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SNPit: a federated data integration system for the purpose of functional SNP annotation

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Abstract

Genome wide association studies can potentially identify the genetic causes behind the majority of human diseases. With the advent of more advanced genotyping techniques, there is now an explosion of data gathered on single nucleotide polymorphisms (SNPs). The need exists for an integrated system that can provide up-to-date functional annotation information on SNPs. We have developed the SNP Integration Tool (SNPit) system to address this need. Built upon a federated data integration system, SNPit provides current information on a comprehensive list of SNP data sources. Additional logical inference analysis was included through an inference engine plug in. The SNPit web servlet is available online for use. SNPit allows users to go to one source for up-to-date information on the functional annotation of SNPs. A tool that can help to integrate and analyze the potential functional significance of SNPs is important for understanding the results from genome wide association studies.

Keywords

Single nucleotide polymorphisms (SNPs); Public health genetics; Biomedical informatics; Data integration; SNP annotation system; SNP integration system

1. Introduction

The majority of leading human diseases have a genetic component [1]. To understand both the genetic component behind human disease as well as to materialize the vision of predictive,

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Availability and requirements

Project name: SNPit, SNPit homepage: http://www.snpit.org, BioMediator homepage: http://www.biomediator.org, Recommended internet browsers: Firefox or Internet Explorer, Programming language: Java

Authors' contributions

TS designed the mediated schema for the SNPit system, coded the wrappers to the different data sources and the web servlet, and wrote the first draft of this paper. CC provided expertise on SNP annotation, provided the heuristic weights for the decision tree, and guided the development of the project. PTH provided biomedical informatics expertise and guided the development of the project. All authors participated in the drafting of this paper and approved the final draft for submission.

preventive, and personalized medicine [2], scientists and researchers need to focus their attentions on the genetic variation within individuals. Genome wide association studies are a powerful epidemiologic method that allows researchers to detect genetic variation, even those variations with subtle effects [3]. With more advanced genotyping techniques, genome wide association studies result in more and more data on single nucleotide polymorphisms.

Single nucleotide polymorphisms (SNPs) are the most common form of genetic variation in the human genome, comprising about 90 percent of the polymorphism in the genome [4]. SNPs play an important role in genome wide association studies because they act as the primary biomarkers. The location of these biomarkers can be tremendously important in terms of predicting functional significance.

The prediction of functional significance or functional annotation of SNPs is complex. There are a limited number of commercial and public projects out there that deal with SNP annotation (PupaSNPFinder [5], SNPer [6], SNPselector [7], LS-SNP [8], SNP Function Portal [9], SNPLims [10]), they look at a certain subset of possible predictors and they use a data warehouse or pipeline approach to storing data. Some of the previous SNP tools are difficult to use and lack current documentation. Furthermore, to our knowledge, none of the previous SNP tools use a federated database approach, and thus, they run the risk of providing out-of-date information.

In addition to making sure that the data is current, a tool that focuses on SNP annotation must address numerous bioinformatics challenges. These include dealing with large numbers of data sources that are involved in SNP annotation, annotation sources of which scientists might not be aware, and the explosion of data due to the combination of all these data sources.

To address all these challenges, we have created a SNP Integration Tool (SNPit) that uses a comprehensive, federated database approach to look at a wide array of possible functional SNP annotation predictors and we seek to provide an easy-to-use integrated interface as well as some expert rules analysis. In contrast to the above mentioned tools, a federated data integration system does not store the information locally, instead it queries, normalizes, and analyzes the data in real time, providing the benefit of real time retrieval [11,12], though the speed of the query is compromised. In addition, the use of a mediated schema within our data integration system provides a common semantic ontology that is not specific to the individual data sources, thus enabling flexibility when new data sources are added.

2. Implementation

SNP Integration Tool (SNPit) is built upon a pre-existing open source federated data integration system called BioMediator [13]. BioMediator is a data integration system developed by the University of Washington. We decided that BioMediator was the optimal choice for the domain of SNP annotation because it is a federated data integration system, it is easy to query, it is XML-based, and it uses a mediated schema which allows for more flexible data modelling.

