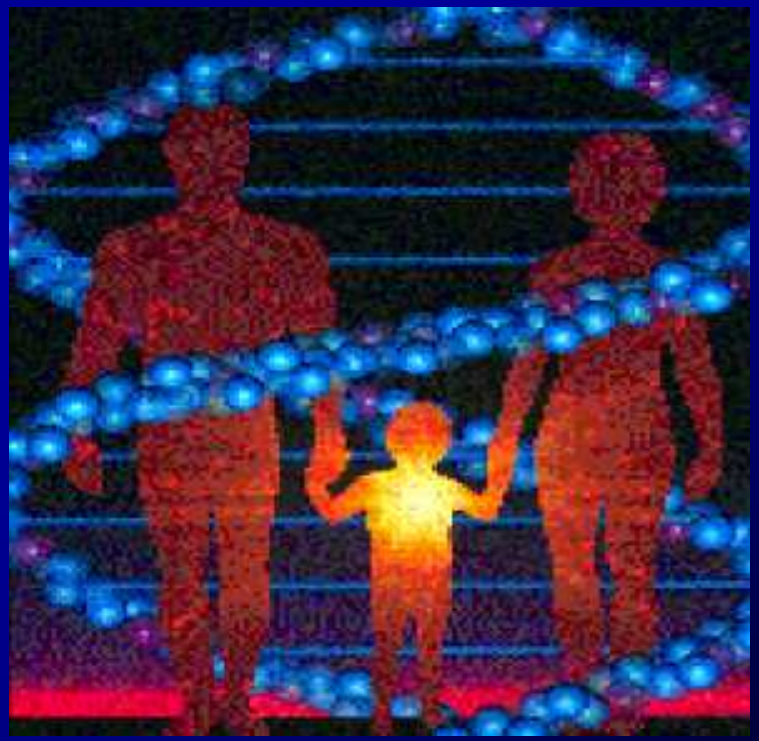
GENETIC COUNSELLING

Process involving the individual and extending to him/her family



GENETIC COUNSELLING

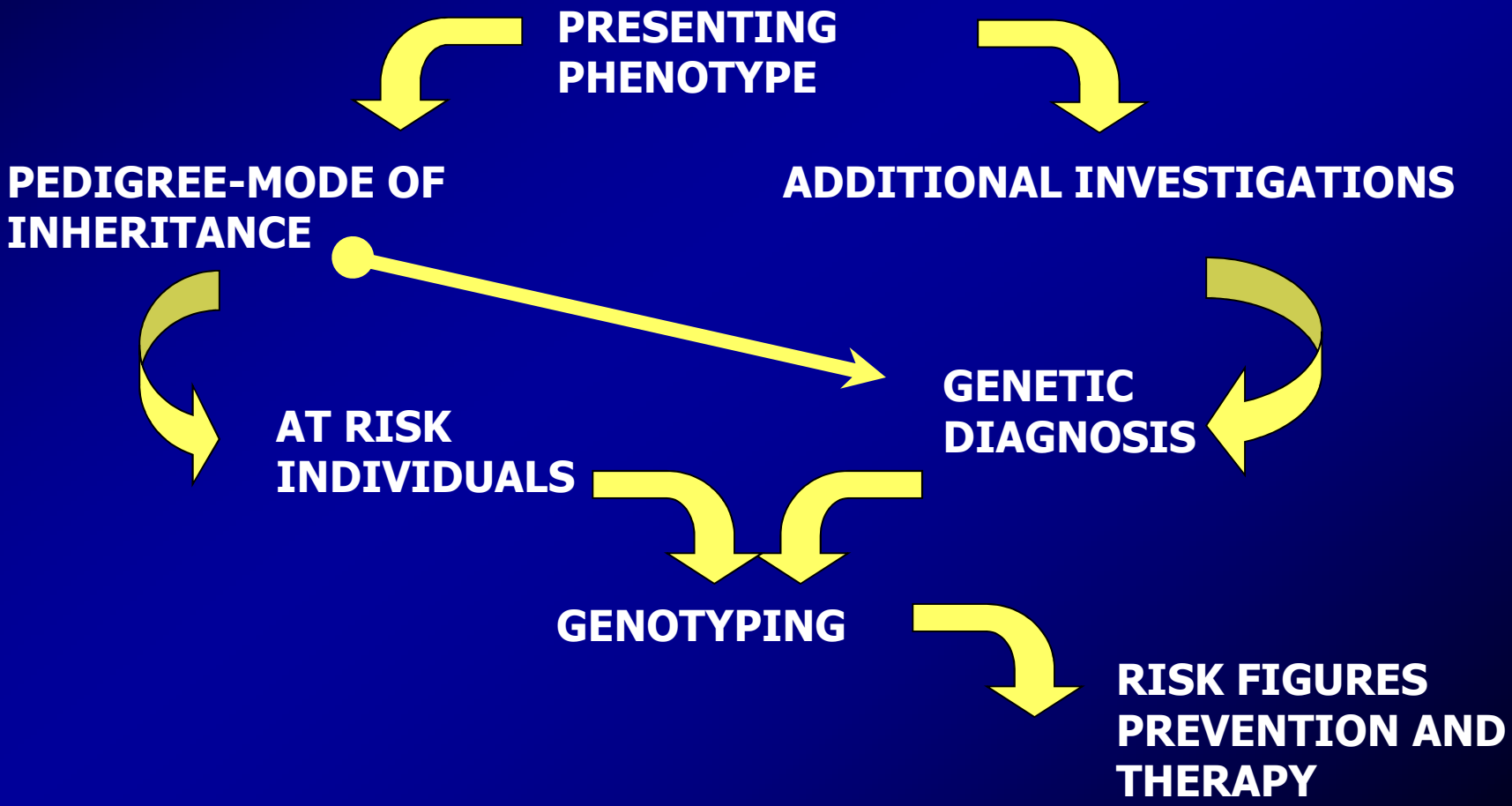
A non directive process by which patients or relatives at risk of a disorder that may be hereditary are advised of the consequences of the disorder, the probability of developing and transmitting it and the ways in which this may be prevented or ameliorated (Harper).

GENETIC COUNSELLING

The genetic counselling has the goal to offer in a collaborative and integrated perspective possible options regarding:

- -the mode of inheritance and related risk figures
- -the cohort of genetic testing available
- -the cohort of reproduction monitoring
- - support in the autonomous decision process

DIAGNOSIS: FUNDAMENTAL ELEMENTS OF GENETIC COUNSELLING



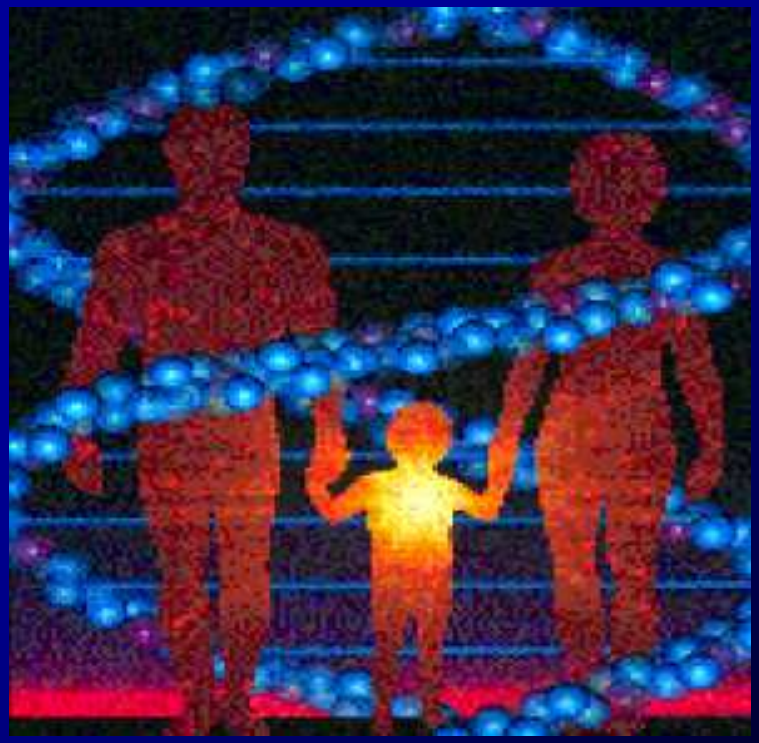
BASIC METHODOLOGY IN GENETIC COUNSELLING: an integrated view

- Collection of the family history and pedigree (mode of inheritance)
- Detailed clinical information regarding the patient and relatives
- Proposing and organising novel clinical or instrumental investigations
- Collecting informed consents and ethical issues
- Addressing laboratory testing
- Interpreting the genetic testing outcome

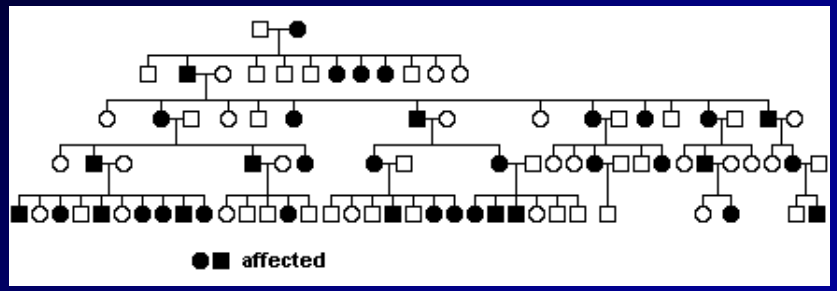
OBJECTIVES OF GENETIC COUNSELLING

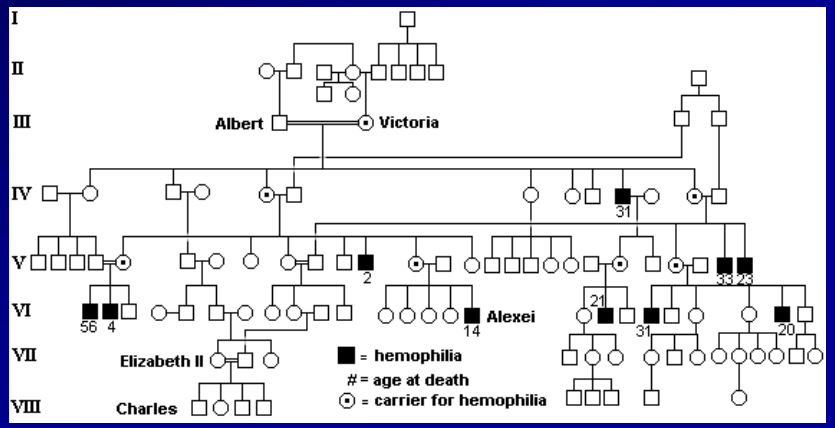
- To discriminate between environmental and genetic factors in the presenting phenotype
- To address a better phenotype definition
- To identify the possible mode of inheritance of the condition
- To identify the causative genotype
- To identify the at risk individuals
- To provide information regarding the quality and quantity of risk
- To provide support in the autonomous decision process in prevention and therapeutic strategies, taking into account the ethical issues

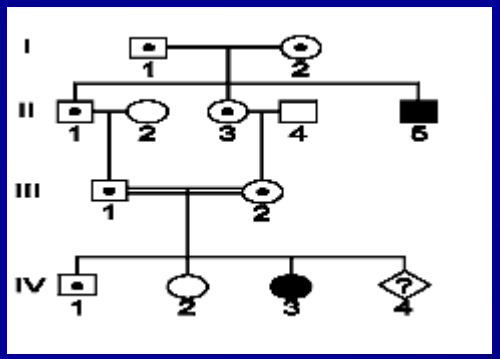
Collection of the family history and pedigree (mode of inheritance)

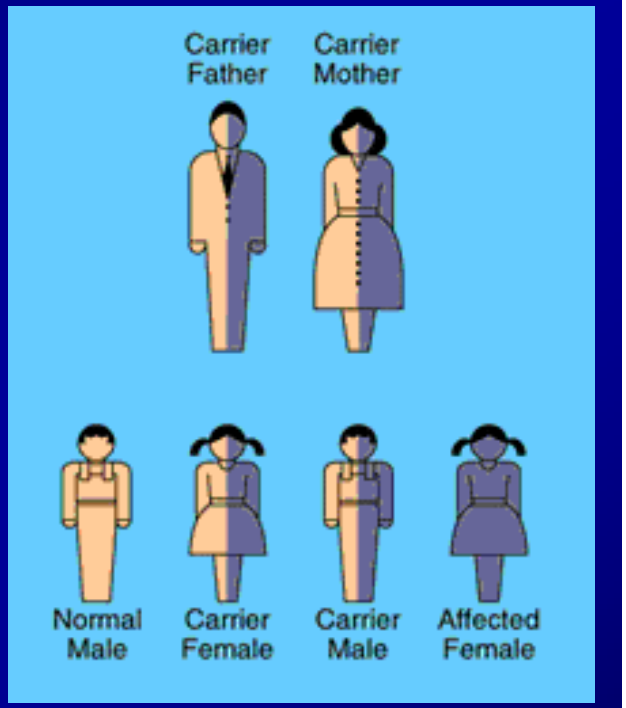


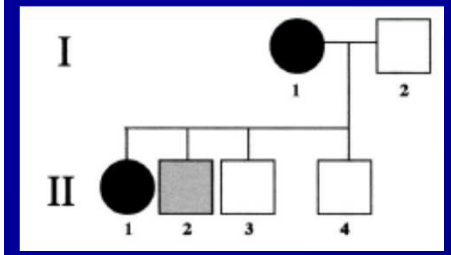
Collection of the family history and pedigree (mode of inheritance)

