The Celera Discovery System™

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Received October 9, 2001; Revised and Accepted November 21, 2001

ABSTRACT

The Celera Discovery System™ (CDS) is a web-accessible research workbench for mining genomic and related biological information. Users have access to the human and mouse genome sequences with annotation presented in summary form in BioMolecule Reports for genes, transcripts and proteins. Over 40 additional databases are available, including sequence, mapping, mutation, genetic variation, mRNA expression, protein structure, motif and classification data. Data are accessible by browsing reports, through a variety of interactive graphical viewers, and by advanced query capability provided by the LION SRS™ search engine. A growing number of sequence analysis tools are available, including sequence similarity, pattern searching, multiple sequence alignment and Hidden Markov Model search. A user workspace keeps track of queries and analyses. CDS is widely used by the academic research community and requires a subscription for access. The system and academic pricing information are available at http://cds.celera.com.

A REFERENCE GENOME PROVIDES AN ANCHOR FOR BIOLOGICAL INFORMATION

Prior to the availability of complete genomes, annotation of genome features, genes and gene products was fragmented, redundant and difficult to organize and efficiently interpret. With a genome assembly available, however, a reference axis exists upon which any type of annotation can be layered. Not only can genomic features such as genes, repeats and map markers be placed upon such a reference axis, but it is also possible to accurately map a variety of other tangential data, such as genetic variation [single nucleotide polymorphisms (SNPs) and mutations], genetics (phenotypes and disease), regulatory signals, mRNA expression [in the form of ESTs, expression tags such as SAGE (1) and MPSS signatures (2), and oligonucleotides from arrays], gene duplication and orthology to genes in other genomes, various ontologies and structures. A major benefit of such feature mapping is that each of these annotations can be cross-referenced to each other. The Celera Discovery System™ takes advantage of this fact to allow users to view and track a wealth of biological information associated with genomes and to enable complex queries across multiple data types.

For this approach to be effective, the genome must be accurately and substantially assembled. A few percent of the genome may be contained in gaps as long as the position and approximate size of the gaps is known. The whole genome shotgun method (3) used by Celera to sequence the human and mouse genomes results in a genome assembly with such characteristics. Briefly, the method results in contigs (regions of ungapped sequence) that are ordered and oriented by mate-pairs (sequence reads from the opposite ends of the same clone) into scaffolds. Sequence gaps within the scaffolds are generally in repeat regions, of known size and most are <2000 bases in size. Over 96% of the human and 95% of the mouse genome have been placed in scaffolds >100 000 bases. Expert annotators examine the scaffolds in an adjacency graph and manually determine correct edges, removing false links and producing a tiling graph. Scaffolds are then mapped to chromosomes using STS markers and these mappings are curated for consistency. If mapping ambiguities cannot be resolved or there is insufficient information to precisely map scaffolds, they are either placed in their approximate position in the assembly (and marked as having low supporting evidence) or in an ‘unmapped’ bin. Over 98% of the human genome and 94% of the mouse genome have been mapped to chromosomes.

Scaffolds are used as input to the gene annotation process. This process uses an automated pipeline called *Otto* (3) to identify exon boundaries and assign putative functions and classifications. A process of expert curation is applied to all predicted genes and refines both the exon structure and function predictions. Curators examine all of the supporting data and make judgments based upon preponderance of evidence. One measure of improvement of the gene structure is a transcript that is a better match to a known protein than the one computationally predicted. Of the roughly 45 000 predicted genes (3), <20% were left unchanged after the expert curation step, highlighting the importance of this process. At this time, all of the predicted human genes have been subjected to expert curation and the curation process for mouse genes is underway.

Tracking changes in sequences and annotation

A sequenced genome is not a static object. Assembly and annotation processes are imperfect and improvements in them often lead to significant refinements of the data. When new sequence data becomes available, or improvements are made to the assembly process, a new assembly may be created.

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When an assembly is updated or new map markers become available, the mapping of the assembly to chromosomes may need to be updated. Each time an assembly is updated, the annotation must be checked to see if it is affected. When new experimental evidence becomes available, annotation must be checked to see if new genes might be discovered or information on previously annotated genes might be updated.

Keeping track of such changes is a complex operation. The standard solution to the updating problem has traditionally been to recalculate assemblies and annotation and then perform a swap of the new data for old. This process is unsustainable for maintaining up-to-date annotation on the human or other complex genomes. If a feature changes in any way, the history of the feature must be maintained so that users of the original feature can update their views of the genome.

Celera has addressed this issue by implementing processes for tracking changes in sequences and annotation. CDS users who have an interest in a particular scaffold can enter its identifier (GA, or Genome Axis) in any appropriate query form in the system. If that sequence has changed due to an update in the assembly or for any other reason, the user will be pointed to the new sequence that replaces the older one. The old sequence is available as a FastA-format file, so that the user can compare it with the newer sequence. All features on the genome are recomputed and placed on new assemblies, so queries by map markers, SNPs or genes will take the user to the latest sequence.

Annotation is also tracked forward at the gene, transcript and protein level. Changes may occur in one of these biomolecules at two levels:

1. Sequence: the actual sequence of the gene, transcript or protein has changed. This may be due to the release of a new assembly, incorporation of new computational evidence or expert curation of the data.
2. Annotation: the annotation associated with the gene, transcript or protein has changed. This may be due to new computational evidence or expert curation of the data. Annotation changes include mapping information (gene), external evidence (transcripts, proteins), functional classifications (proteins) and domain information (proteins) associated with a record.

In some cases, two or more sequence features may merge into a single new feature (merge) or a feature may break into multiple new features (split). The mapping of these relationships is also tracked. History pages are available on each BioMolecule Report (see below) and display the date and type of change, a formatted comment about the reason for the change (Assembly Update, Compute Update, Expert Reviewed), and a link to a FastA-format file of the obsolete record.

