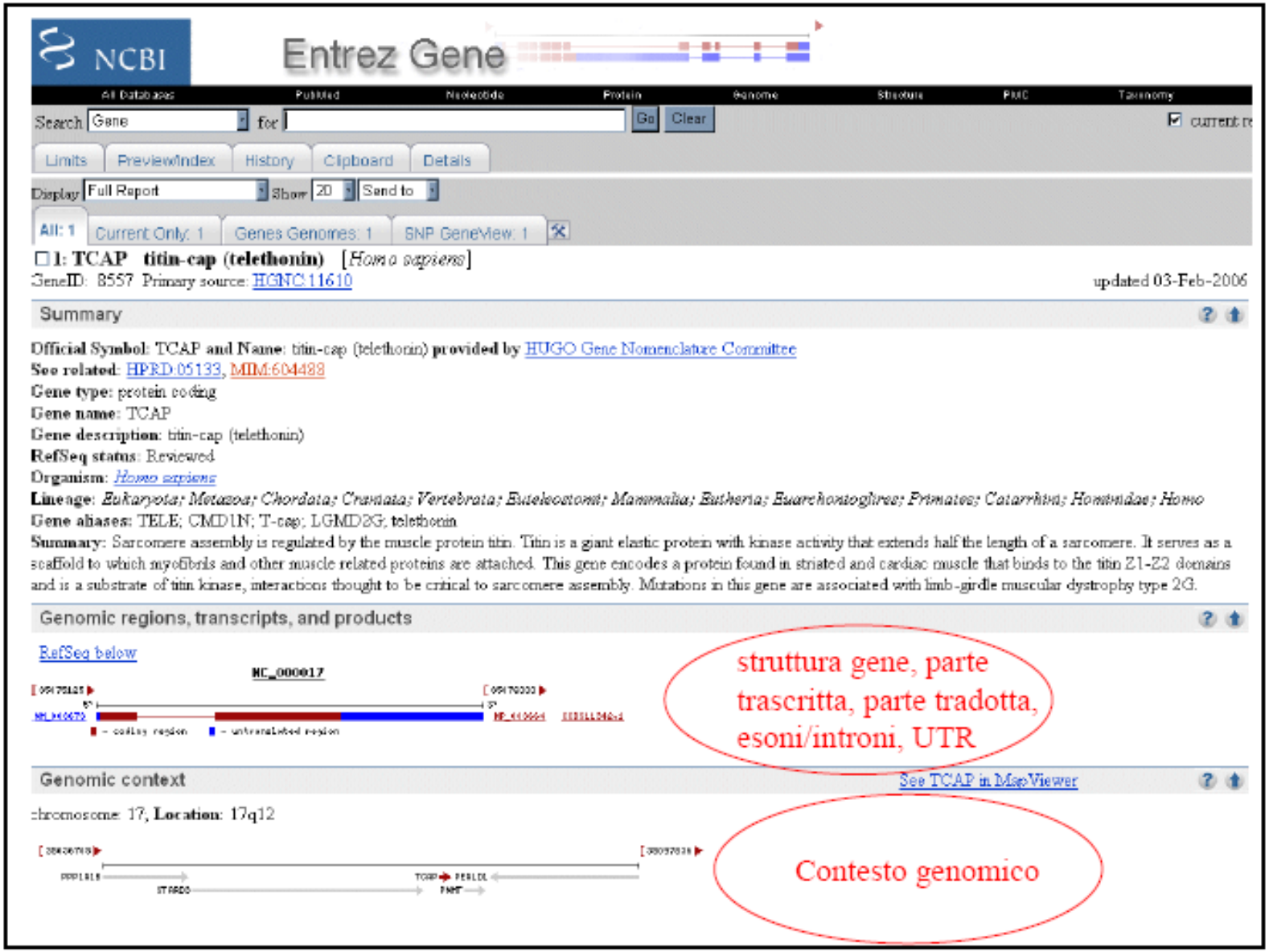
tipo molecola (DNA, mRNA...)