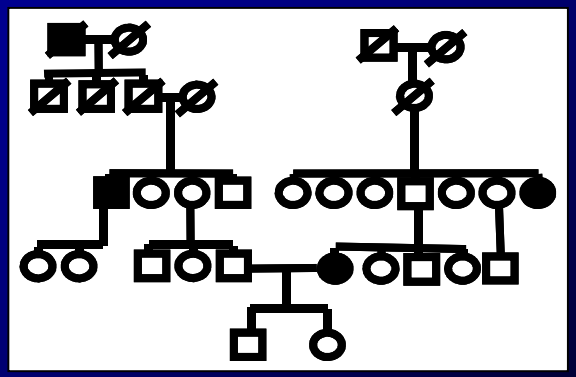




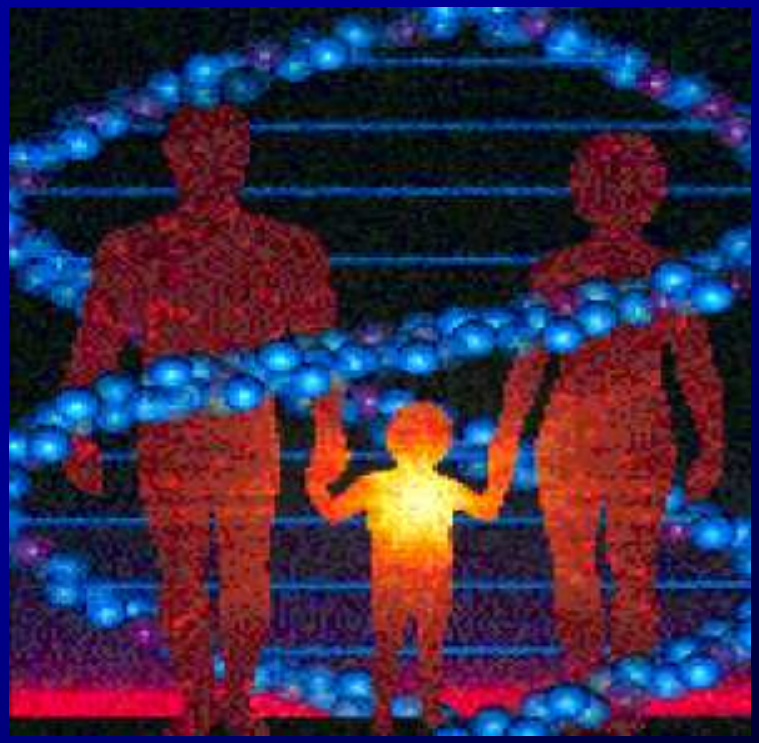




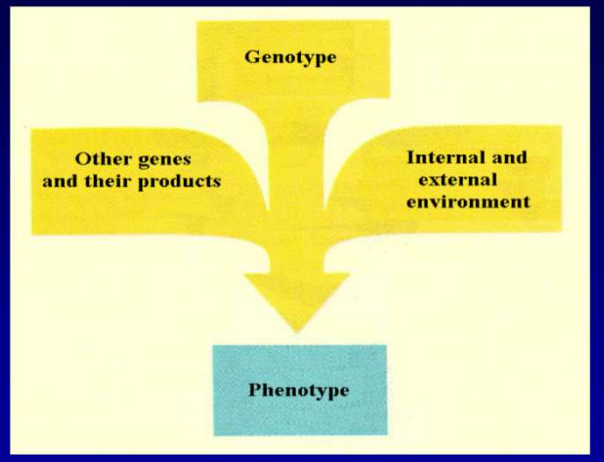




Detailed clinical information regarding the patient and relatives



PHENOTYPE DIAGNOSIS (PHENOMICS)



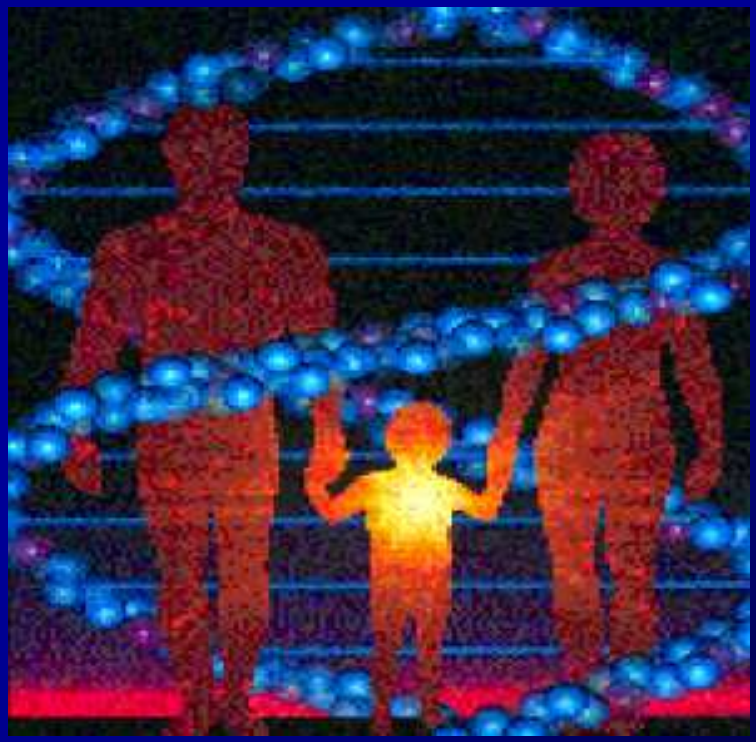
CLINICAL
INSTRUMENTAL
BIOCHEMICAL
IMMUNOCYTOCHEMICAL

CLOSE INTERACTIONS BETWEEN MEDICAL GENETICIST AND OTHER SPECIALISTS

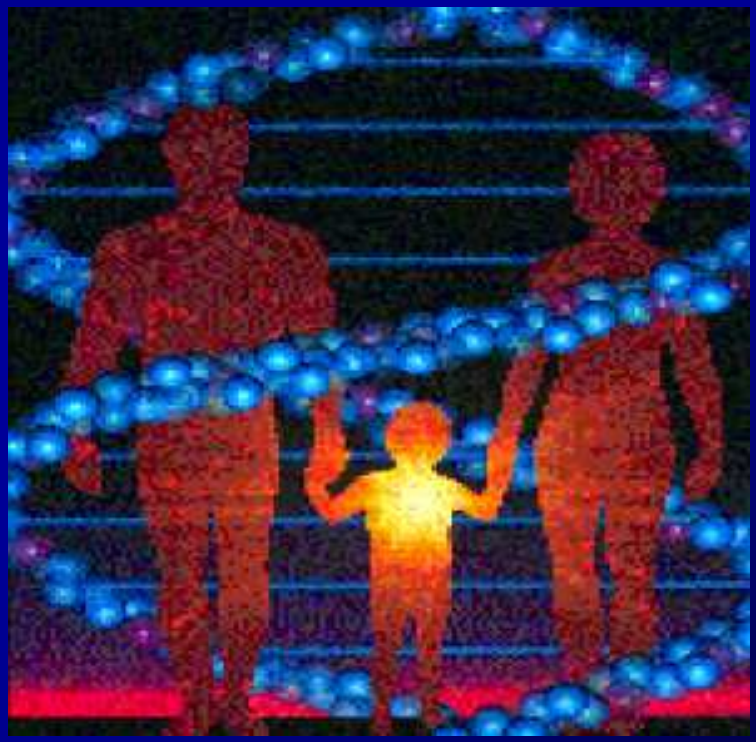
Common pedigree problems

- Different mutations can result in the same phenotype
  - Locus heterogeneity - mutations in different genes eg. Alpha and beta thalassemia
  - Allelic heterogeneity - different mutations in same gene e.g. Hb S and C

- Proposing and organising novel clinical or instrumental investigations



- Collecting informed consents and ethical issues

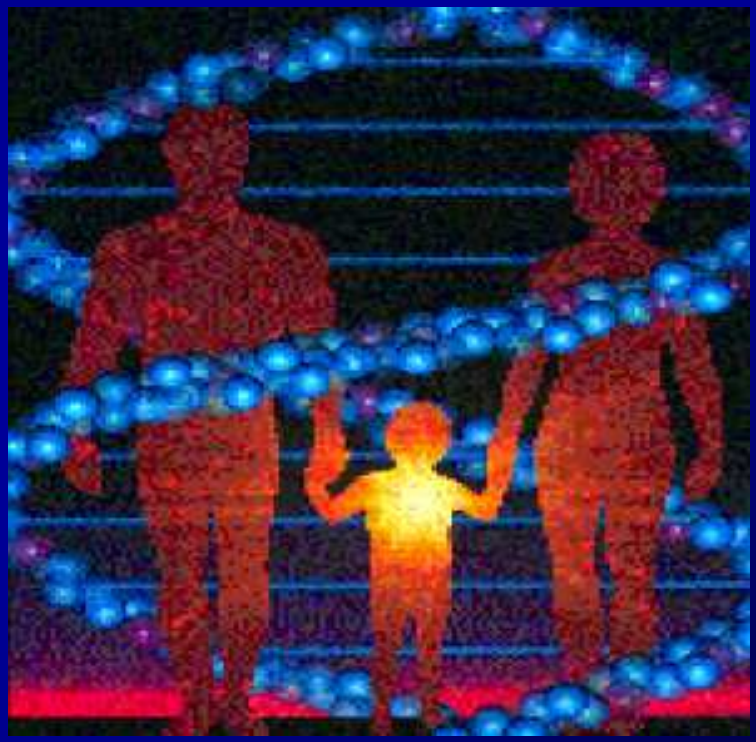


Linee guida etiche per test genetici *(WHO)*

- they should be encouraged when the information might be used for prevention and therapy (health benefit)
- they should be voluntary and based on the informed consent *(autonomy)*
- they should be offered to adult individuals, even if a therapy ore prevention are not available *(autonomy)*
- the genetic tests on asymptomatic children should be avoided if a clear impact on prevention or therapy does not exist (health benefit)
- Schools, education and governative programs, insurance and job providers must not have access to genetic testing results

The informed consent must always be collected informing the individuals about:
-significance of the test
-limits of the test
-possible results
-impact of the test on the reproductive life

- Addressing and interpreting laboratory testing



GENETIC TESTS

Genetic tests
are the most important
product,
in terms of clinical impact, of
applied research

- Definition

The analysis of human DNA, RNA, chromosomes in order to detect heritable disease-related genotypes/ mutations for clinical purposes

(US Task force on genetic testing 1999)

GENETIC TESTS

Investigations carried out

- **Prenatal**
- Perinatal
- Postnatal

* The typing of DNA/RNA and chromosomal regions will allow the identification of the genetic constitution of each individual

GENETIC TESTS

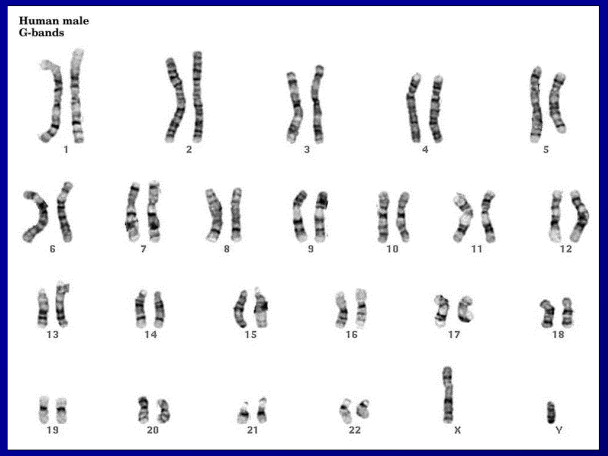
Tests done on the genome as a whole

- cytogenetics
- gene profiling (arrays)

Test done on specific genes/regions

- molecular genetics
- molecular cytogenetics

GENETIC TESTS: cytogenetics



-Can review the whole genome

-Used for gross rearrangement abnormalities

Characteristics:

low resolution (standard karyotype)
intermediate resolution (FISH)
high resolution (CGH)

GENETIC TESTS: molecular genetics

-Can identify both small mutations
and gross rearrangements

-Characteristics:
define the genotype
are gene-specific

Limitations:
time consuming
expensive
requires high specialisation
mutations screening often difficult to be set up
(allele heterogeneity, private mutations, atypical mutations)

SCOPE OF GENETIC TESTS

- Diagnostic Test
- Carrier identification test
- Presymptomatic (or preclinical) test
- Predisposition test
- Screening test
- Medical/legal test