GENOME NAVIGATION IN CDS

CDS offers a number of ways to retrieve information about a genome. These include query and browse functions at the level of chromosomes, genes, transcripts, proteins and SNPs. All of the genome annotations are cross-referenced in CDS and are accessible from a number of different routes. At the highest level, users can query or browse the genome itself, retrieving genomic sequences, feature maps or lists of genes from any chromosomal region. At a more detailed level, users can query any biological molecule (gene, transcript, protein) by any of its characteristics, retrieving gene lists or BioMolecule Reports.

Genome Assembly

The Genome Assembly query function in CDS allows users to query relationships among chromosomes and scaffolds. The user may select an entire chromosome, optionally select a sub-region, and filter scaffolds by size. The query returns a Chromosome Map Report that lists scaffolds ordered by location on the chromosome. The GA, location, orientation and length of each scaffold is returned in the scaffold list. The GA links to a Scaffold Report that lists 500 000-base regions of the scaffold. The user can retrieve any one of these in turn and launch a BlastN or BlastX query against a variety of databases. The user also has the option of exporting a text file of the sequence, or generating a graphical map of the region or a list of genes contained within the region (see below).

Searching Genome Maps

The CDS Genome Map Query page offers users the ability to create graphical maps of genome features using the MapView applet or create lists of genes within selected boundaries. The parameters from which a user may select include an entire chromosome, or any region defined by cytogenetic bands, map positions using Celera's coordinate system, STS markers or public BAC clones. In addition, users may select a region around a gene, defined by its Celera gene, transcript or protein unique identifier, gene symbol, or RefSeq [National Center for Biotechnology Information (NCBI); www.ncbi.nlm.nih.gov/LocusLink/refseq.html] identifier. In each of the cases mentioned, the user can retrieve a map or list of genes for just the region identified or a region up to 10 million bases in length flanking either side.

If after selecting the desired parameters, the user chooses the Map function, the MapView applet is launched. MapView is an interactive viewer that displays a variety of features and allows zooming and panning across a chromosome (Fig. 1).

Alternatively, if after selecting the desired parameters, the user chooses the Gene List function, a Gene List Report is returned (Fig. 2). This report displays all of the appropriate BioMolecule identifiers (gene, transcript, protein), an assigned gene name, gene symbol, chromosome location and orientation, Panther protein family/subfamily classification, definition from best match to a non-redundant amino acid database (NRAA), and the transcript class. The transcript class is a symbol that defines the amount of evidence in support of the existence of the gene.

BioMolecule Reports

CDS BioMolecule reports are the core information summaries for genes, transcripts and proteins. BioMolecule Reports can be reached from Gene Lists, directly from the MapView applet, and from SNP Reports (see below). The top of each report lists all of the appropriate Celera identifiers for the related molecules, Panther protein family/subfamily classification (see below), the organism, gene name and symbol, any aliases, and the chromosomal location. If there are multiple transcripts for the gene, all identifiers are displayed. The report for a gene contains three sections, referred to as 'tabs', labeled Chromosome, mRNA and Protein. Each tab contains the sequence of the appropriate molecule and the option to launch analysis tools appropriate to that type of molecule. Each tab has a link to the revision history for the sequence and annotation as described above.