BioMediator's main objective is to take information from disparate sources and integrate it together through a multi-tiered system (Figure 1) [12,14]. The researcher issues a single query, and the system gathers the information from the relevant sources. The central component to BioMediator's system is its source knowledge base, which consists of descriptions of the various data sources, mappings from the source to the mediated schema, and the mediated schema itself. The mediated schema is an outline of the data sources' objects and mappings, it can be thought of as an ontology of the entities and relationships in a domain [13]. In addition to the source knowledge base, components of the BioMediator system include wrappers that conduct syntactic translations by translating the returned data results into an XML document,

a metawrapper that conducts semantic translations by mapping the returned XML document onto the mediated schema, and a query processor that queries against the mediated schema.

The BioMediator system has a modular architecture; thus, it is easily extendable to additional analytical tools. One additional component that was added for the SNPit tool was the Java Expert System Shell (Jess) [15] rule-based system plug-in, which permitted us to add logical inference [16]. Jess allowed us to include a declarative programming approach and create new knowledge from a set of rules [17]. The inference engine allowed us to formulate sets of rules over the returned result sets in order to conduct various analyses and filtering of the data.

Much of the challenge when it comes to integrating a large number of data sources is that sometimes the result sets become overwhelming and difficult to understand to a human annotator. Owing to this unsatisfactory situation, we have also begun incorporating expert rules into the BioMediator system to enable proper filtering of data as well as improving the repeatability of the results. For example, it is difficult for a human to continually apply sets of expert-defined rules in a consistent fashion, especially when there are dependencies among rules. Additionally, given the proper framework, rules in the BioMediator system could be easily modified, shared, and applied repeatedly for iterative refinement.

Thus, SNPit builds upon both BioMediator and the Jess plug-in. A mediated schema and wrappers were created to model the different data sources that help to reveal important SNP information. Various data sources have been included such as dbSNP [18], EntrezGene [19], HGMD [20], Haplotter [21], GVS [22], SIFT [23], UCSC [24,25,26], Transfac [27], BDGP [28]. Table 1 includes the list of data sources from which SNPit currently pulls information (Table 1). SNPit is currently available in two different user interfaces: a graph-based visualization tool entitled Touchgraph which is available over the BioMediator website and a web servlet available over the SNPit website. The speed of the queries depends on both the number of SNPs submitted as well as the speed of the individual data sources that SNPit integrates with. Figure 2 demonstrates the components of SNPit with the data sources section, BioMediator section, and interfaces section.

The current version of SNPit includes a query interface, query processor, semantic translation engine, and interfaces to each of the data sources. By collaborating with different experts in both public health genetics and as well as genome sciences, various data sources have been identified that provide functional predictions for SNP annotation. Wrappers have been created to interface with these disparate data sources. A central data model (mediated schema) has been created and the necessary translational rules that translate the source specific data models into the common data model have been written. Implemented in the Protégé [29] ontology editor, Figure 3 is a graphical representation of a subset of the mediated schema, demonstrating the SNP, gene, evolutionary conservation, and splice site entities and the relationships between those entities. The SNPit system comes in two different user query interfaces that allow the users to access the common data model with a particular query: the graphical user interface implemented through TouchGraph [30] as well as a text-based web servlet. Most of our focus was on the development of the web servlet's Internet accessibility; in particular, we designed it for simplicity and ease-of-use. Using the left-hand-side of the interface, a user can query a number of different entities. The user can also examine details of each entity, in text-form, by clicking on the resource.