La bioinformatica come tool per la analisi di geni malattia

Gene cards

National Center for Biotechnology Information

National Library of Medicine National Institutes of Health

The AceView genes

(*last updated September 13th, 2005*)

gcgcctgccatgggggagggtgccaggggagaggcactgggggtgtctgagcgac
ccccacccctgttgcaggacttcagggccacaggtgctgccaagATGCTCCAGGG
CACCTGCTCCGTGCTCCTGCTCTGGGGAATCCTGGGGGCCATCCAGGCCCAGCAG
CAGGAGGTCATCTCGCCGGACACTACCGAGAGAAACAACAACTGCCCAGgtgcca
ggggtcgggggccgggggctctgggcatttgggggggcagttgggaccagtaccca
ggtgccaggggtcgggggccgggggctctgggcatttgggggggcagttgggacca
gtacccaggtgccaggggtcgggggccgggggctctgggcatttgggggggcagtt
gggaccagtacccaggtgccaggggtcgggggccgggggctctgggcatttgggg
ggcagttgggaccagtacccaggtgccaggggttgggggccgggggctctggcat
tcgggggcagtgaggtcaaacccacaaacaggcacggggccaggaaacggggctc
caacagcagtccctcctgaggctggctcgtgacaggtcctgtgccccacaAGAAG
ACCGACTGCCCCATCCACGTGTACTTCGTGCTGGACACCTCGGAGAGCGTCACCA
TGCAGTCCCCCACGGACATCCTGCTCTTCCACATGAAGCAGTTCGTGCCGCAGTT
CATCAGCCAGCTGCAGAACGAGTTCTACCTGGACCAGGTGGCGCTGAGCTGGCGC
TACGGCGGCCTGCACTTCTCTGACCAGGTGGAGGTGTTCAGCCCACCGGGCAGCG
ACCGGGCCTCCTTCATCAAGAACCTGCAGGGCATCAGCTCCTTCCGCCGCGGCAC
CTTCACCGACTGCGCGCTGGCCAACATGACGGAGCAGATCCGGCAGGACCGCAGC
AAGGGCACCGTCCACTTCGCCGTGGTCATCACCGACGGCCACGTCACCGGCAGCC
CCTGCGGGGGCATCAAGCTGCAGGCCGAGCGGGCCCGCGAGGAGGGCATCCGGCT
CTTCGCCGTGGCCCCCAACCAGAACCTGAAGGAGCAGGGCCTGCGGGACATCGCC
AGCACGCCGCACGAGCTCTACCGCAACGACTACGCCACCATGCTGCCCGACTCCA
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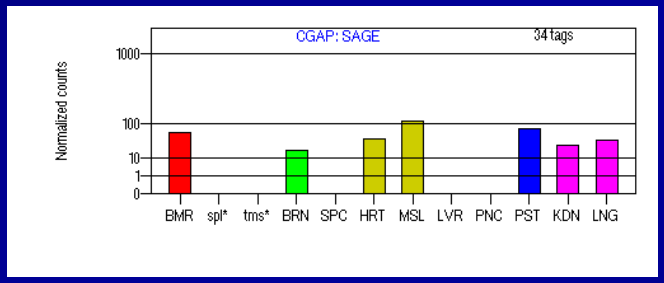
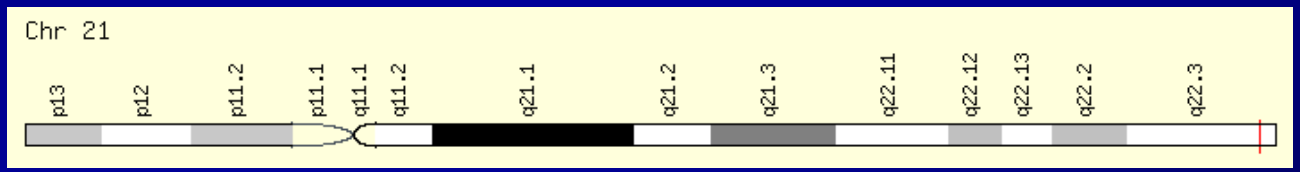
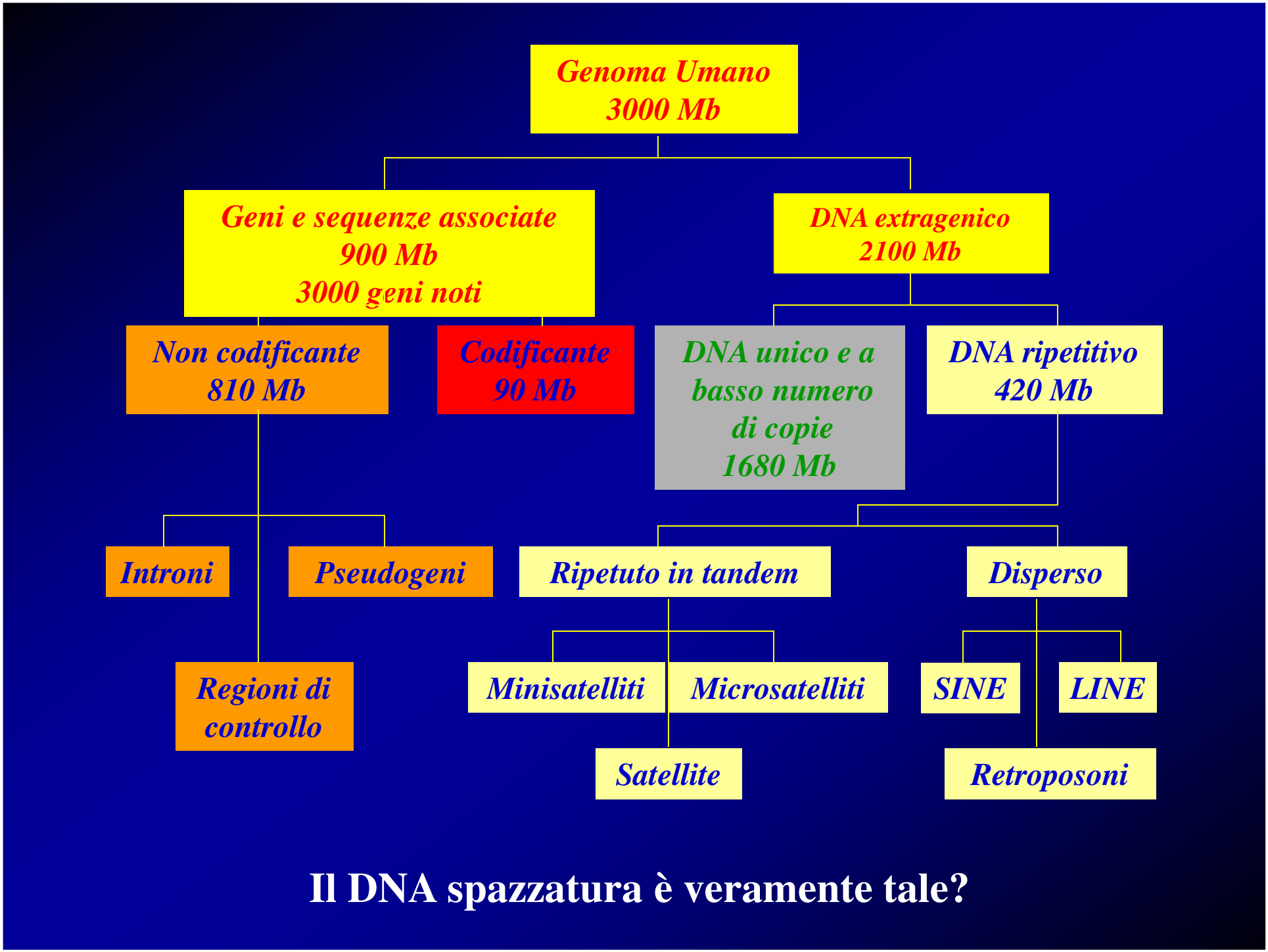




Gene card for COL6alpha1

(congenital muscular dystrophy Ullrich type)



Il DNA spazzatura è veramente tale?

LINK AL GENE

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

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                     /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"
```

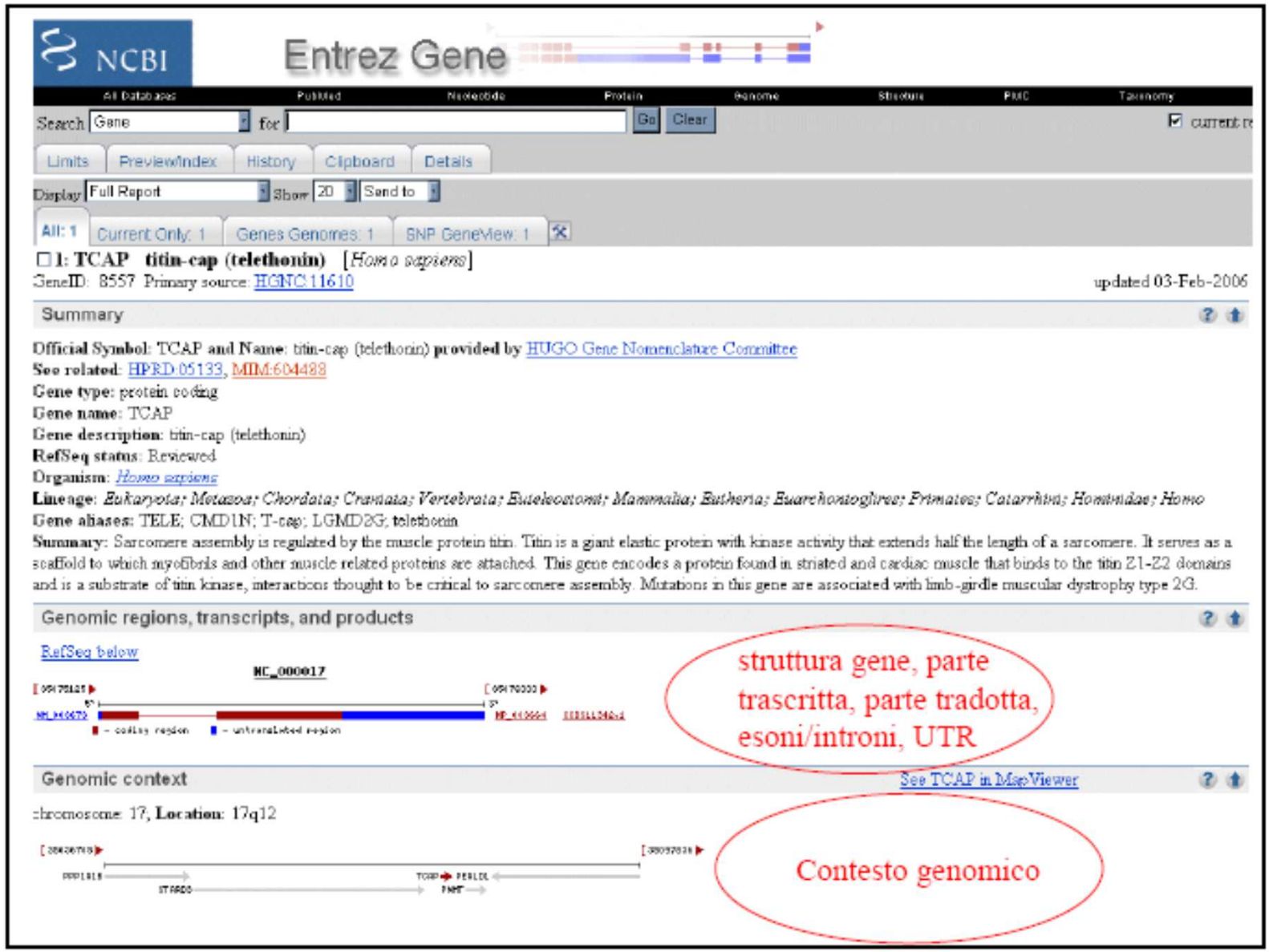
tipo molecola (DNA, mRNA...)

cromosoma e posizione di mappa

nome ufficiale del gene e sinonimi

link al database dei geni Entrez Gene

link a malattie genetiche

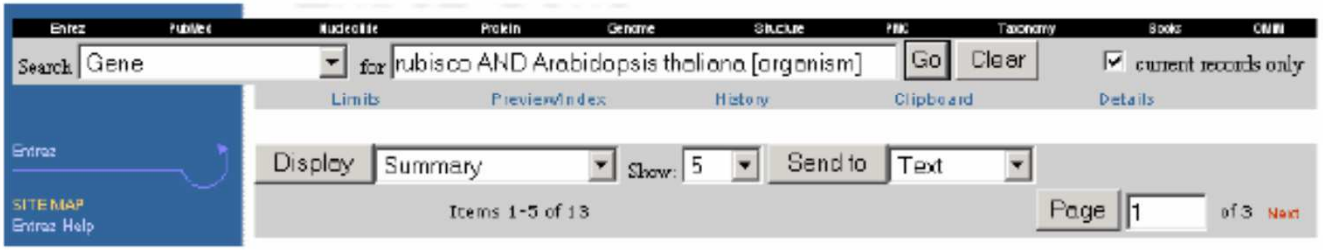

NCBI
Entrez Gene
All Databases
PubMed
Nucleotide
Protein
Genome
Structure
PMC
Taxonomy
Search Gene for
Go
Clear
Limits
Preview/Index
History
Clipboard
Details
Display Full Report
Show 20
Send to
All: 1
Current Only: 1
Genes Genomes: 1
SNP GeneView: 1
1: TCAP titin-cap (telethonin) [Homo sapiens]
GeneID: 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

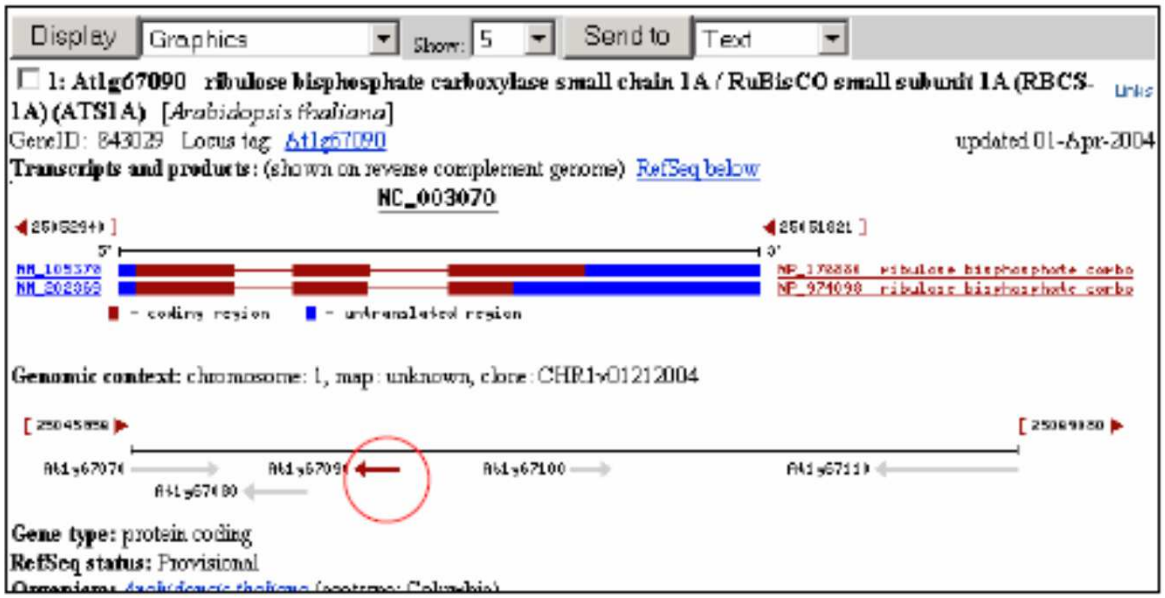
Getting started	Sample queries
Look for genes by name part and multiple species	transporter AND ("Drosophila melanogaster"[orgn] OR "Mus musculus"[orgn]) more...
Look for genes by chromosome and symbol	(II[chr] OR 2[chr]) AND adh*[sym] more...

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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                     /mol_type="mRNA"
                     /db_xref="taxon:9606"
                     /chromosome="17"
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                     /db_xref="GeneID:8557"
                     /db_xref="LocusID:8557"
                     /db_xref="MIM:604488"
```