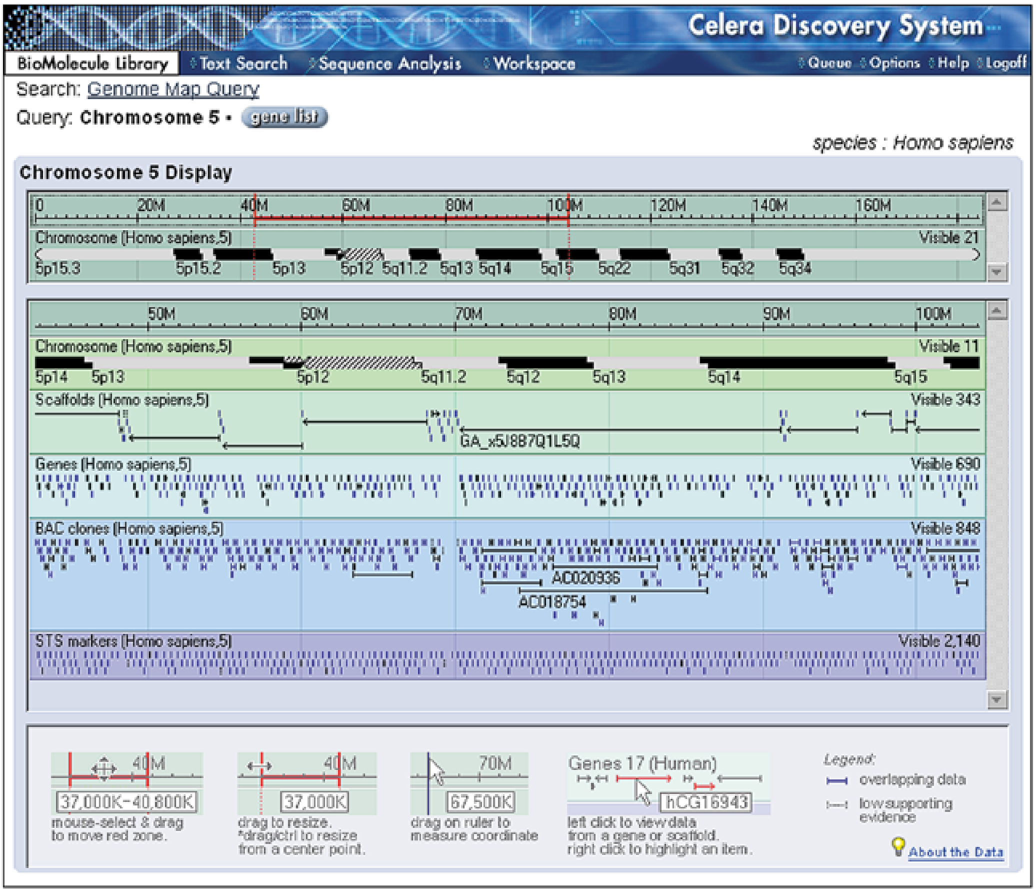


Figure 1. MapView. The MapView applet is divided into two main panels. The upper panel contains a cytogenetic band representation of the entire selected region, a coordinate scale and a pan/zoom bar (red). The lower panel contains a number of panes that represent features contained in the region defined by the pan/zoom bar: cytogenetic bands, scaffolds from Celera's assembly, identified genes, public BAC clones mapped to Celera's assembly and STS markers. The number of visible objects in each pane is reported. Holding the mouse cursor over any object reveals its identifier. Clicking on a gene or scaffold takes the user to a gene BioMolecule Report or Scaffold Report, respectively.

Chromosome tab. The main section of this tab is the MapView applet with a zoomed-in view of the gene of interest. The tab also contains the sequence of the gene, including all exons and introns and up to 10 000 bases upstream and downstream.

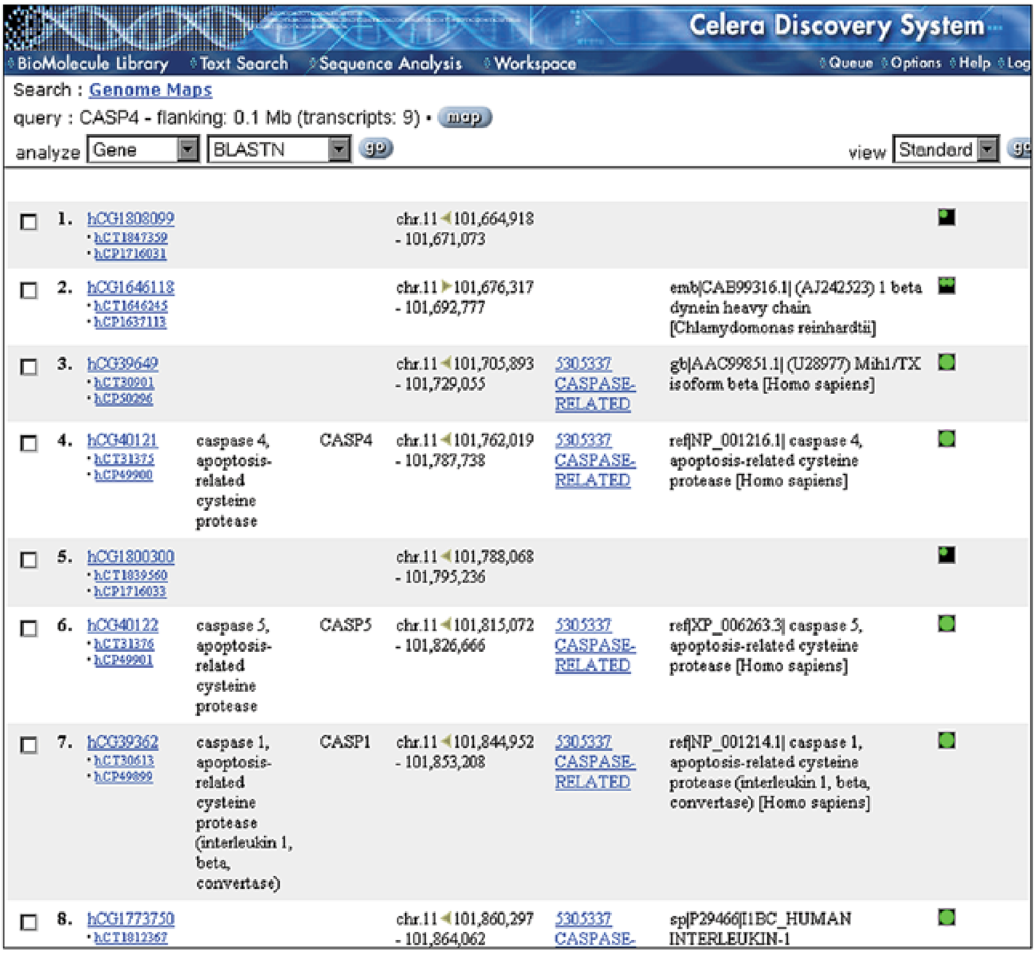
mRNA tab. The main section of this tab is a modified version of the MapView applet that shows the exon structure of the transcript. The confidence in the prediction is represented by the Transcript Class, a measure of the amount of supporting evidence for the transcript structure. These lines of evidence are listed on the tab. Those sequences from Celera and public sources that have the highest sequence similarity to the transcript are listed with the best NRAA match emphasized on the tab. Other sources of matches include Celera's Human Gene Index (clusters of ESTs), rodent ESTs and best protein matches from human and model organisms. Links to the BLAST alignments and the original records for the matches are available. In addition, probable paralogs based upon Celera's LEK clustering method (3) are listed.

Protein tab. This tab (Fig. 3) provides the same access to best sequence matches as the mRNA tab. The Gene Ontology (GO) classifications (4) for cellular process, molecular function and cellular location are presented with links to other proteins in the same categories. In addition, the Panther protein family, subfamily and Panther ontology categories are listed with a link to the Panther Function-Family Browser (see below).

PROTEIN CLASSIFICATION

CDS currently incorporates two methods for classifying proteins. The first uses the full GO to organize proteins by biological process, molecular function and cellular location. The second method is Celera's proprietary Panther system, which is based on a library of over 40 000 Hidden Markov Models (HMMs) that have been assigned by biologist curators to the Panther biological process and molecular function ontologies. The Panther ontology is a simplified version of the full set of GO classification terms, and Celera is working with the GO Consortium to map this ontology to GO.