cromosoma e posizione di mappa

nome ufficiale del gene e sinonimi

link al database dei geni Entrez Gene

link a malattie genetiche

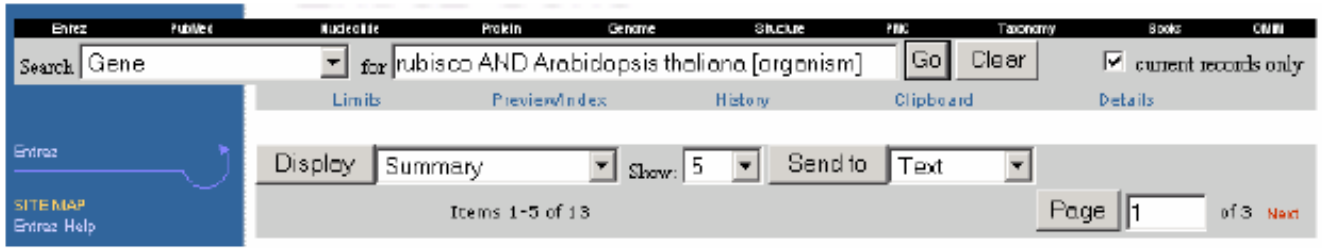

NCBI
Entrez Gene
All Databases
PubMed
Nucleotide
Protein
Genome
Structure
PMC
Taxonomy
Search Gene for
Go
Clear
Limits
Preview/Index
History
Clipboard
Details
Display Full Report
Show 20
Send to
All: 1
Current Only: 1
Genes Genomes: 1
SNP GeneView: 1
1: TCAP titin-cap (telethonin) [Homo sapiens]
GeneID: 8557 Primary source: HGNC:11610
updated 03-Feb-2006
Summary
Official Symbol: TCAP and Name: titin-cap (telethonin) provided by HUGO Gene Nomenclature Committee
See related: HPRD:05133, MIM:604488
Gene type: protein coding
Gene name: TCAP
Gene description: titin-cap (telethonin)
RefSeq status: Reviewed
Organism: Homo sapiens
Lineage: Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Catarrhini; Hominidae; Homo
Gene aliases: TELE; CMD1N; T-cap; LGMD2G; telethonin
Summary: Sarcomere assembly is regulated by the muscle protein titin. Titin is a giant elastic protein with kinase activity that extends half the length of a sarcomere. It serves as a scaffold to which myofibrils and other muscle related proteins are attached. This gene encodes a protein found in striated and cardiac muscle that binds to the titin Z1-Z2 domains and is a substrate of titin kinase, interactions thought to be critical to sarcomere assembly. Mutations in this gene are associated with limb-girdle muscular dystrophy type 2G.
Genomic regions, transcripts, and products
RefSeq below
NC_000017
struttura gene, parte trascritta, parte tradotta, esoni/introni, UTR
Genomic context
See TCAP in MapViewer
chromosome: 17, Location: 17q12
Contesto genomico