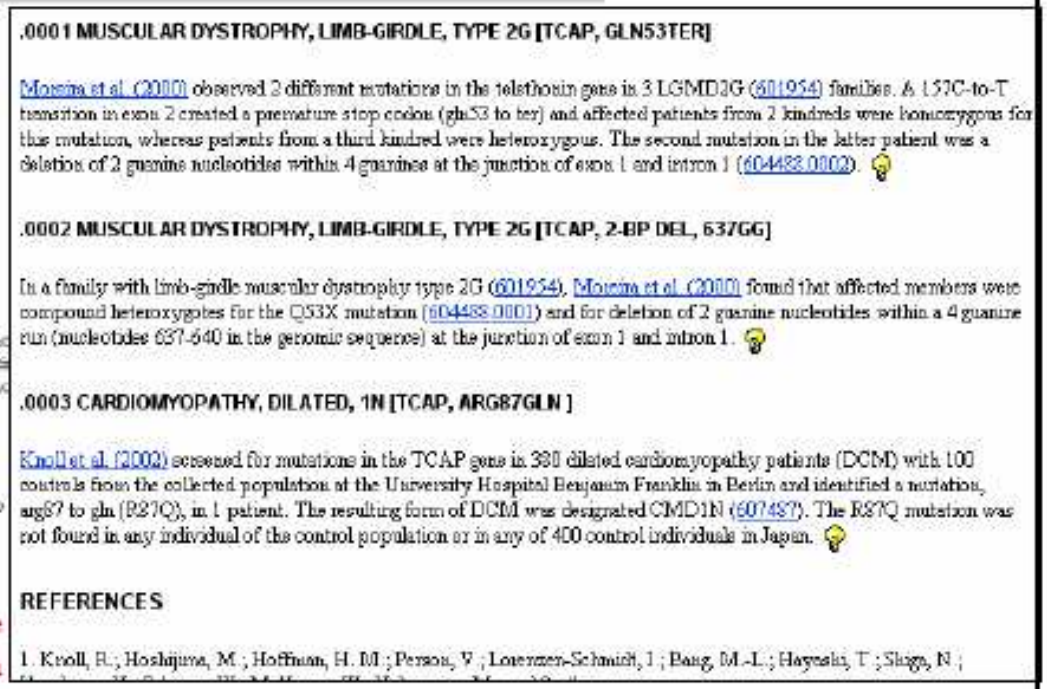
Mutazioni (alterazioni della sequenza nucleotidica di un gene) possono riflettersi in alterazioni della funzionalità della proteina da esso codificata. Questo mutazioni possono causare le cosiddette **malattie genetiche**.

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



.0001 MUSCULAR DYSTROPHY, LIMB-GIRDLE, TYPE 2G [TCAP, GLN53TER]

Moreira et al. (2000) observed 2 different mutations in the telethonin gene in 3 LGMD2G (601954) families. A 157C-to-T transition in exon 2 created a premature stop codon (gln53 to ter) and affected patients from 2 kindreds were homozygous for this mutation, whereas patients from a third kindred were heterozygous. The second mutation in the latter patient was a deletion of 2 guanine nucleotides within 4 guanines at the junction of exon 1 and intron 1 (604488.0002).

.0002 MUSCULAR DYSTROPHY, LIMB-GIRDLE, TYPE 2G [TCAP, 2-BP DEL, 637GG]

In a family with limb-girdle muscular dystrophy type 2G (601954), Moreira et al. (2000) found that affected members were compound heterozygotes for the Q53X mutation (604488.0001) and for deletion of 2 guanine nucleotides within a 4 guanine run (nucleotides 637-640 in the genomic sequence) at the junction of exon 1 and intron 1.

.0003 CARDIOMYOPATHY, DILATED, 1N [TCAP, ARG87GLN]

Knoll et al. (2002) screened for mutations in the TCAP gene in 330 dilated cardiomyopathy patients (DCM) with 100 controls from the collected population at the University Hospital Benjamin Franklin in Berlin and identified a mutation, arg87 to gln (R87Q), in 1 patient. The resulting form of DCM was designated CMD1N (607487). The R87Q mutation was not found in any individual of the control population or in any of 400 control individuals in Japan.

REFERENCES

1. Kroll, R.; Hoshijima, M.; Hoffman, H. M.; Person, V.; Lorenzen-Schmidt, I.; Bang, M.-L.; Hayashi, T.; Shiga, N.;

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

```
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                /note="synonyms: TELE, CMD1N, T-cap, LGMD2G, telethonin"
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                go_function: structural constituent of muscle [goid
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                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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                KEEREDTPIQLQELLALETALGGQCVDRQEVAEITKQLPPVVPVSKPGALRRSLSRSM
                SQEAQDC"
```