The primary distinction between the Panther and GO assignments in CDS is the methodology used for assignment. There are two types of GO assignment: computational and expert-curated. The computational approach uses BLAST with a fixed



Search : Genome Maps

query : CASP4 - flanking: 0.1 Mb (transcripts: 9)

analyze Gene BLASTN

view Standard

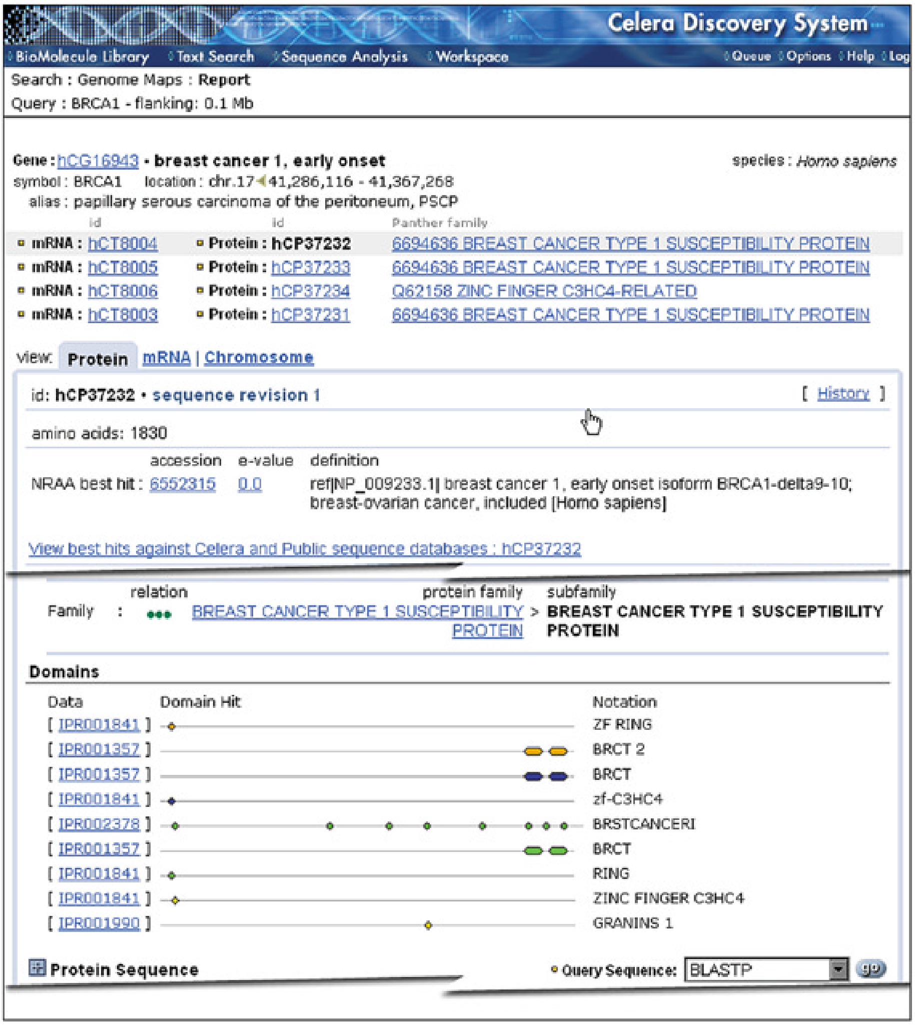
□	1.	hCG1808099 • hCT1847359 • hCP1716031			chr.11 ◀ 101,664,918 - 101,671,073			■
□	2.	hCG1646118 • hCT1646245 • hCP1637113			chr.11 ▶ 101,676,317 - 101,692,777		emb|CAB99316.1| (AJ242523) 1 beta dynein heavy chain [Chlamydomonas reinhardtii]	■
□	3.	hCG39649 • hCT30901 • hCP50296			chr.11 ◀ 101,705,893 - 101,729,055	5305337 CASPASE-RELATED	gb|AAC99851.1| (U28977) Mih1/TX isoform beta [Homo sapiens]	🟩
□	4.	hCG40121 • hCT31375 • hCP49900	caspase 4, apoptosis-related cysteine protease	CASP4	chr.11 ◀ 101,762,019 - 101,787,738	5305337 CASPASE-RELATED	ref|NP_001216.1| caspase 4, apoptosis-related cysteine protease [Homo sapiens]	🟩
□	5.	hCG1800300 • hCT1839560 • hCP1716033			chr.11 ◀ 101,788,068 - 101,795,236			■
□	6.	hCG40122 • hCT31376 • hCP49901	caspase 5, apoptosis-related cysteine protease	CASP5	chr.11 ◀ 101,815,072 - 101,826,666	5305337 CASPASE-RELATED	ref|XP_006263.3| caspase 5, apoptosis-related cysteine protease [Homo sapiens]	🟩
□	7.	hCG39362 • hCT30613 • hCP49899	caspase 1, apoptosis-related cysteine protease (interleukin 1, beta, convertase)	CASP1	chr.11 ◀ 101,844,952 - 101,853,208	5305337 CASPASE-RELATED	ref|NP_001214.1| caspase 1, apoptosis-related cysteine protease (interleukin 1, beta, convertase) [Homo sapiens]	🟩
□	8.	hCG1773750 • hCT1812367			chr.11 ◀ 101,860,297 - 101,864,062	5305337 CASPASE-	sp|P29466|I1BC_HUMAN INTERLEUKIN-1	🟩

Figure 2. Gene List Report. Gene lists can be generated from many places within CDS and display identifiers that link to BioMolecule Reports and other information important to understanding the potential function of the gene product. The protein family assignment links to the Panther Function-Family Browser (Fig. 4). There is an option to view an expanded version of the Gene List, which contains gene aliases and RefSeq and NRAA identifiers with links to GenBank reports.