RICERCA DI GENI

Proviamo a fare una ricerca complessa usando gli operatori booleani

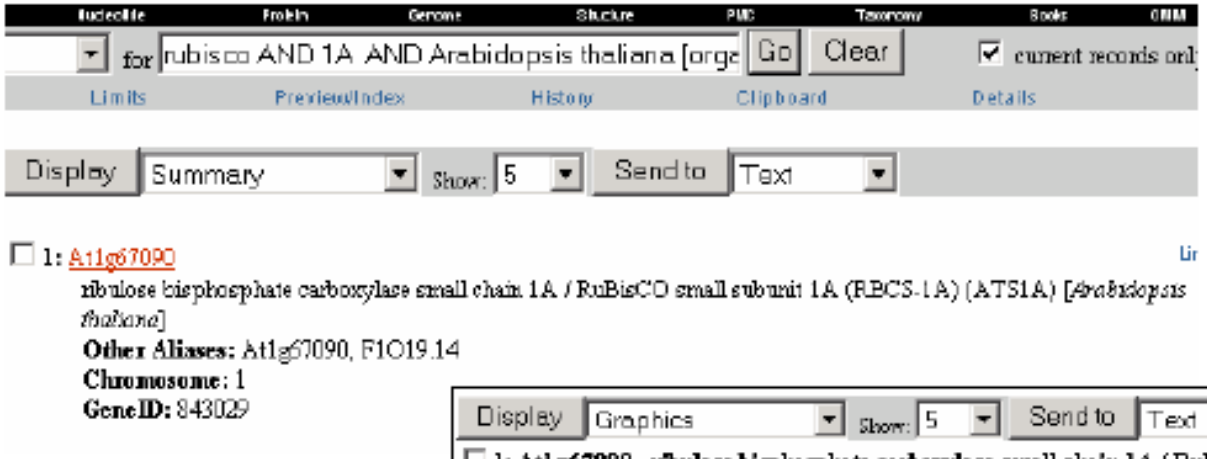
Getting started	Sample queries
Look for genes by name part and multiple species	transporter AND ("Drosophila melanogaster"[orgn] OR "Mus musculus"[orgn]) more...
Look for genes by chromosome and symbol	(II[chr] OR 2[chr]) AND adh*[sym] more...

Cerchiamo uno dei geni della rubisco
http://www.rcsb.org/pdb/molecules/pdb11_1.html
in Arabidopsis thaliana

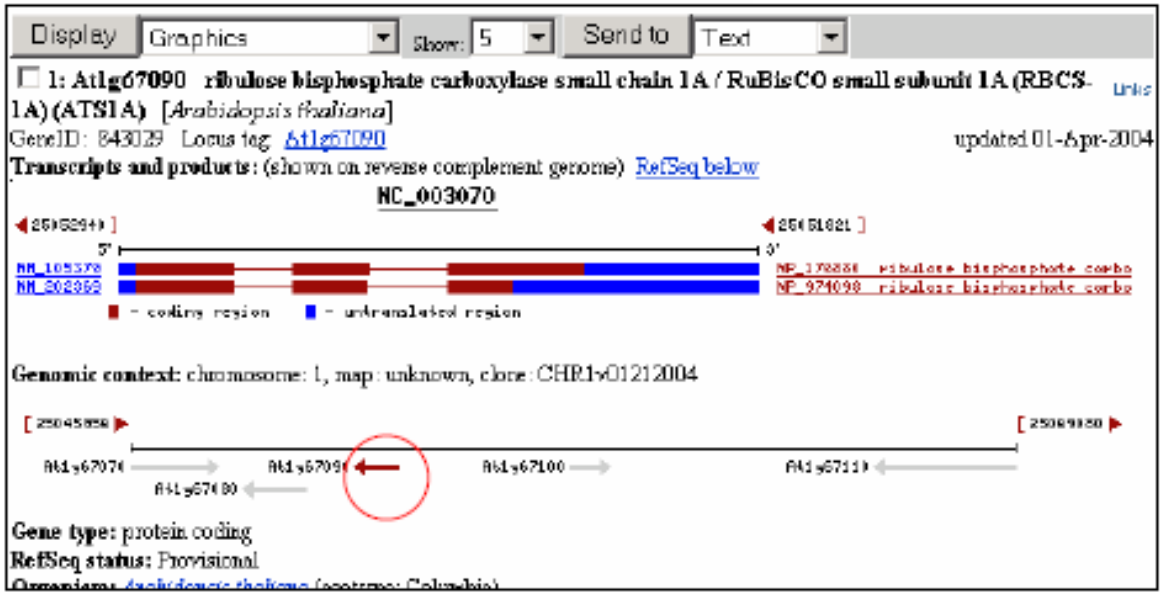


RICERCA DI GENI

•**Siamo interessati al gene "subunità 1A" di rubisco.**



struttura gene, parte trascritta (elica complementare!), parte tradotta, esoni/introni, UTR