Data has been collected on a variety of possible prioritization attributes. The Human Gene Mutation Database (HGMD) provides information on whether a particular SNP might be within a gene known to cause an inherited disease. Genomic context, which is defined as whether a SNP is in an intron, exon, promoter, or coding region, is provided by the UCSC Browser's Genscan Gene Prediction track. The UCSC's Tissue Expression track contains information on

a polymorphism's transcriptional expression over 79 human tissues. The ECR Browser captures the evolutionary relationships between the genomes of vertebrates and non-vertebrates. Haplotter tells us about recent positive selection within the human genome of certain SNPs. SIFT returns predictions for which SNPs will affect protein function. Genome Variation Server (GVS) provides information on linkage disequilibrium (LD) between two SNPs, LD is calculated using the Hill method [31]; users can select LD information specific to the population they are studying when querying the LD component of SNPit, HapMap provides the source of the genotype data. SNPit was created for the purpose of human SNP annotation integration and analysis; however, SNP data from other genomes can be queried through SNPit, depending on whether or not those genomes are supported by the data sources that SNPit integrates with. All of the collected functional annotation data enabled us to implement some preliminary inference rules which provide expert system decision ability.

Various publications have confirmed the predictive potential of in silico tools for SNPs in coding regions and evolutionarily conserved regions [32,33]. Prioritization schemes for SNPs based on biological plausibility can already be determined [34]; for example, SNPs in coding regions would be given higher priority over non-coding SNPs. Researchers who manually created and used a similar decision tree with rankings 1, 2, 3, and 4 were able to identify 119 polymorphisms with low or neutral predictive power in a test set of 140 SNPs [35], demonstrating the potential value of prioritization strategies either before or after an association study. In our research, we used a similar approach, though we acknowledge that variations in both the prioritization scheme and heuristic weights are possible.

Preliminary logical inference rules were applied to the returned SNP annotation data by first creating a decision tree building upon biological knowledge [35,34]. The initial decision tree was then vetted and revised as appropriate with the input of two experts, one of whom co-authored this paper; the experts also assigned weighted scores to the functional categories of different SNPs. The scores ranged from 1 to 4, with higher scores indicating a higher predicted relative risk of developing the phenotype. Potentially functional SNPs can be prioritized using different criteria; for example, the type of variant (nonsense, missense, splice site, promoter) can help to provide possible clues to the SNP's biological relevance [34]. Currently, numerous bioinformatics tools access online biological databases and return information on both experimental and epidemiologic evidence; a decision tree was created to reflect the prioritization rankings of SNPS. Figure 4 demonstrates the preliminary rules and heuristic weights assigned to different SNP characteristics; heuristic weights were assigned to each node in the decision tree, with the score of the final node calculated by multiplying the previous nodes in its' path. For example, SNPs that are in a coding region, that are non-synonymous and damaging, have a risk of moderate to very high; a heuristic weight of 3.375 was assigned to this branch of the tree. Using these expert heuristic weights, we were able to create some preliminary rules in Jess that capture the relative rankings of SNPs based on the evidence integrated together through the BioMediator federated integration system (Figure 5). The results of the rankings are then displayed in text-form through the web servlet interface.

3. Results

Using the SNP rs405509 as a user case scenario, the following results can be observed from the different SNPit interfaces.

SNPit Touchgraph Interface

The graphical user interface (GUI) component to SNPit can be accessed as a separate download from the web servlet component. Starting from an initial seed query of rs405509, the GUI expands out to reveal all the different pieces of information collected on rs405509. The different pieces of information are displayed in the form of nodes - which represent the entities - and

edges - which represent the relationships – of the queried SNP. In the example, Figure 6, linkage disequilibrium information is displayed for rs405509. For SNP rs405509, the results demonstrate that the initial queried SNP is in linkage disequilibrium with SNPs rs10119, rs8106922, rs225925, rs439401, and rs405697. This result indicates that rs405509 is correlated with rs10119, rs8106922, rs225925, rs439401, and rs405697; this correlation can be an indication of which additional SNPs need to be studied.