E-value cut-off to score each predicted protein against a database of sequences that have already been assigned to GO by the Gene Ontology Consortium (http://www.geneontology.org). The set of computational GO assignments for the predicted protein is then defined as the union of all assignments for all GO proteins with a BLAST score above the cut-off. The goal is to provide the user with a list of all possible GO assignments for a given protein (based on sequence similarity), and the approach is therefore much more prone to false positive predictions than false negative. Celera is now in the process of subjecting these computational GO assignments to expert review.

Panther, on the other hand, was designed to avoid the problem of false positive predictions in homology-based function prediction. First, a training set of sequences is clustered into families of related sequences. These families define the set of possible functional inferences for a new family member. The families are divided by expert curators into subfamilies whose members generally share much closer relationships and can all be assigned the same biologically meaningful name, molecular function and biological process(es). Statistical models (HMMs) are built for both families and subfamilies, so that function can be inferred differently for the case of a family-level relationship versus a subfamily-level relationship. For example, a new protein found to have a subfamily-level relationship to cathepsin K can be inferred to be involved in the process *skeletal development*, while a new protein found to have a more distant family-level relationship to the cathepsin-like cysteine protease family could only be inferred to have the molecular function *protease*.

The Panther Protein Library (PPL 3.0) contains over 2200 alignments of related protein sequences (protein families), containing a total of 188 000 non-redundant sequences from a variety of organisms. These families are further subdivided into nearly 40 000 subfamilies of closely related protein sequences. For both families and subfamilies, HMMs are built that describe the shared characteristics (‘signature’) of the member sequences. The Panther HMMs are used to score all protein sequences predicted in a given genome, and therefore give a probabilistic prediction of the protein’s name, molecular function(s) and biological role(s). The Panther ontology covers the higher-level categories of the full GO, but it is designed for



Search : Genome Maps : **Report**
Query : BRCA1 - flanking: 0.1 Mb

Gene : hCG16943 • **breast cancer 1, early onset** species : *Homo sapiens*
symbol : BRCA1 location : chr.17 41,286,116 - 41,367,268
alias : papillary serous carcinoma of the peritoneum, PSCP

id	id	Panther family
mRNA : hCT8004	Protein : **hCP37232**	6694636 BREAST CANCER TYPE 1 SUSCEPTIBILITY PROTEIN
mRNA : hCT8005	Protein : hCP37233	6694636 BREAST CANCER TYPE 1 SUSCEPTIBILITY PROTEIN
mRNA : hCT8006	Protein : hCP37234	Q62158 ZINC FINGER C3HC4-RELATED
mRNA : hCT8003	Protein : hCP37231	6694636 BREAST CANCER TYPE 1 SUSCEPTIBILITY PROTEIN

id: **hCP37232** • **sequence revision 1**

amino acids: 1830

	accession	e-value	definition
NRAA best hit :	6552315	0.0	ref|NP_009233.1| breast cancer 1, early onset isoform BRCA1-delta9-10; breast-ovarian cancer, included [Homo sapiens]

View best hits against Celera and Public sequence databases : hCP37232

		relation	protein family		subfamily
Family	:	●●●	BREAST CANCER TYPE 1 SUSCEPTIBILITY PROTEIN	>	**BREAST CANCER TYPE 1 SUSCEPTIBILITY PROTEIN**

Domains

Data	Domain Hit	Notation
[IPR001841]		ZF RING
[IPR001357]		BRCT 2
[IPR001357]		BRCT
[IPR001841]		zf-C3HC4
[IPR002378]		BRSTCANCERI
[IPR001357]		BRCT
[IPR001841]		RING
[IPR001841]		ZINC FINGER C3HC4
[IPR001990]		GRANINS 1