LINK ALLE MALATTIE GENETICHE

Si possono esaminare le malattie genetiche associate a quella posizione di mappa (gene)

```
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                     /db_xref="taxon:9606"
                     /chromosome="17"
                     /map="17q12"
     gene            1..963
                     /gene="TCAP"
                     /note="synonyms: TELE, CMD1N, T-cap, LGMD2G, telethonin"
                     /db_xref="GeneID:8557"
                     /db_xref="LocusID:8557"
                     /db_xref="MIM:604488"
```

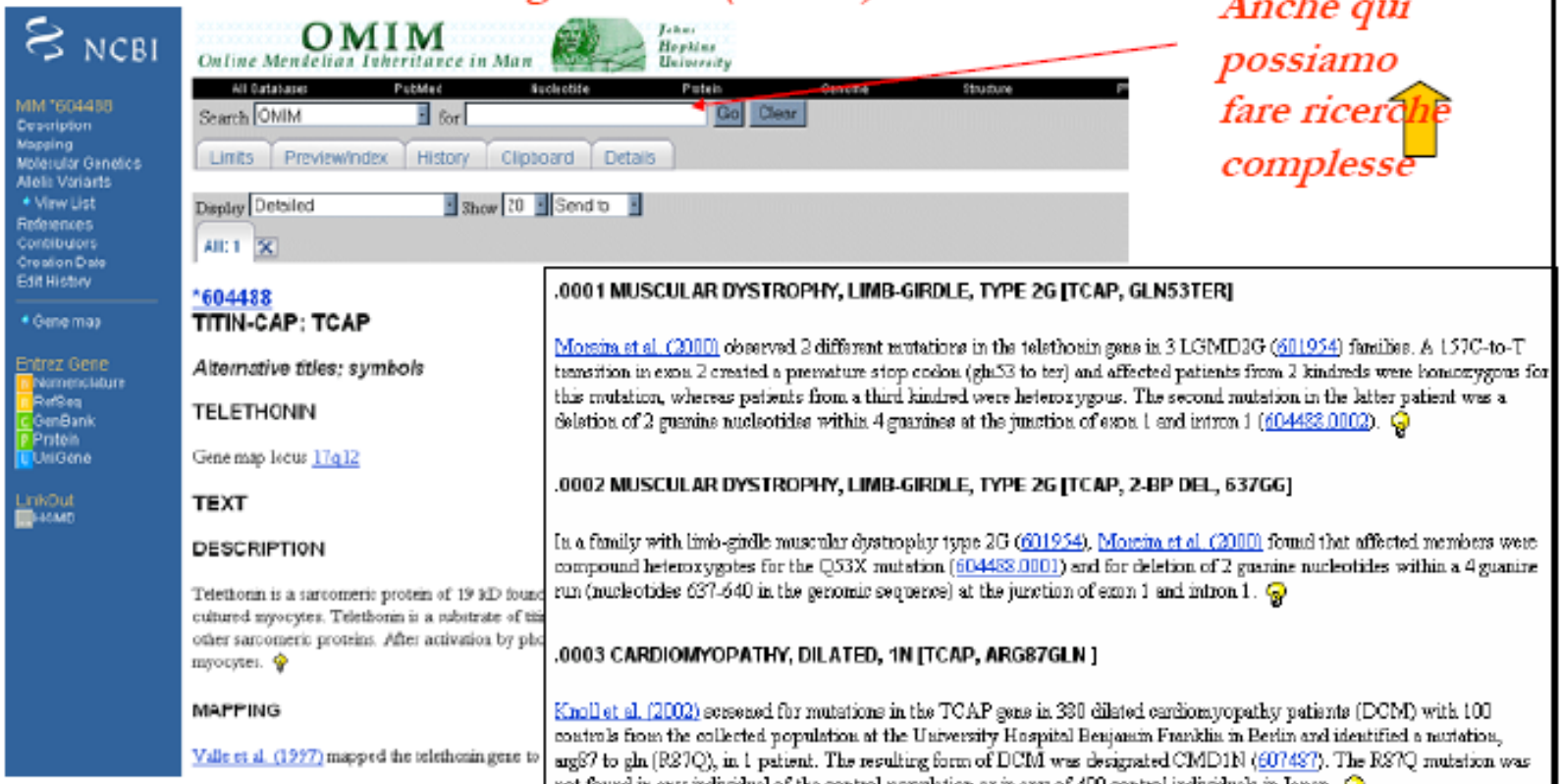
Mutazioni (alterazioni della sequenza nucleotidica di un gene) possono riflettersi in alterazioni della funzionalità della proteina da esso codificata. Questo mutazioni possono causare le cosiddette **malattie genetiche**.