Il trascritto è lungo 963 nucleotidi

CDS: La parte tradotta va dalla base 15 alle 518

componente cellulare

funzione

processo biologico

GENE ONTOLOGY

http://www.geneontology.org/

Link alla proteina

Sequenza Proteina

LINK ALLA PROTEINA

Clickando sul link protein_id si arriva al record della proteina corrispondente

```
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
            the Z-disk periphery
REFERENCE   2  (residues 1 to 167)
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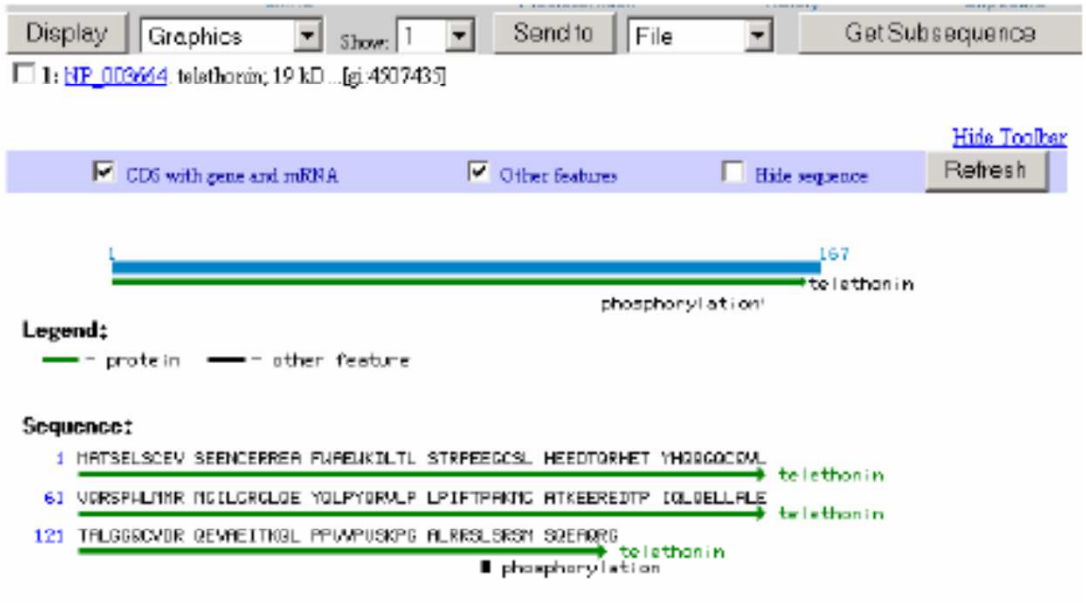
/protein_id="NP_003664.1"

PROTEINA

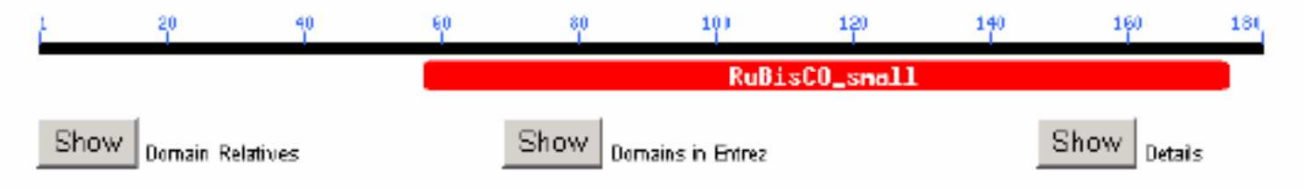
Modalità grafica. Vedere il funzionamento delle opzioni

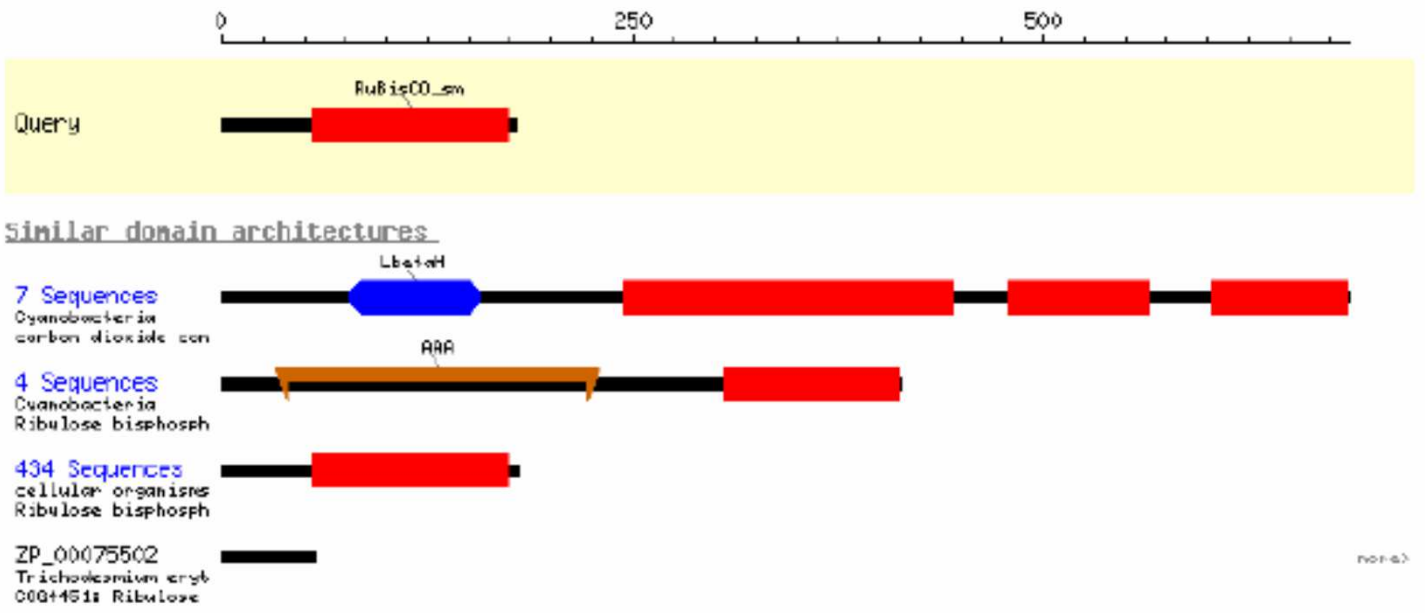


Domini funzionali della proteina

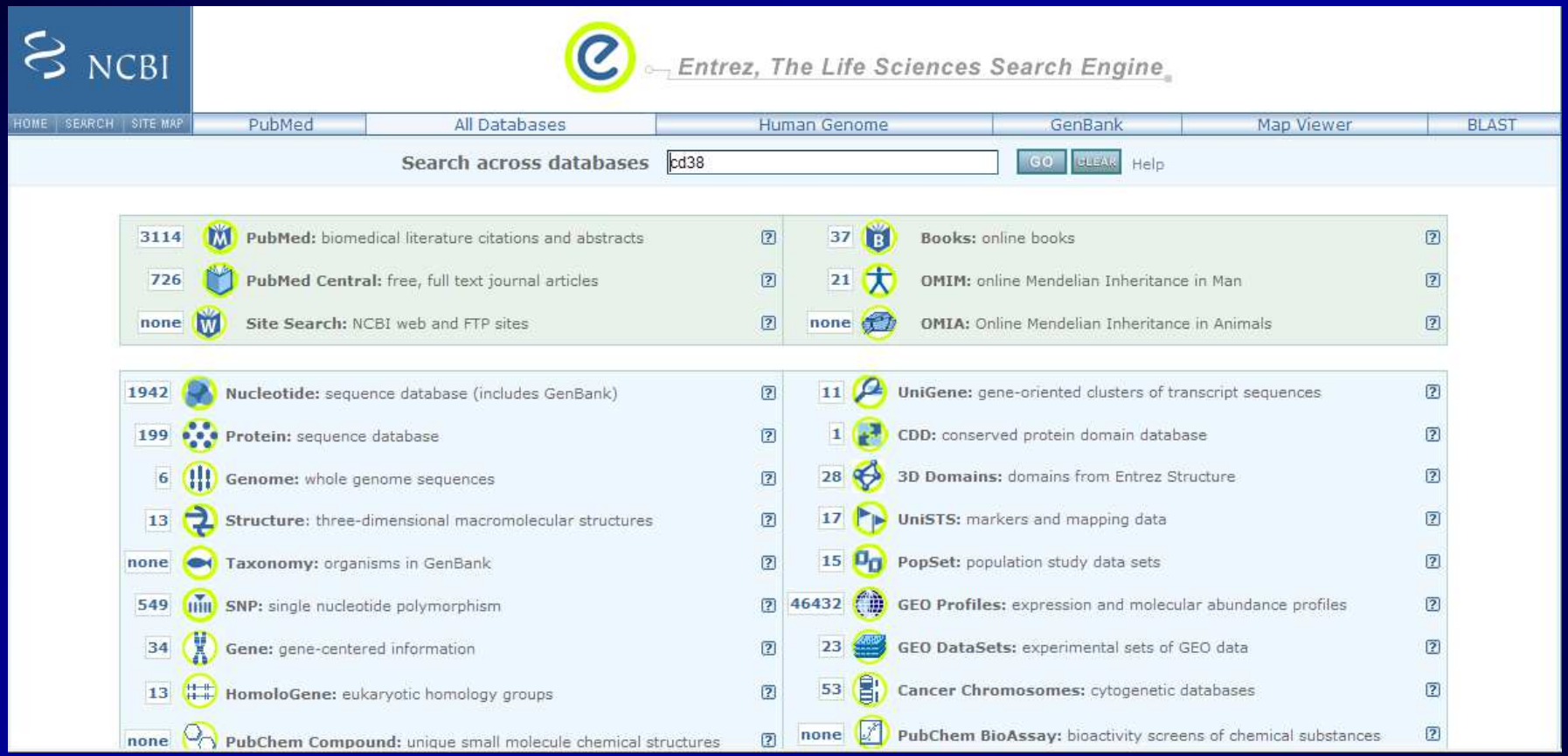
PROTEINE CON GLI STESSI DOMINI

Sono immediatamente accessibili anche proteine aventi gli stessi domini



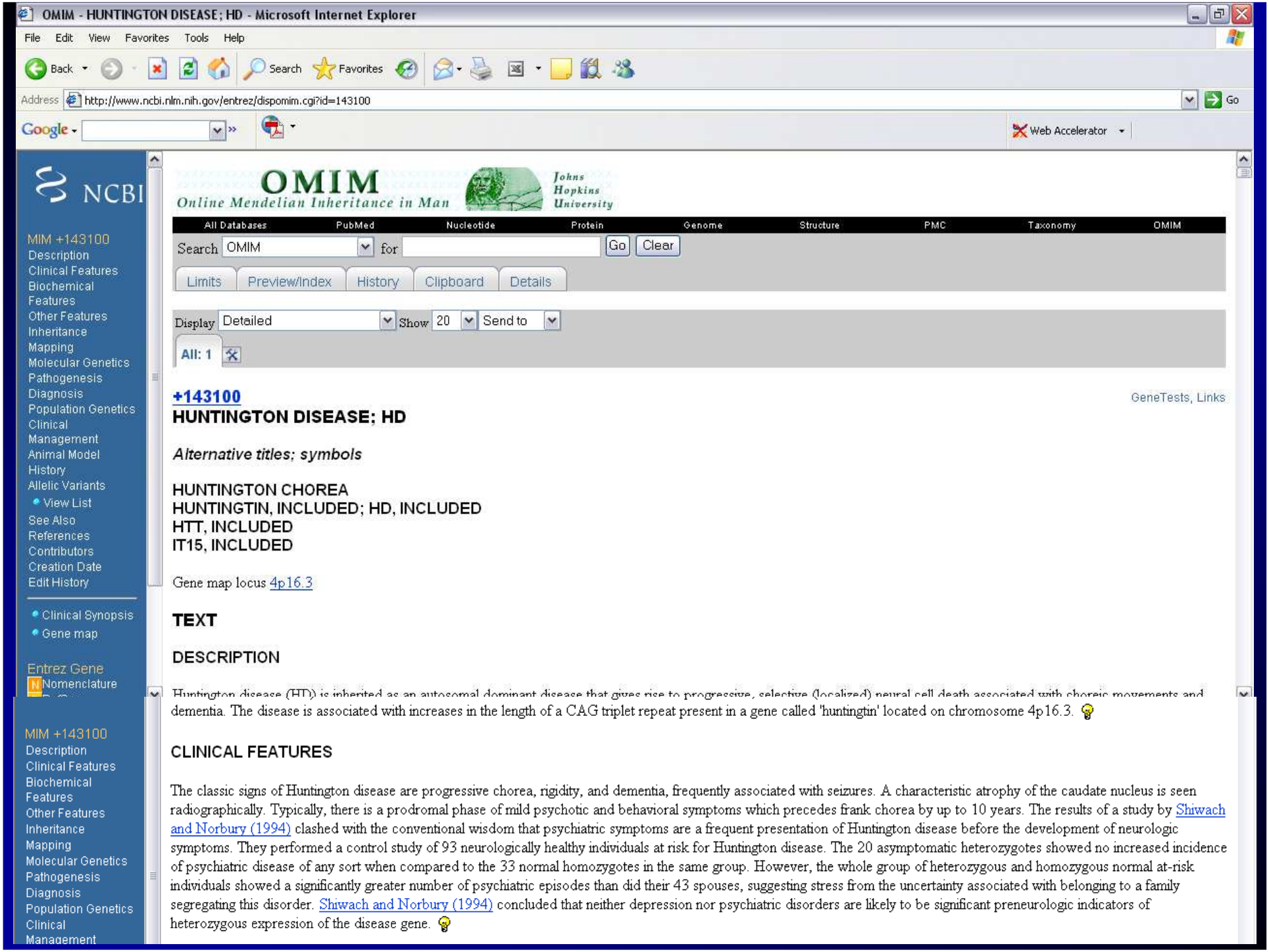


http://www.ncbi.nlm.nih.gov/genome/guide/human/



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

- 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


OMIM - HUNTINGTON DISEASE; HD - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=143100
Go
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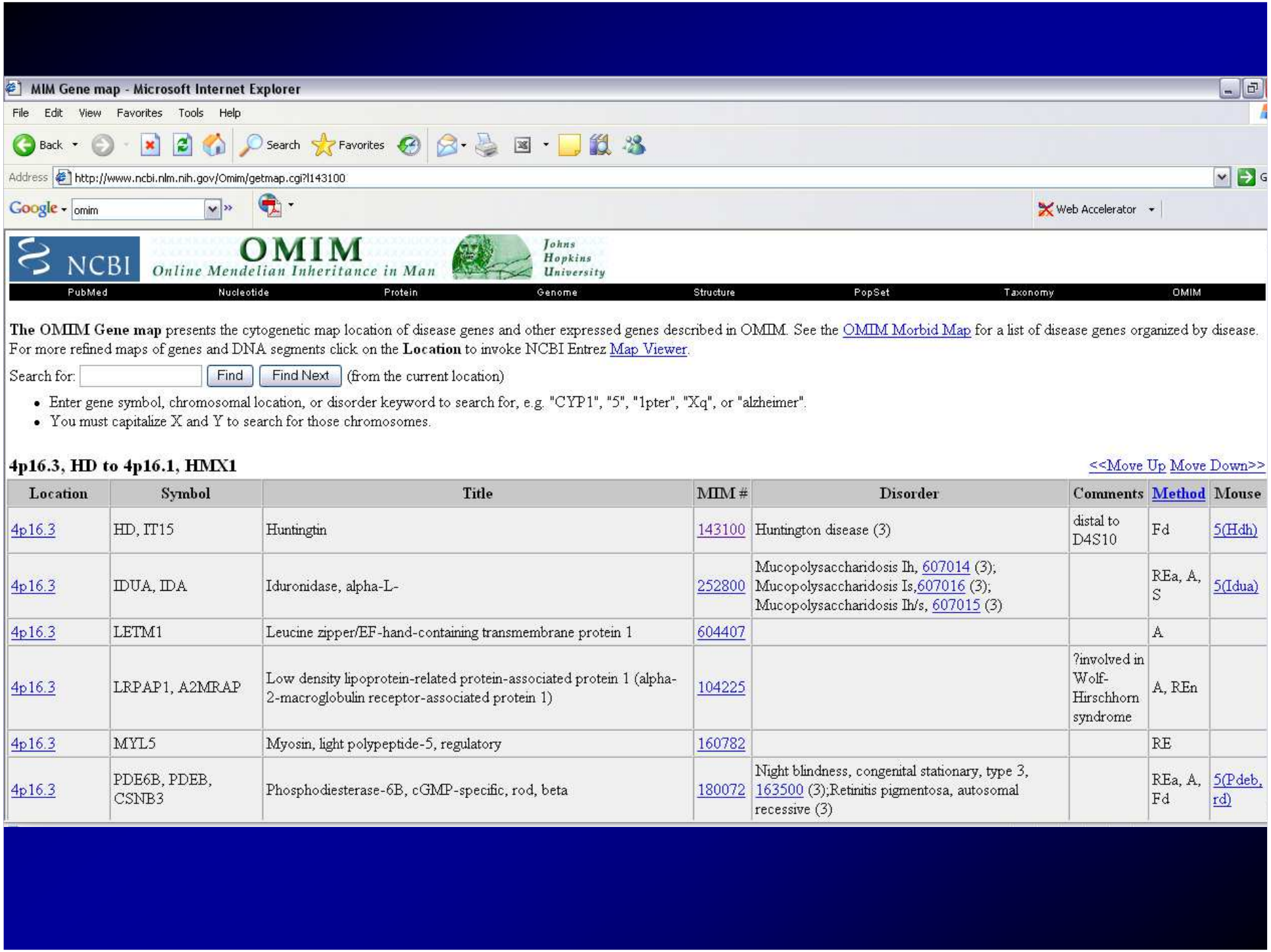
Web Accelerator
NCBI
OMIM
Online Mendelian Inheritance in Man
Johns Hopkins University
All Databases PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM
Search OMIM for Go Clear
Limits Preview/Index History Clipboard Details
Display Detailed Show 20 Send to
All: 1
MIM +143100
Description
Clinical Features
Biochemical Features
Other Features
Inheritance
Mapping
Molecular Genetics
Pathogenesis
Diagnosis
Population Genetics
Clinical Management
Animal Model
History
Allelic Variants
View List
See Also
References
Contributors
Creation Date
Edit History
Clinical Synopsis
Gene map
Entrez Gene
Nomenclature
+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
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.



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.

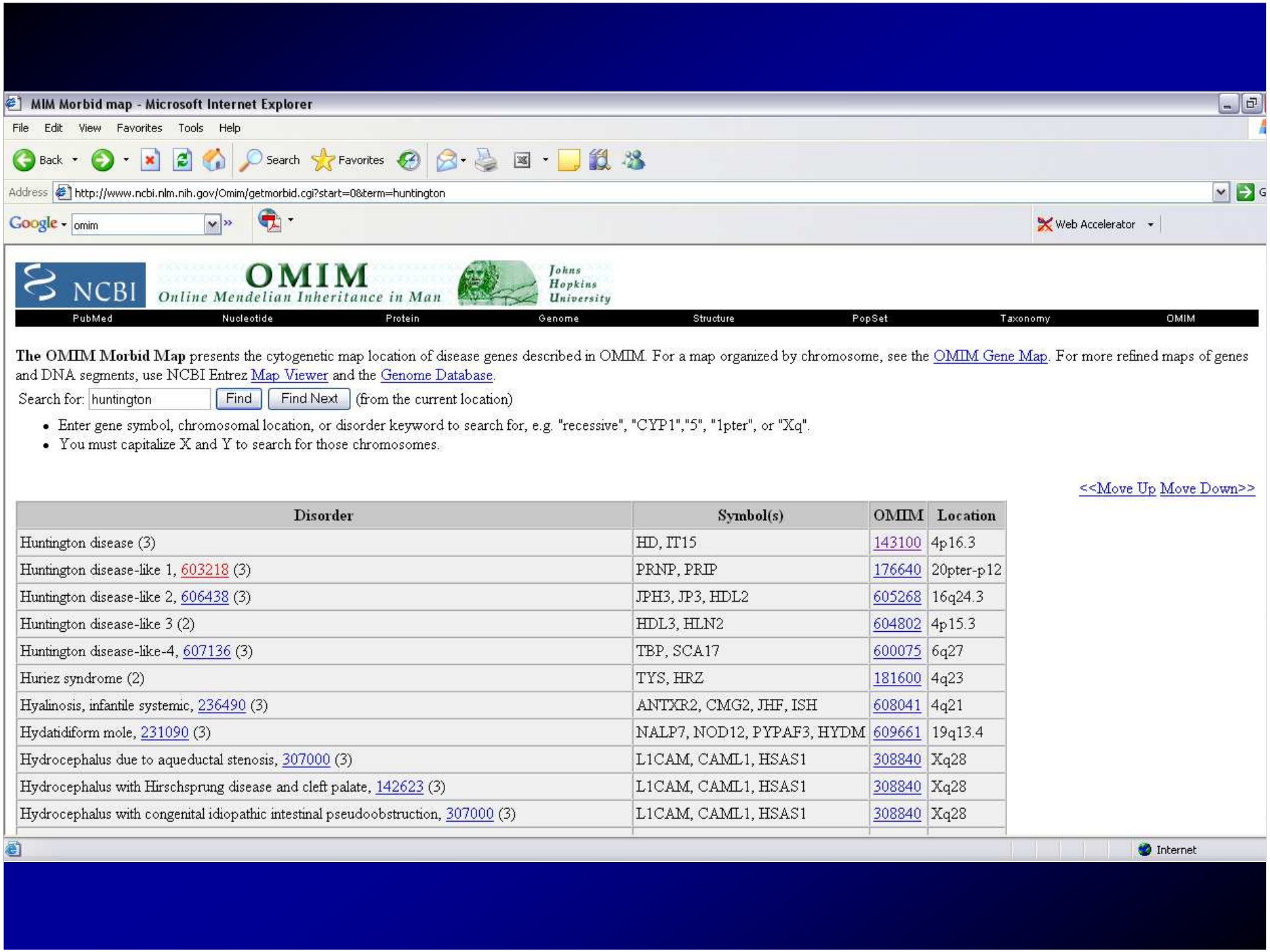
Search for: Find Find Next (from the current location)

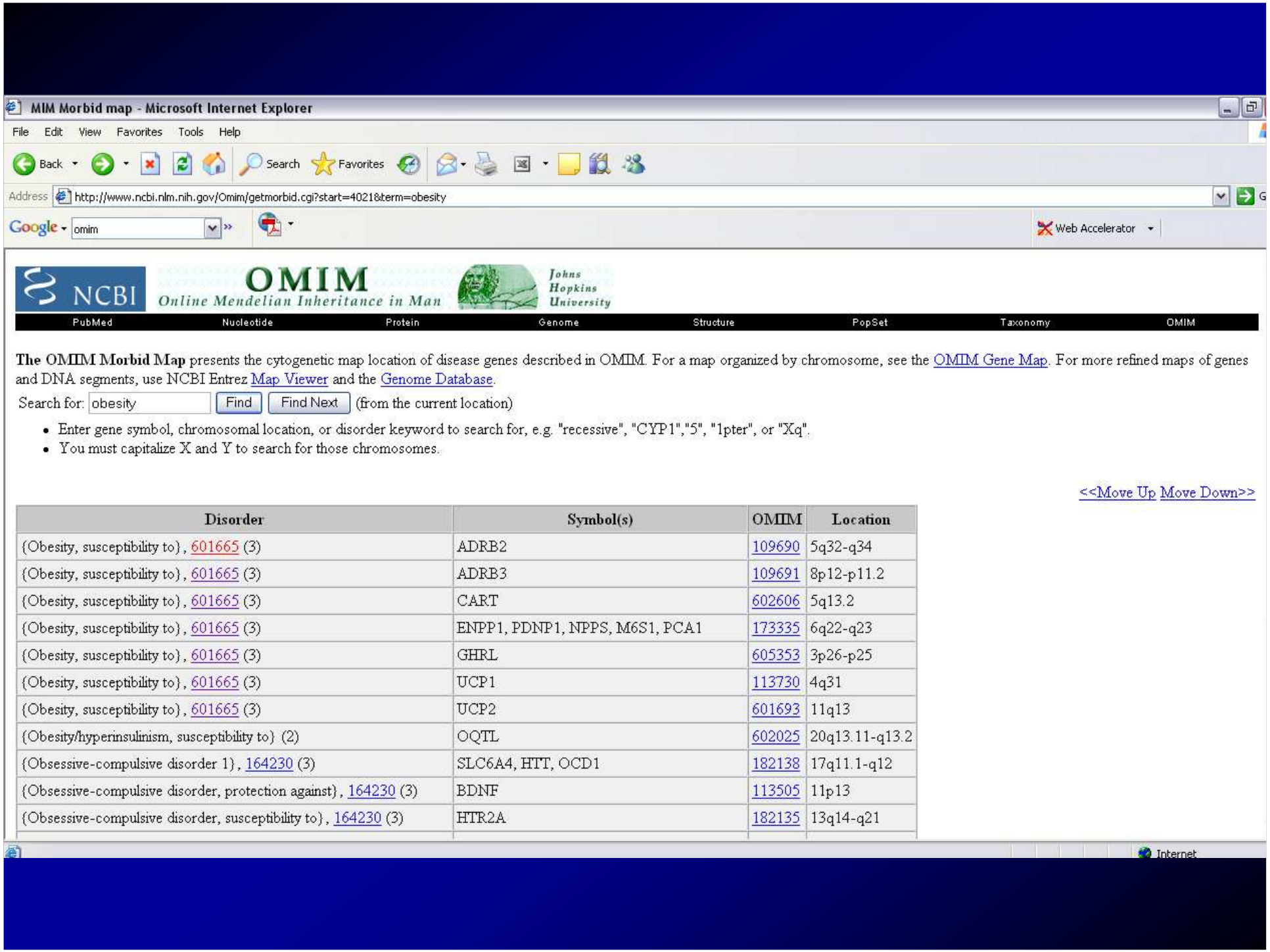
- Enter gene symbol, chromosomal location, or disorder keyword to search for, e.g. "CYP1", "5", "1pter", "Xq", or "alzheimer".
- You must capitalize X and Y to search for those chromosomes.

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)


MIM Morbid map - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.ncbi.nlm.nih.gov/Omim/getmorbid.cgi?start=0&term=huntington
Google omim
Web Accelerator
NCBI
OMIM
Online Mendelian Inheritance in Man
Johns Hopkins University
PubMed Nucleotide Protein Genome Structure PopSet Taxonomy OMIM
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
Internet



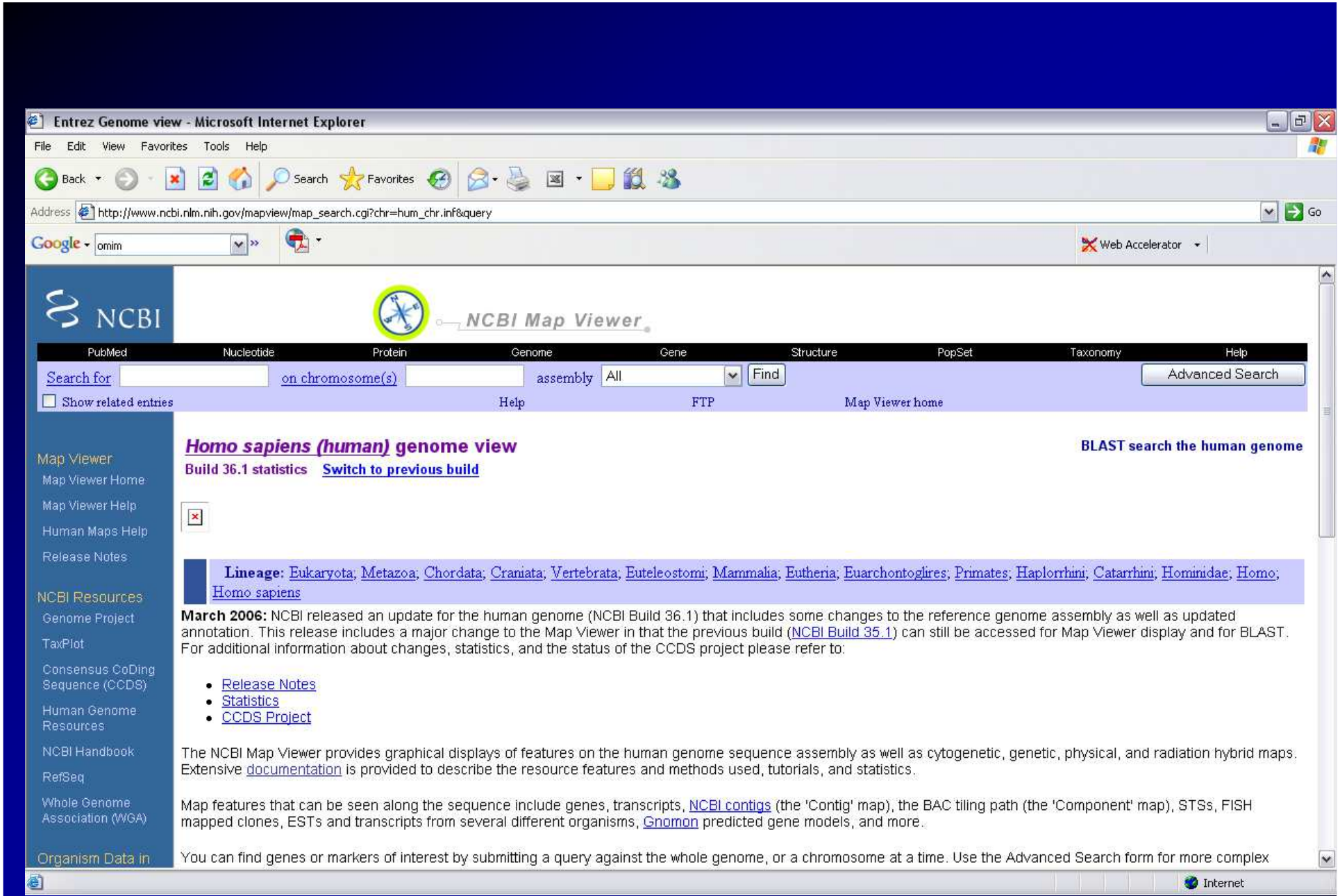
The OMIM Morbid Map presents the cytogenetic map location of disease genes described in OMIM. For a map organized by chromosome, see the OMIM Gene Map. For more refined maps of genes and DNA segments, use NCBI Entrez Map Viewer and the Genome Database.

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
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Web Accelerator
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NCBI Map Viewer
PubMed Nucleotide Protein Genome Gene Structure PopSet Taxonomy Help
Search for
on chromosome(s)
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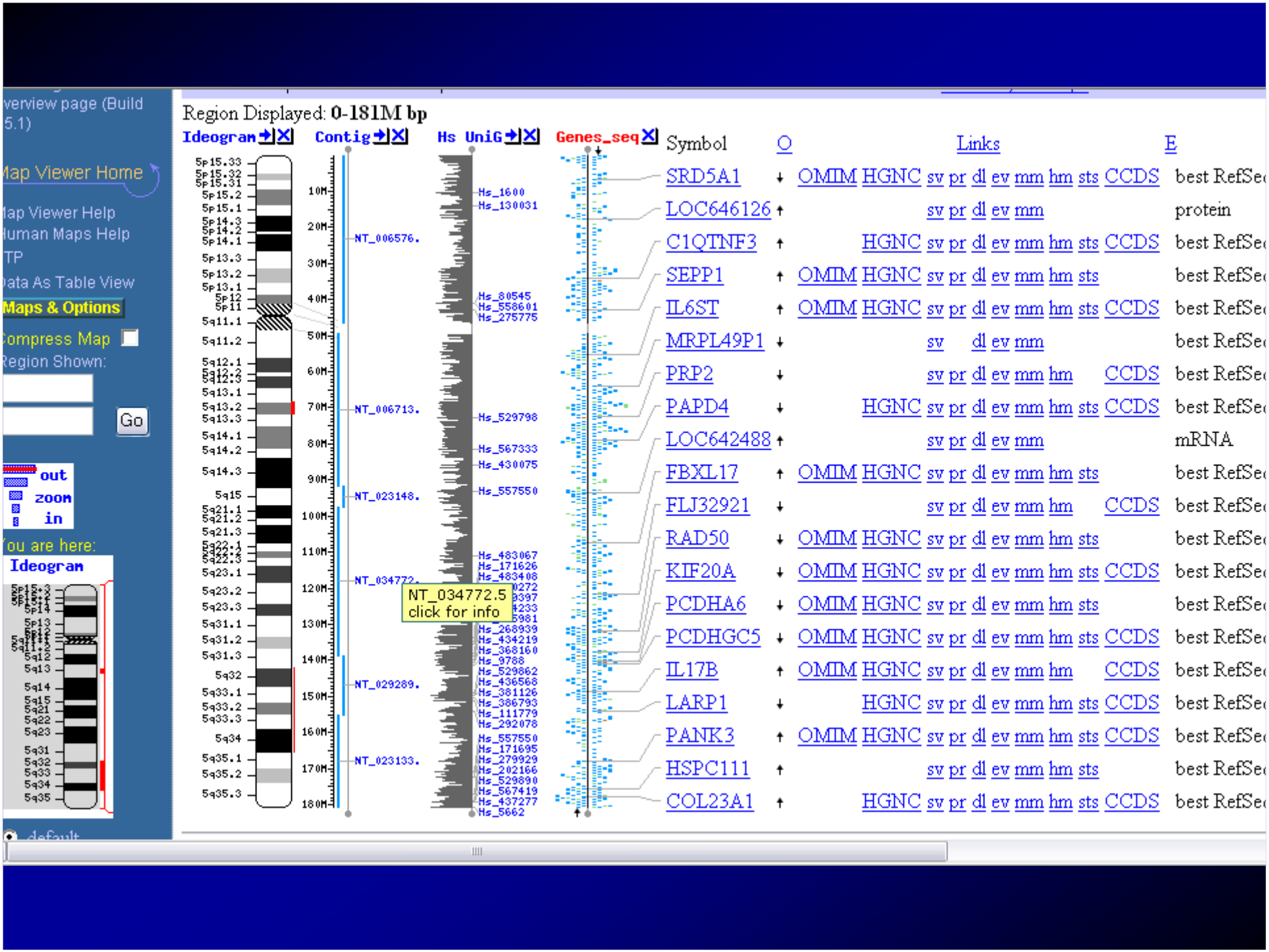
Advanced Search
Show related entries
Help FTP Map Viewer home
Map Viewer
Map Viewer Home
Map Viewer Help
Human Maps Help
Release Notes
NCBI Resources
Genome Project
TaxPlot
Consensus CoDing Sequence (CCDS)
Human Genome Resources
NCBI Handbook
RefSeq
Whole Genome Association (WGA)
Organism Data in
Homo 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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Map Viewer Home
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NT_034772.
NT_029289.
NT_023133.
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SRD5A1 OMIM HGNC sv pr dl ev mm hm sts CCDS best RefSe