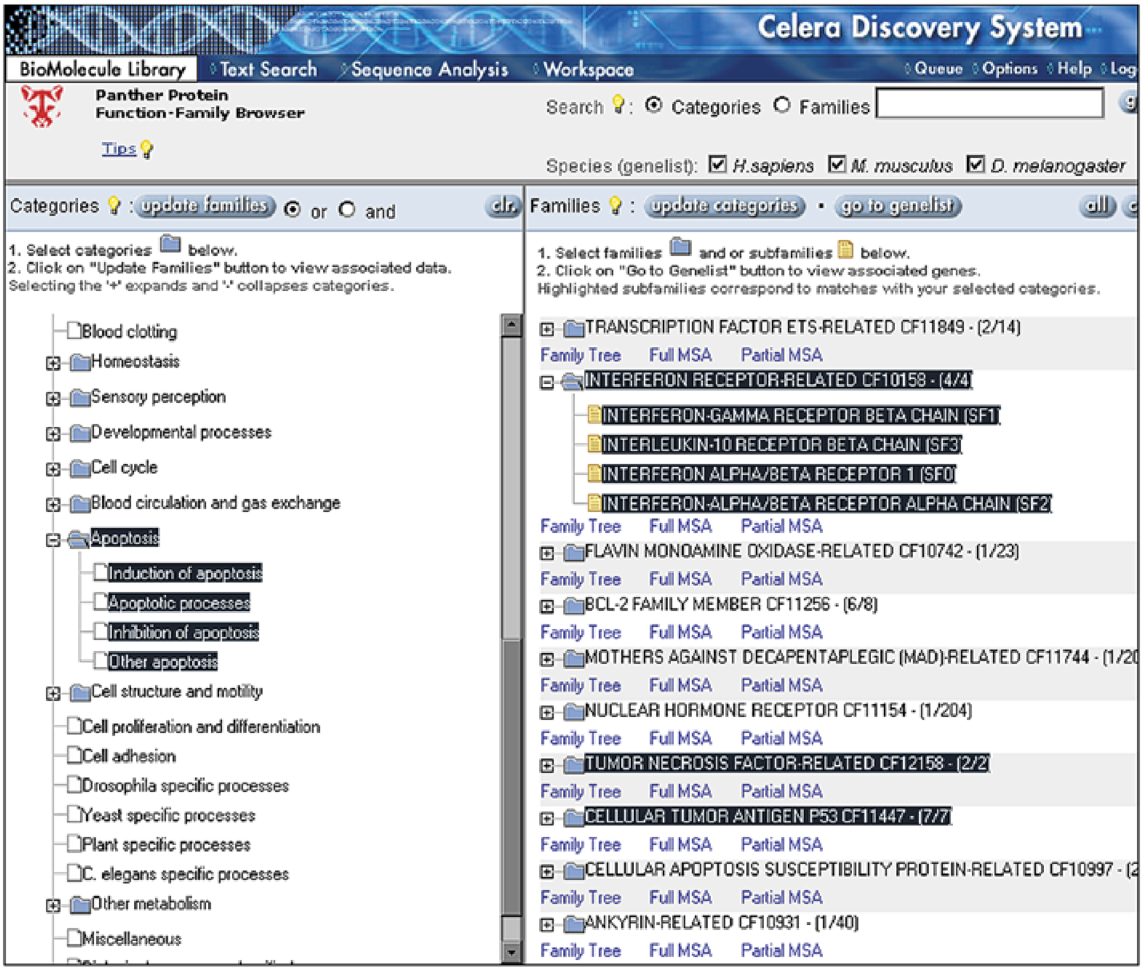
Figure 3. Representative features from a Protein BioMolecule Report. The report for the BRCA1 gene shows that four alternative splice forms have been identified leading to four protein BioMolecule Reports (hCP37232 shown). The GO classification is not shown for brevity.

facilitating navigation and whole genome-level views rather than for detailed annotation vocabulary. Each ontology (molecular function and biological process) contains about 250 categories total in three levels (in contrast, the full GO molecular function hierarchy is up to 12 levels deep and contains nearly 4000 categories).

There are several routes for accessing Panther classifications in CDS. Panther and GO classifications are available on each protein BioMolecule Report (Fig. 3). In addition, the Panther classifications can be browsed directly by using the CDS Protein Function-Family Browser (Panther Browser; Fig. 4). Proteins can be browsed either by molecular function or by biological process, or searched by family or subfamily. The Panther Browser supports creating lists of proteins based on (i) evolutionary relationships at the family level (e.g. all cysteine proteases) or subfamily level (e.g. cathepsin K), and (ii) functional relationships as defined by shared molecular function(s) (e.g. all proteins predicted to be proteases) or biological processes (e.g. all proteins predicted to be involved in skeletal development). Boolean and/or operations are also supported to construct lists of, e.g. all proteases involved in skeletal development. These gene lists contain Panther annotations, are linked to BioMolecule Reports, and can be exported. The Panther Browser view also has links to phylogenetic trees and multiple sequence alignments for each family and subfamily.

The Web Tree Viewer allows users to explore protein family/subfamily relationships in the library of 'distance trees'. The views include both Celera-assigned subfamily annotations and SWISS-PROT and GenBank-assigned sequence-level annotation. The library of multiple sequence alignments highlights positions that are conserved across an entire family as well as subfamily-specific positions, revealing amino acid-level determinants of function and specificity.

The Panther family/subfamily classifications are also used in CDS to enhance BLAST search results. The results are organized by family and subfamily, listing the curated name and functional assignments. This can drastically reduce the amount of data for an end user to sift through (only one sequence per subfamily is shown since they all have the same function) as well as provide additional annotation information from the Panther classification.


Celera Discovery System
BioMolecule Library
Text Search
Sequence Analysis
Workspace
Queue
Options
Help
Log
Panther Protein
Function-Family Browser
Tips
Search : ● Categories ○ Families
Species (genelist): ☑ H.sapiens ☑ M. musculus ☑ D. melanogaster
Categories : update families ● or ○ and
clr.
Families : update categories • go to genelist
all

1. Select categories below.
2. Click on "Update Families" button to view associated data.
Selecting the '+' expands and '-' collapses categories.

- Blood clotting
- ⊞ Homeostasis
- ⊞ Sensory perception
- ⊞ Developmental processes
- ⊞ Cell cycle
- ⊞ Blood circulation and gas exchange
- ⊟ Apoptosis
  - Induction of apoptosis
  - Apoptotic processes
  - Inhibition of apoptosis
  - Other apoptosis
- ⊞ Cell structure and motility
- Cell proliferation and differentiation
- Cell adhesion
- Drosophila specific processes
- Yeast specific processes
- Plant specific processes
- C. elegans specific processes
- ⊞ Other metabolism
- Miscellaneous

1. Select families and or subfamilies below.
2. Click on "Go to Genelist" button to view associated genes.
Highlighted subfamilies correspond to matches with your selected categories.