Esempio: una mutazione a carico del gene della β globina fa sì che una particolare base del gene venga sostituita con un'altra, ciò altera il codone e nella proteina ciò si riflette nella sostituzione di un glutamato con una valina e in una ridotta funzionalità della proteina che causa una malattia genetica detta anemia a cellule falciformi (anemia falciforme).

Mutazioni a carico di geni differenti causano molte malattie genetiche diverse per questo è stato costituito il database OMIM.

Database di malattie genetiche (umane)

Anche qui possiamo fare ricerche complesse



Esempio di una query sul database OMIM: da notare l'estensiva descrizione di quanto noto sulla/e malattia/e determinate da mutazioni a carico del gene in esame

LA REGIONE CODIFICANTE (CDS)

Consideriamo ora solo la parte codificante (tradotta in aminoacidi) della sequenza di RNA messaggero

```
gene            1..963
                /gene="TCAP"
                /note="synonyms: TELE, CMD1N, T-cap, LGMD2G, telethonin"
                /db_xref="GeneID:8557"
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CDS             15..518
                /gene="TCAP"
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                go_function: structural constituent of muscle [goid
                0008307] [evidence TAS] [pmid 9350988];
                go_process: sarcomere alignment [goid 0006938] [evidence
                TAS] [pmid 9817758];
                go_process: cell shape and cell size control [goid
                0007148] [evidence E] [pmid 9817758];
                go_process: protein complex assembly [goid 0006461]
                [evidence TAS] [pmid 9817758]"
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componente cellulare

funzione

processo biologico

GENE ONTOLOGY

http://www.geneontology.org/

Il trascritto è lungo 963 nucleotidi

CDS: La parte tradotta va dalla base 15 alle 518

Link alla proteina

Sequenza Proteina

LINK ALLA PROTEINA

Clickando sul link protein_id si arriva al record della proteina corrispondente

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LOCUS       NP_003664                167 aa            linear   PRI 20-DEC-2003
DEFINITION  telethonin; 19 kDa sarcomeric protein [Homo sapiens].
ACCESSION   NP_003664
VERSION     NP_003664.1  GI:4507435
DBSOURCE    REFSEQ: accession NM_003673.2
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (residues 1 to 167)
  AUTHORS   Zou,P., Gautel,M., Geerlof,A., Wilmanns,M., Koch,M.H. and