LOC646126 sv pr dl ev mm protein
C1QTNF3 HGNC sv pr dl ev mm hm sts CCDS best RefSe
SEPP1 OMIM HGNC sv pr dl ev mm hm sts best RefSe
IL6ST OMIM HGNC sv pr dl ev mm hm sts CCDS best RefSe
MRPL49P1 sv dl ev mm best RefSe
PRP2 sv pr dl ev mm hm CCDS best RefSe
PAPD4 HGNC sv pr dl ev mm hm sts CCDS best RefSe
LOC642488 sv pr dl ev mm mRNA
FBXL17 OMIM HGNC sv pr dl ev mm hm sts best RefSe
FLJ32921 sv pr dl ev mm hm CCDS best RefSe
RAD50 OMIM HGNC sv pr dl ev mm hm sts best RefSe
KIF20A OMIM HGNC sv pr dl ev mm hm sts CCDS best RefSe
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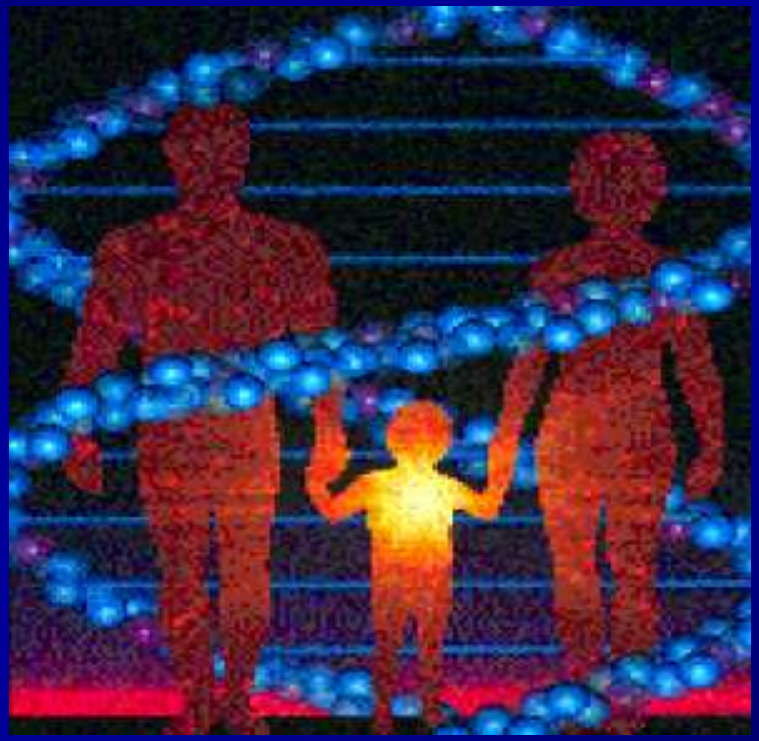
PCDHGC5 OMIM HGNC sv pr dl ev mm hm sts CCDS best RefSe
IL17B OMIM HGNC sv pr dl ev mm hm CCDS best RefSe
LARP1 HGNC sv pr dl ev mm hm sts CCDS best RefSe
PANK3 OMIM HGNC sv pr dl ev mm hm sts CCDS best RefSe
HSPC111 sv pr dl ev mm hm sts best RefSe
COL23A1 HGNC sv pr dl ev mm hm sts CCDS best RefSe

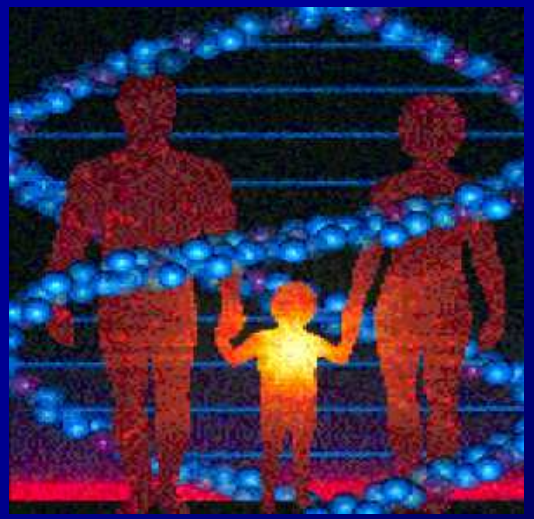
url per bioinformatica IN GENETICA MEDICA

- OMIM
- http://www.ncbi.nlm.nih.gov/omim
- NCBI
- http://www.ncbi.nlm.nih.gov/
- GENECARDS
- http://www.genecards.org/
- GENEREVIEWS
- http://www.ncbi.nlm.nih.gov/sites/GeneTests/review?db=GeneTests
- ORPHANET
- http://www.orphanet-italia.it/national/IT-IT/index/homepage/
- EUCERD
- http://www.eucerd.eu/

ETICA IN GENETICA MEDICA



Introduciamo il concetto di BioEtica



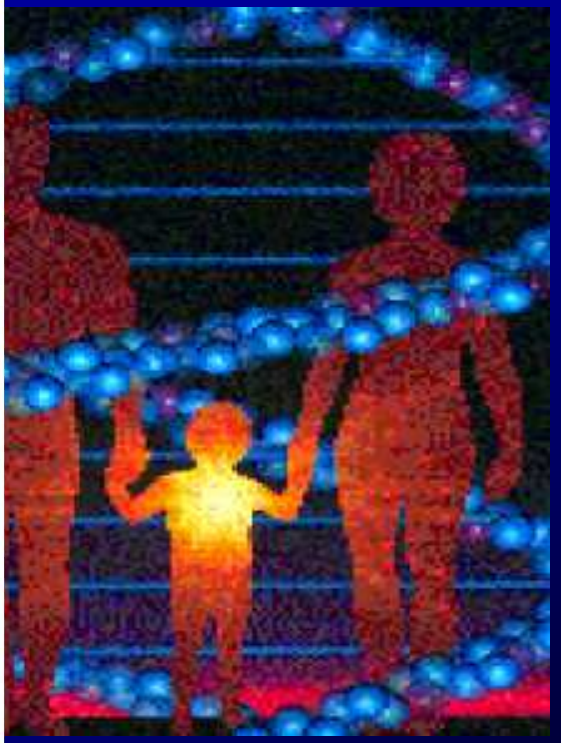
BioEtica : le origini

Quali sono le origini della bioetica?

1. Il *Codice di Norimberga* (1947) con la condanna di ogni **sperimentazione** sull'uomo senza il suo consenso

2. Allarme suscitato da talune **sperimentazioni** negli USA

3. La *Dichiarazione di Helsinki* sulla **sperimentazione** clinica (1964-2000)



BioEtica: il termine

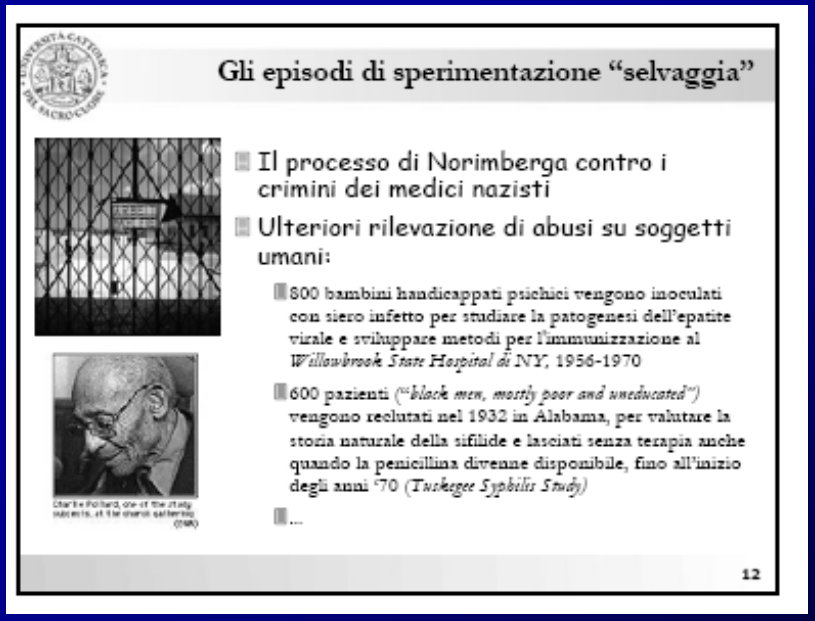
Chi ha coniato il termine *Bioetica?*

- 1970-71: **l'oncologo americano V. R. POTTER**
  - prima volta del termine "BIOETICA"
    - 1970 - *Bioethics. The science of survival*
    - 1971 – *Bioethics. Bridge to the future*

– Di fronte al pericolo per la sopravvivenza dell'intero ecosistema, la BIOETICA come "una nuova disciplina che combinasse la conoscenza biologica con la conoscenza del sistema dei valori umani"

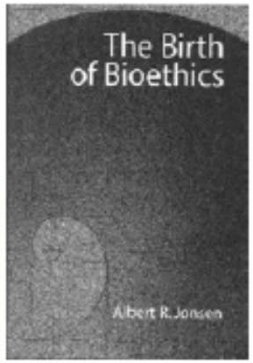
•Un "ponte" tra due culture: scientifica e umanistica

BioEtica e sperimentazione



BioEtica e genetica

A parte il nome … i problemi che portarono allo sviluppo della bioetica. 2



- **La sperimentazione sull'uomo**
- **Le scoperte della genetica**

La genetica e la nascita della *Bioetica*

- *Stanford University, inizi degli anni '70:* programmazione di esperimento di integrazione nell'*Escherichia Coli del genoma del virus SV40 (tumori nella scimmia, non infettivo per l'uomo, in associazione a tumori cerebrali)*

  Interrogativi:

  1) Se l'E.Coli fosse sfuggito al controllo?
  2) Se avesse infettato i ricercatori?
  3) Se si fossero scatenate epidemie di cancro?

  L'ESPERIMENTO NON FU PIÙ ESEGUITO!

- La genetica entra nei Parlamenti: audizioni di scienziati e ricercatori (lo stesso Watson nel 1971, che illustra gli enzimi di restrizione)

Genetica e bioetica nel terzo millennio

I pericoli delle biogenetica: la storia

- Piano **eugenetico nazista**: eliminazione degli ebrei abitanti in Europa, dei gruppi "inferiori" e di quelli "difettosi"
- "Legge di sterilizzazione genetica": sterilizzazione di 225.000 persone per ordine della Corte di Sanità Ereditaria
- Leggi di Norimberga, 1935: piano diventa esplicitamente antisemita, proibiti i matrimoni tra persone di provenienza etnica differente
- 1939: programma di eutanasia per gli individui "inutili"

Principi guida per i test genetici

- Tutela della confidenzialità dei dati, rispetto dell'autonomia personale, conoscenza più approfondita della genetica, previsione di beneficio, equità d'accesso (President's Commission, *Linee guida*, 1981)
- Screening genetici obbligatori: mai per ottenere un *pool* genetico sano o una riduzione dei costi sanitari

Documenti internazionali