- ⊞ TRANSCRIPTION FACTOR ETS-RELATED CF11849 - (2/14)
  Family Tree Full MSA Partial MSA
- ⊟ INTERFERON RECEPTOR-RELATED CF10158 - (4/4)
  - INTERFERON-GAMMA RECEPTOR BETA CHAIN (SF1)
  - INTERLEUKIN-10 RECEPTOR BETA CHAIN (SF3)
  - INTERFERON ALPHA/BETA RECEPTOR 1 (SF0)
  - INTERFERON-ALPHA/BETA RECEPTOR ALPHA CHAIN (SF2)
  Family Tree Full MSA Partial MSA
- ⊞ FLAVIN MONOAMINE OXIDASE-RELATED CF10742 - (1/23)
  Family Tree Full MSA Partial MSA
- ⊞ BCL-2 FAMILY MEMBER CF11256 - (6/8)
  Family Tree Full MSA Partial MSA
- ⊞ MOTHERS AGAINST DECAPENTAPLEGIC (MAD)-RELATED CF11744 - (1/20
  Family Tree Full MSA Partial MSA
- ⊞ NUCLEAR HORMONE RECEPTOR CF11154 - (1/204)
  Family Tree Full MSA Partial MSA
- ⊞ TUMOR NECROSIS FACTOR-RELATED CF12158 - (2/2)
  Family Tree Full MSA Partial MSA
- ⊞ CELLULAR TUMOR ANTIGEN P53 CF11447 - (7/7)
  Family Tree Full MSA Partial MSA
- ⊞ CELLULAR APOPTOSIS SUSCEPTIBILITY PROTEIN-RELATED CF10997 - (2
  Family Tree Full MSA Partial MSA
- ⊞ ANKYRIN-RELATED CF10931 - (1/40)
  Family Tree Full MSA Partial MSA

Figure 4. Panther Protein Function-Family Browser for exploring the relationship between protein function and sequence. The Panther ontology can be browsed or searched in the left panel. Protein families and/or subfamilies assigned to the selected categories are displayed in the right panel. Families and subfamilies can be also be searched separately and displayed in the right panel. Gene lists can be created by retrieving all proteins assigned to selected families and subfamilies. For each family, links are provided to a distance tree, sequence-level annotation and multiple sequence alignment.

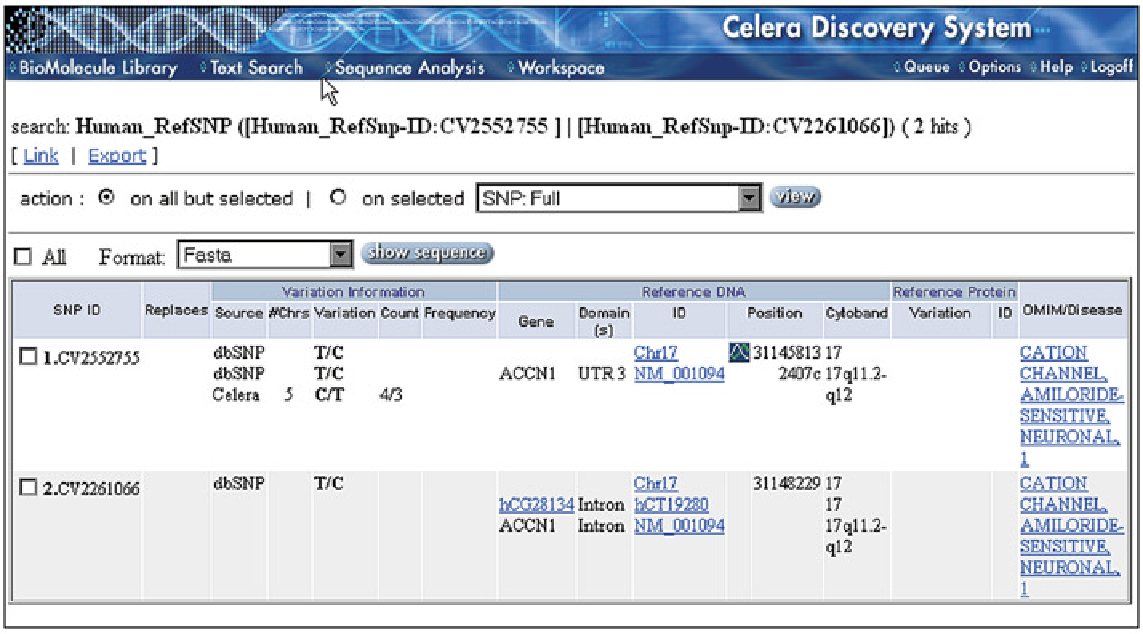
COMPARATIVE GENOMICS

Comparative analysis of genomes can provide major benefits to the study of genomic organization and biological function. Conservation of features, be they genes, genomic organization or even stretches of sequence, can provide clues to previously unidentified features in one of the genomes being examined. They also provide a way to correlate experimental information determined for one species with that of another. Since a variety of features have been mapped to the assembled human and mouse genomes, the opportunity exists to exploit the relationships of these features between the two genomes. An analysis of conserved regulatory regions is available in CDS. Analyses of synteny and orthologous proteins will be available in the near future (see below).

Conserved regulatory regions

The identification of transcription factor binding sites (TFBS) is hampered by the fact that the sites are very short signals having many false positive occurrences in a genome. Leveraging sequence conservation between human and mouse can provide higher confidence identification of TFBS associated with gene regulatory regions. A set of genomic segments conserved between human and mouse (hmCS, or human/mouse conserved segment) were computed from the assembled human and mouse genomes and used to filter a set of vertebrate TRANSFAC (5) binding sites on the human genome assembly. These data were mapped to Celera genes to provide locations (upstream, intron, downstream) relative to the genes. Binding sites contained in coding regions were removed.