            Svergun,D.I.
  TITLE     Solution scattering suggests cross-linking function of telethonin
            in the complex with titin
  JOURNAL   J. Biol. Chem. 278 (4), 2636-2644 (2003)
   PUBMED   12446666
  REMARK    GeneRIF: telethonin may play a role in linking titin filaments at
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REFERENCE   2  (residues 1 to 167)
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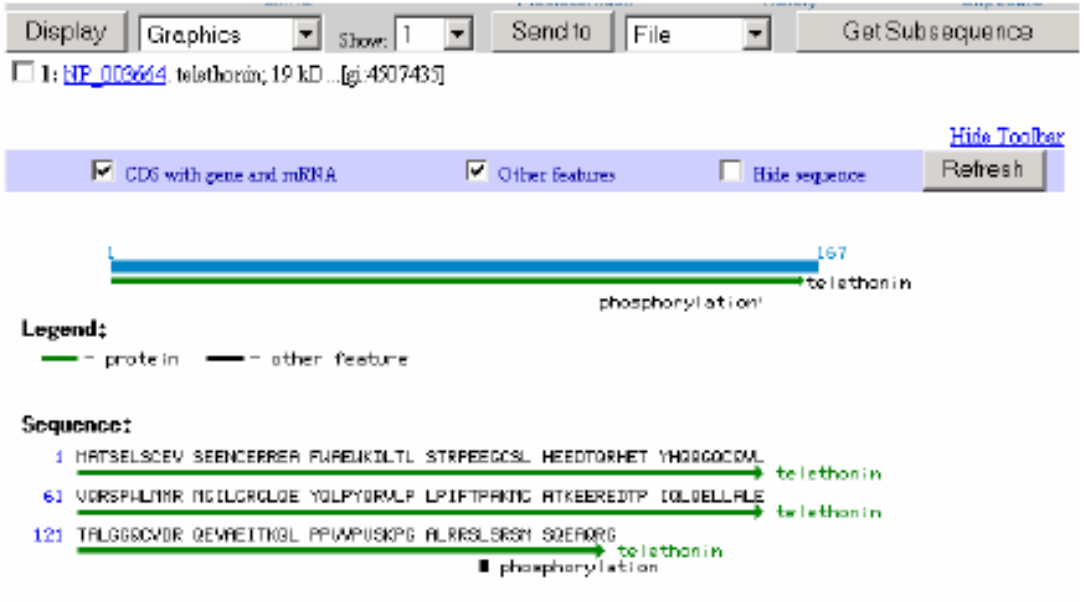
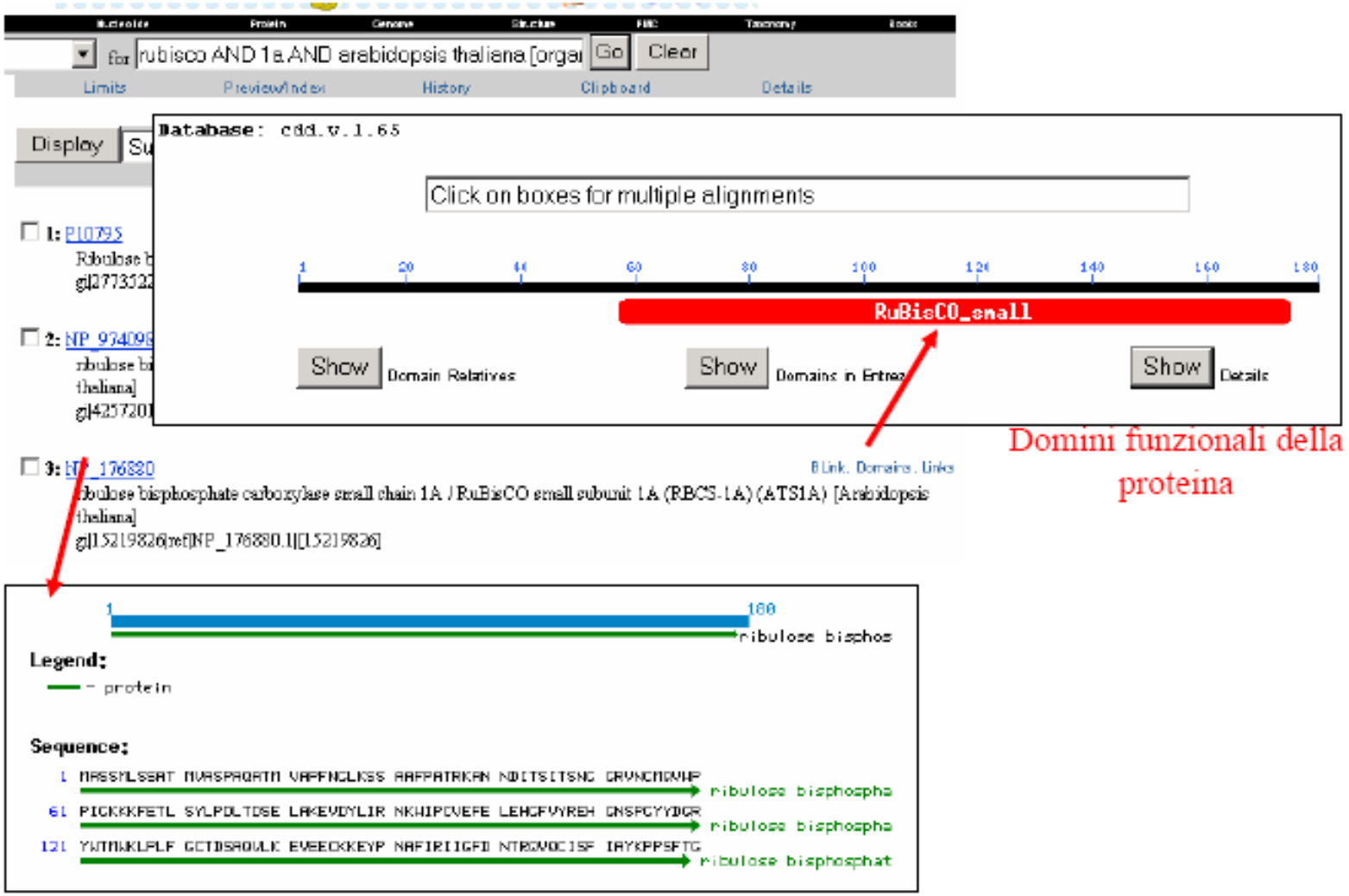
PROTEINA

Modalità grafica. Vedere il funzionamento delle opzioni

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Limits
Preview/Index
History
Clipboard
Details
Display
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Click on boxes for multiple alignments
1
20
40
60
80
100
120
140
160
180
RuBisCO_small
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Domains in Entrez
Show
Details
1: P10795
2: NP_974099
3: NP_176880
Blink Domains Links
ribulose bisphosphate carboxylase small chain 1A / RuBisCO small subunit 1A (RBCS-1A) (ATS1A) [Arabidopsis thaliana]
gi|15219826|ref|NP_176880.1|[15219826]
Domini funzionali della proteina
1
100
ribulose bispho
Legend:
protein
Sequence:
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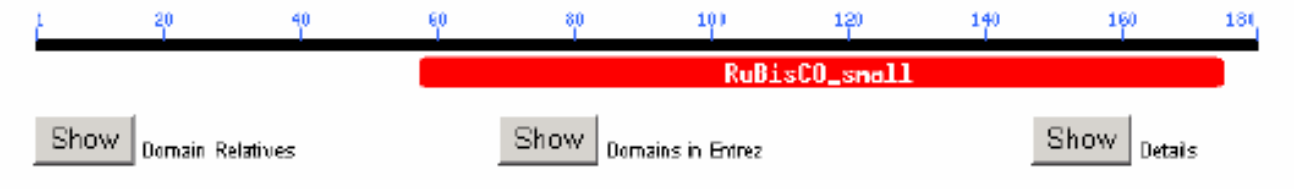
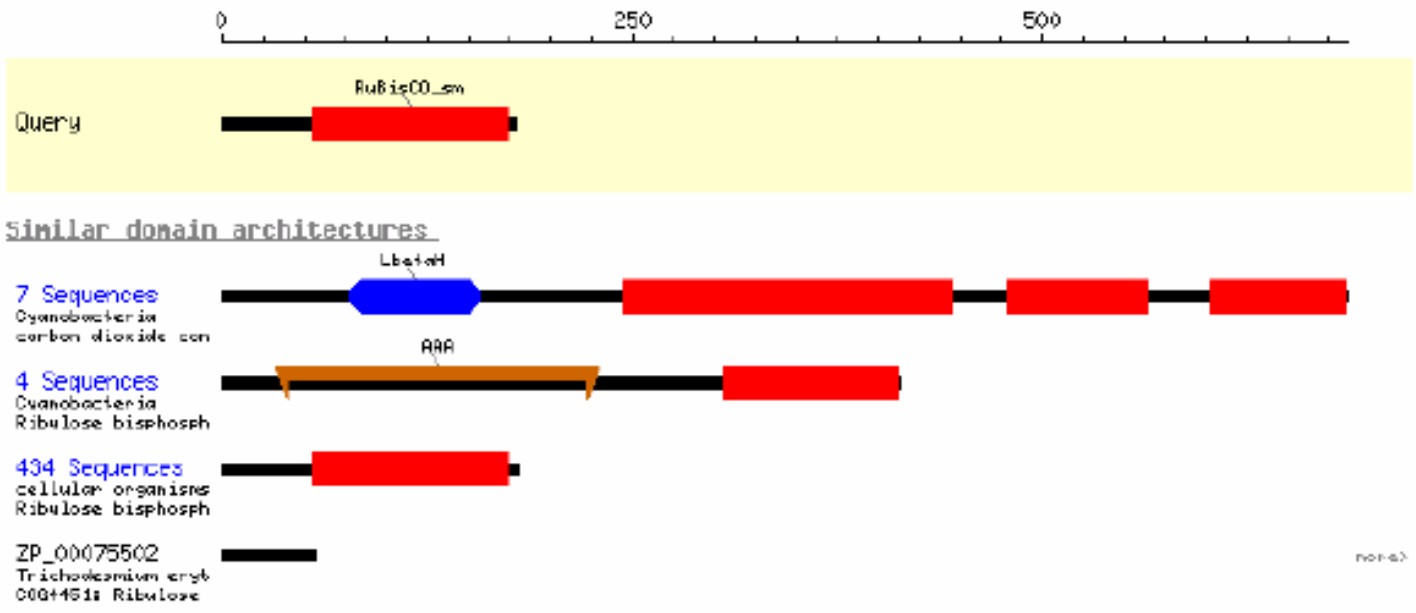
ribulose bisphospha
61 PIGKKKFETL SYLPDLTDSE LAKEVDYLIR NKWIPCVEFE LEHGFVYREH ENSPGYYDGR
ribulose bisphospha
121 YWTMWKLPLF GCTDSAQVLK EVEEAKKEYP NAFIRIIGFD NTRQVQCISF IAYKPPSFTG
ribulose bisphosphat

PROTEINE CON GLI STESSI DOMINI

Sono immediatamente accessibili anche proteine aventi gli stessi domini





How to build up a gene-specific molecular testing

Gene cards

National Center for Biotechnology Information

National Library of Medicine National Institutes of Health

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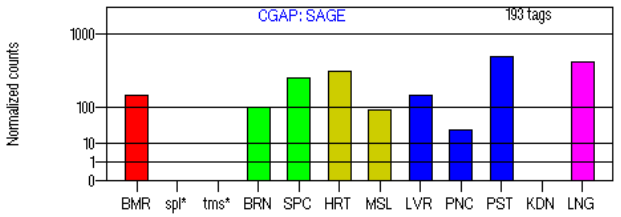
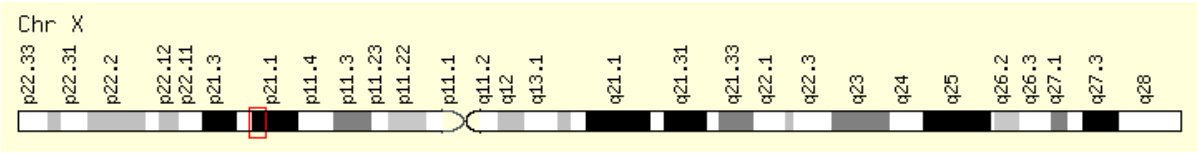
Exon 44





- mRNA summary
- cDNA clones
- Gene summary
- Protein annotation
- mRNA structure
- Sequences
- Diagram
- Phenotype
- Function
- Expression and regulation
- Introns and exons

Gene card

Tools bioinformatici in genetica medica

Esercizi effettuati su:

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

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

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

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

http://www.orpha.net/consor/cgi-bin/index.php