- Consiglio d'Europa, *Convenzione di bioetica* : "Non si potrà procedere a *test predittivi di malattie genetiche* o che permettano di *identificare il soggetto come portatore* di un gene responsabile di una malattia o di scoprire una predisposizione o suscettibilità genetica ad una malattia, se non *a fini medici o di ricerca medica*, e sotto riserva di un *counseling genetico appropriato*"

Terapie geniche

- Somatiche: si interviene sul patrimonio genetico di cellule dell'organismo (soma=corpo)

- Germinali: si interviene nelle prime fasi di formazione dello zigote o dell'embrione, o sui gameti, e si elimina il difetto genetico, trasmettendo così la modificazione anche agli eventuali discendenti

A favore delle terapie geniche

- Dovere di cura
- utilità terapeutica
- efficienza preventiva
- rispetto della scelta autonoma delle coppie
- rispetto della libertà della ricerca

Contro l'uso delle terapie geniche

- Imprevedibilità dei rischi
- effetti sulle generazioni future
- costi alti delle pratiche: questioni di giustizia?
- integrità del patrimonio genetico
- "pendio scivoloso": da cura a manipolazione?
- Eugenetica?
- Confine terapia - potenziamento?
- Discrimine salute - malattia?

La clonazione

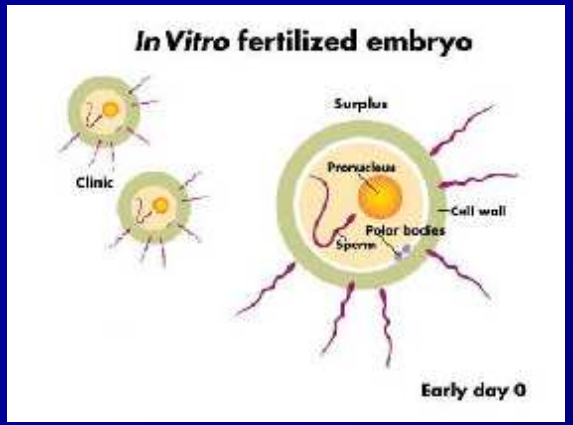
Anno II Numero 29 del 21 Febbraio 2003

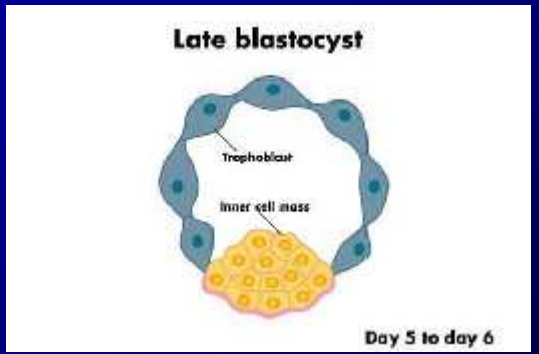
Articolo

Gb. E' morta Dolly, un mito, la prima pecora clonata

La clonazione

- Clone: dalla biologia vegetale, la talea, che può duplicare un'intera pianta (greco *clon* = germoglio)
- "Clonazione": tecniche di laboratorio che comportano la produzione di un insieme di individui (molecole di DNA, cellule o interi organismi) derivanti per duplicazioni successive da un unico progenitore, di cui risultano copie identiche
- Febbraio 1997, Roslin Institute, Edimburgo: Ian Wilmut pubblica i risultati dell'esperimento di clonazione di un agnellino, la pecora Dolly (per trasferimento nucleare)





Tecniche di clonazione

- Clonazione per scissione embrionale: formazione di più embrioni per separazione delle cellule, all'inizio della divisione (*embryo splitting*)

- Clonazione per trapianto/trasferimento nucleare: inserimento del nucleo di una cellula somatica in un ovocita enucleato

Genetica medica: luci e ombre

- Consulenza genetica e diagnosi prenatale
- Le malattie ereditarie
- Test genetici
- La rivoluzione del progetto genoma

Conclusioni – l'importanza della consulenza genetica

L' obiettivo della consulenza genetica è quello di aiutare il consultante, la coppia o la famiglia a….

- comprendere le informazioni mediche, inclusa la diagnosi, la prognosi e le terapie disponibili
- rendersi conto del contributo ereditario alla malattia e del rischio di ricorrenza
- prendere le decisioni che sembrano appropriate in rapporto al rischio di ricorrenza, ai progetti familiari, agli standard etici e religiosi e ad agire in accordo con queste decisioni
- ottenere il miglior possibile adattamento alla malattia (in un soggetto affetto) o al rischio di ricorrenza

Ogni consulenza è un caso a sé, con problematiche diverse legate sia alla patologia sia alla particolare situazione di chi richiede la consulenza

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•Un "ponte" tra due culture: scientifica e umanistica

TEST GENETICI : ASPETTI ETICI
"GENI e SREGOLATEZZA"?

Il mito delle perfezione

Il "PACCHETTO BAMBINO SANO" IN DIAGNOSI PRENATALE

- Effetto della riduzione della fitness Darwiniana nella popolazione Caucasica (riduzione del numero medio di figli)
- Conseguente investimento emotivo e sociale nell'unica gravidanza
- Tendenza ad uniformare socialmente (social mimicry) il proprio bambino alle aspettative della società
- Ruolo dei Media sulla informazione di strumenti preventivi
- Aumento dell'offerta di test genetici > aumento della richiesta

PROBLEMI

Se i test genetici **non sono esaustivi** (detection rate # 99%)

-possono comunque generare un falso senso di sicurezza nella coppia

-non sono considerati "affidabili"

TEST GENETICI : ASPETTI ETICI
GENI e REGOLATEZZA?

Il mito della conoscenza