The results of this analysis are available in CDS and can be queried using a number of different parameters, including gene and protein name, chromosome, BAC and STS coordinates, human and mouse conserved region unique identifier (hmCS), TFBS name, TRANSFAC position weight matrix, and score. A variety of data views are available to show a summary of results or a more detailed report. A file of hmCS data is available for export in FASTA format and as a BLAST-accessible data set within CDS. The mRNA tab in BioMolecule Reports have a link to a gene regulatory report that provides a list of all TFBS and hmCS data for a given transcript. Lastly, the



search: **Human_RefSNP ([Human_RefSnp-ID:CV2552755] | [Human_RefSnp-ID:CV2261066]) (2 hits)**
[Link | Export]

action : ● on all but selected | ○ on selected SNP: Full

☐ All Format: Fasta

SNP ID	Replaces	Variation Information					Reference DNA					Reference Protein		OMIM/Disease
		Source	#Chrs	Variation	Count	Frequency	Gene	Domain (s)	ID	Position	Cytoband	Variation	ID	
☐ 1.CV2552755		dbSNP dbSNP Celera	 5	T/C T/C C/T	 4/3		 ACCN1	 UTR 3	Chr17 NM_001094	31145813 2407c	17 17q11.2-q12			CATION CHANNEL, AMILORIDE-SENSITIVE, NEURONAL, 1
☐ 2.CV2261066		dbSNP		T/C			 hCG28134 ACCN1	 Intron Intron	Chr17 hCT19280 NM_001094	31148229	17 17 17q11.2-q12			CATION CHANNEL, AMILORIDE-SENSITIVE, NEURONAL, 1

Figure 5. SNP report. The Report displays information such as source (Celera, dbSNP, HGMD), the number of chromosomes sampled, the nucleotide variation, the count and frequency, gene name, structural position, chromosomal location (number, cytogenetic band, scaffold position), links to Celera and RefSeq DNA sequences with location within that sequence, and links to OMIM for disease information associated with the gene. If the SNP is in a coding region, the codon, its position and affected amino acid are displayed. For Celera SNPs, the raw electropherogram data are also available.

MapView applet in the mRNA tab enables users to view hmCS and TFBS data in relation to the transcript, providing a simple way to visualize the spatial organization of these features.

GENETIC VARIATION: THE SNP REFERENCE DATABASE

As a result of applying the whole genome shotgun sequencing method to DNA from five individuals, a number of computationally derived SNPs were generated (3). These were combined with SNPs from the dbSNP database (NCBI; www.ncbi.nlm.nih.gov/SNP/) and put through a series of quality control processes to assure unique mapping to the genome and collapse redundancy. The curated set of mutations from the Human Gene Mutation Database (HGMD) (6) was added to the database. HGMD is a comprehensive collection of data on published germline mutations in nuclear genes underlying human inherited disease. Celera has exclusive commercial distribution rights for this database through CDS.

SNPs are integrated with other Celera annotation, allowing precise placement of the SNP on a chromosome or in a gene. Users can navigate from SNP reports to any of the appropriate BioMolecule Report Tabs. The SNP Reference Database can be queried using a large number of parameters, including unique identifier (CV), chromosome number and location, data source, allele statistics, population of source DNA, gene and protein name, location of SNP within the gene such as intron, exon (silent, missense, nonsense), or regulatory region, affected codon or amino acid, disease or OMIM (NCBI, www3.ncbi.nlm.nih.gov/omim/) identifier, and RefSeq identifier. The results of the query are returned in SNP Reports (Fig. 5). A variety of views are available that show either summary or full-detail information. SNP sequences (the SNP position with 300 nt upstream and downstream) can be exported.

The SNP database requires an additional subscription fee as outlined at http://cds.celera.com.

FUTURE DIRECTIONS

The CDS has been designed to provide access to a wealth of experimental and computationally derived information for completed genomes. Keeping such a system current with all of the new data being generated in the quest to understand biological processes is a task that will continue well into the future. Enhancements are constantly being made to the CDS infrastructure. These include the addition of new databases and analysis tools as well as improvements to query and visualization tools and especially expert curation of datasets.

Celera will also be making significant enhancements to CDS to support mRNA expression research. Users can currently query an extensive EST collection and cDNA library information to retrieve a view of transcript expression patterns. This is being enhanced by the mapping of SAGE and MPSS™ data for additional evidence for gene structures as well as to provide a Body Atlas of tissue expression data. Public identifiers from databases such as RefSeq and UniGene (NCBI, www.ncbi.nlm.nih.gov/UniGene) are being mapped to Celera's transcripts to provide a linkage point for users conducting their own microarray experiments to correlate their results with the annotation available in CDS. Application Programming Interfaces (APIs) are being enhanced to allow commercial expression visualization tools to inter-operate with CDS.

Several methods were employed to identify syntenic genomic regions in the human and mouse genomes, including direct comparison of the DNA sequences and comparison of the predicted proteins from each organism. A set of conserved locations between both genomes, called Syntenic Anchors, was generated by comparing the sequences using BLASTN and identifying hits that are bi-directionally unique between human and mouse.

The density of Syntenic Anchors does not appear to be significantly affected by gene density, making the syntenic anchors an important complement to the orthologous protein pairs. Orthologous protein pairs were determined by either the suffix-tree comparison method, MUMmer (7), or alternatively by matches which have mutual best tBlastX scores.

The results of these analyses will be available in CDS for searching using a variety of parameters. Gene list views will have the ability to display orthologs in another species. BioMolecule Reports will have links to the appropriate orthology or syntenic information for protein and genomic data. MapView is being enhanced to enable the user to load two genomes and view genomic scaffolds, syntenic anchors, genes and orthologous proteins.

CDS is one of several integrated ways that Celera delivers genomic and related data. For example, there is a growing set of APIs which allow access to all of the fields represented on BioMolecule Reports. There is also a Java-client tool, the Genome Browser, which works interactively with CDS. Through applications such as these, Celera is constantly working to improve integration of data generated by users with that delivered by Celera.

ACKNOWLEDGEMENTS

The authors wish to acknowledge the work of a large number of people in the Product Development, Software Engineering, Scientific Annotation, Protein Informatics and Informatics Research Teams at Celera for their contributions to the development of CDS and its content. The authors also wish to thank Sam Broder, Joyce Fuhrmann, Sam Levy, Jason Mollé and Karin Remington for helpful comments on this manuscript.

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