Test genetici razionali e razionalizzati

-esami esaustivi >> detection rate vicina al 100%
-tecniche diagnostiche validate e armonizzate con le linee guida europee
-abbattimento dell'errore diagnostico tramite tecniche non PCR-BASED
-costi sostenibili
-offerta test genetici :
a chi?
quando?

TEST GENETICI
A CHI POSSONO ESSERE RIVOLTI E QUANDO?

TEST GENETICI SUL PRODOTTO DEL CONCEPIMENTO

PROS

TEST SINGOLO

IDENTIFICAZIONE DI MUTAZIONI "DE NOVO"

CONS

-INVASIVO

-PROBLEMI INTERPRETATIVI (POLIMORFISMI, NUOVE VARIAZIONI)

-PROBLEMI TECNICI (LEGATI ALL'UTILIZZO DEL MATERIALE FETALE)

TEST GENETICI SULLA COPPIA

CONS

TEST DOPPIO

PROS

-ESEGUIBILE SIA IN EPOCA PRECONCEZIONALE CHE PRENATALE

-NON COINVOLGE IL FETO

-NON IDENTIFICA MUTAZIONI "DE NOVO"

-GESTIONE EMOTIVA DEL RISULTATO

-GESTIONE DELLE CONSEGUENZE

LA GENETICA DEL TERZO MILLENNIO HIGHTHROUGHPUT OMIC ANALYSIS

- Harmonizing genetic testing across Europe
- Harmonizing guidelines for genetic testing across Europe

EMQN
The European Molecular Genetics Quality Network

EuroGentest

ESHG

http://www.eurogentest.org/

COSTI A CONFRONTO

Table 1 Second-generation DNA sequencing technologies

	Feature generation	Sequencing by synthesis	Cost per megabase	Cost per instrument	Paired ends?	1° error modality	Read-length	References
454	Emulsion PCR	Polymerase (pyrosequencing)	~$60	$500,000	Yes	Indel	250 bp	14,20
Solexa	Bridge PCR	Polymerase (reversible terminators)	~$2	$430,000	Yes	Subst.	36 bp	17,22
SOLiD	Emulsion PCR	Ligase (octamers with two-base encoding)	~$2	$591,000	Yes	Subst.	35 bp	13,26
Polonator	Emulsion PCR	Ligase (nonamers)	~$1	$155,000	Yes	Subst.	13 bp	13,20
HeliScope	Single molecule	Polymerase (asynchronous extensions)	~$1	$1,350,000	Yes	Del	30 bp	18,30

The pace with which the field is moving makes it likely that estimates for costs and read-lengths will be quickly outdated. Vendors including Roche Applied Science, Illumina, and Applied Biosystems have major upgrade releases currently in progress. Estimated costs-per-megabase are approximate and inclusive only of reagents. Read-lengths are for single tags. Subst., substitutions; indel, insertions or deletions; del, deletions.

nature biotechnology

SCREENING GENETICI?

PATOLOGIE MENDELIANE PROPONIBILI PER SCREENING PRECONCEZIONALI O PRENATALI DI COPPIA IN BASE ALL'INICIDENZA

AMIOTROFIA SPINALE (SMA) 1:10.000

FIRBOSI CISTICA 1:2.000-1:6.000

TALASSEMIA 1/250 **

SORDITA' EREDITARIE (TUTTE CIRCA 35 GENI) 1/1000 nati

DISTROFIE MUSCOLARI (TUTTE, CIRCA 70 GENI) 1:10.000

E LE PATOLOGIE POLIGENICHE?

MAJOR GENES

GENE SUSCETTIBILITA'

POTENZIALMENTE COINVOLGONO CIRCA IL 50% DELLA POPOLAZIONE

MA A TUTT'OGGI

DATI SCIENTIFICI NON SUFFICIENTI PER LA PREDICIBILITA' DEL FENOTIPO

OCCORRE UNA QUANTIFICAZIONE DELLA PENETRANZA ACCURATA
CHE SIA IN GRADO DI STABILIRE
IL REALE RISCHIO DI SVILUPPARE LA PATOOGIA

Se i geni sono regolati…

- Come “gestire” i test genetici “senza sregolatezza”??
- La Genetica medica deve avere delle linee guida?
- I test genetici devono essere offerti a tutti (principio di autonomia)?
- Quali sono i costi sostenibili per i test genetici?
- Può il sistema sanitario naizionale sostenere questi cosi?
- Se sì, per quali “livelli di rischio”?
- Quale rapporto fra pubblico e privato?
- RIFLESSIONI……..

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- Come “gestire” i test genetici “senza sregolatezza”??
- La Genetica medica deve avere delle linee guida?
- I test genetici devono essere offerti a tutti (principio di autonomia)?
- Quali sono i costi sostenibili per i test genetici?
- Ruolo dei LEA (livelli essenziali di assistenza) nell’offerta SSN dei test genetici
- Può il SSN sostenere questi cosi?
- Se sì, per quali “livelli di rischio”?
- Quale rapporto fra pubblico e privato?
- RIFLESSIONI……..

GENI E SREGOLATEZZA

- STIAMO ANDANDO VERSO….
- **Capacità di sequenziare l'intero genoma di 1 individuo (300 milioni di basi) in 48 ore con un costo di 1000 euro**

- CHE RIFLESSIONI FARE?
- QUALI LE RIPERCUSSIONI SULLA SANITA' PUBBLICA?
- QUALI RIPERCUSSIONE SULLA BIOETICA?