SNPit Web Interface

The main website to the SNPit system was designed for simplicity and ease of use (Figure 7). The left side menu offers the ability to search by SNP or search by Gene. SNP input to the system can come from a variety of places including genome wide association study results. Within these categories, users can select either an entity to search by (Allele Frequency, Evolutionary Conservation, Gene Prediction, Linkage Disequilibrium, Population, Positive Selection, Protein Function Prediction, SNP, Tissue Expression, Gene, and Human Gene Mutation). Users can also select the Main Search option to search all the data sources together or the Rank SNPs option to view a list of queried SNPs ranked by potential functionality.

Results from the Main Search option using the user case scenario rs405509 demonstrates a portion of the information that is returned from both dbSNP and HGMD (Figure 8). Background information from dbSNP reveals that rs405509 has the chromosome location chr19: 50100675–50100676, resides in the APOE gene, and has a predicted functional class (defined by dbSNP as the classification of the polymorphism and its nearby gene features [18]) of being in a locus region, meaning that the variation is 2 kb 5′ or 500 bp 3′ of a gene. Results from the Rank SNPs option using a collection of other SNPs demonstrate how the inference rules and heuristic weights are displayed to the user (Figure 9). Depending on the potential function of a SNP, a ranking and determination is assigned and displayed.

4. Discussion

The SNPit system's federated integration approach and its focus on a comprehensive set of data sources differentiates it from existing SNP annotation tools. Additional functional annotation considerations will be added during future developments, and we plan on incorporating these information sources as they become available and are deemed feasible. Additional features and functionality to the SNPit website will also be pursued as deemed appropriate. This includes providing the results in tab-delimited table format as well as the present flat file format. There are currently plans on incorporating uncertainty measurements into the SNPit system, which will help to address the issue of the accuracy in different data sources. That way, we'd be able to parameterize the confidence of the results reported. Our primary objective continues to be the creation of a quality system that is actively used by population geneticists, and we hope to accomplish this goal by continuing to include as many users as we can in both the design and development stages. IRB approval has been attained to develop a survey that can measure the usability and usefulness of the SNPit website. This utility survey will eventually be distributed over the SNPit website, allowing us to continue refining the design of the system.

5. Conclusions

Genome wide association studies hold enormous potential in terms of uncovering the genetic mechanisms behind human diseases. Advances in genotyping result in ever increasing amounts of information on SNPs. The ability to integrate and analyze SNP data is instrumental to understanding the results of genome wide association studies. SNPit is a tool that attempts to use a federated data integration system to predict the functional annotation of SNPs.

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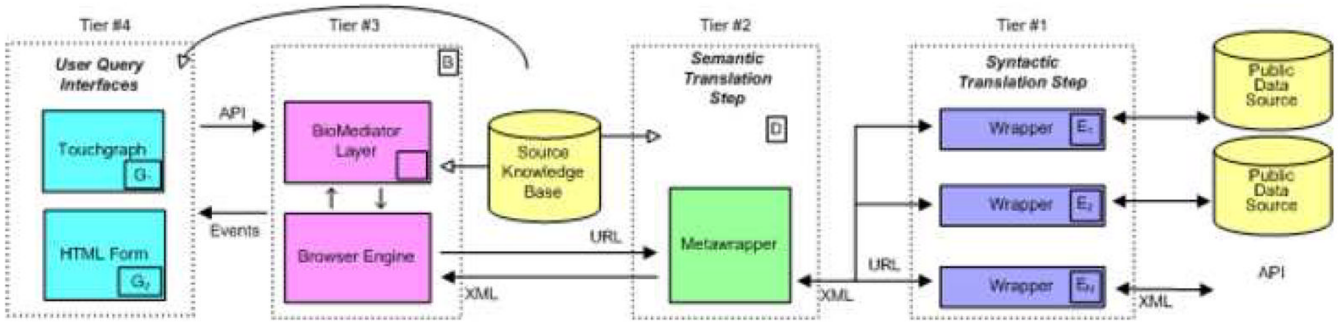


Figure 1. System architecture of BioMediator

The various components of BioMediator. Includes the multi-tiered components of the system – the query processor, mediated schema, and wrappers to the different data sources.

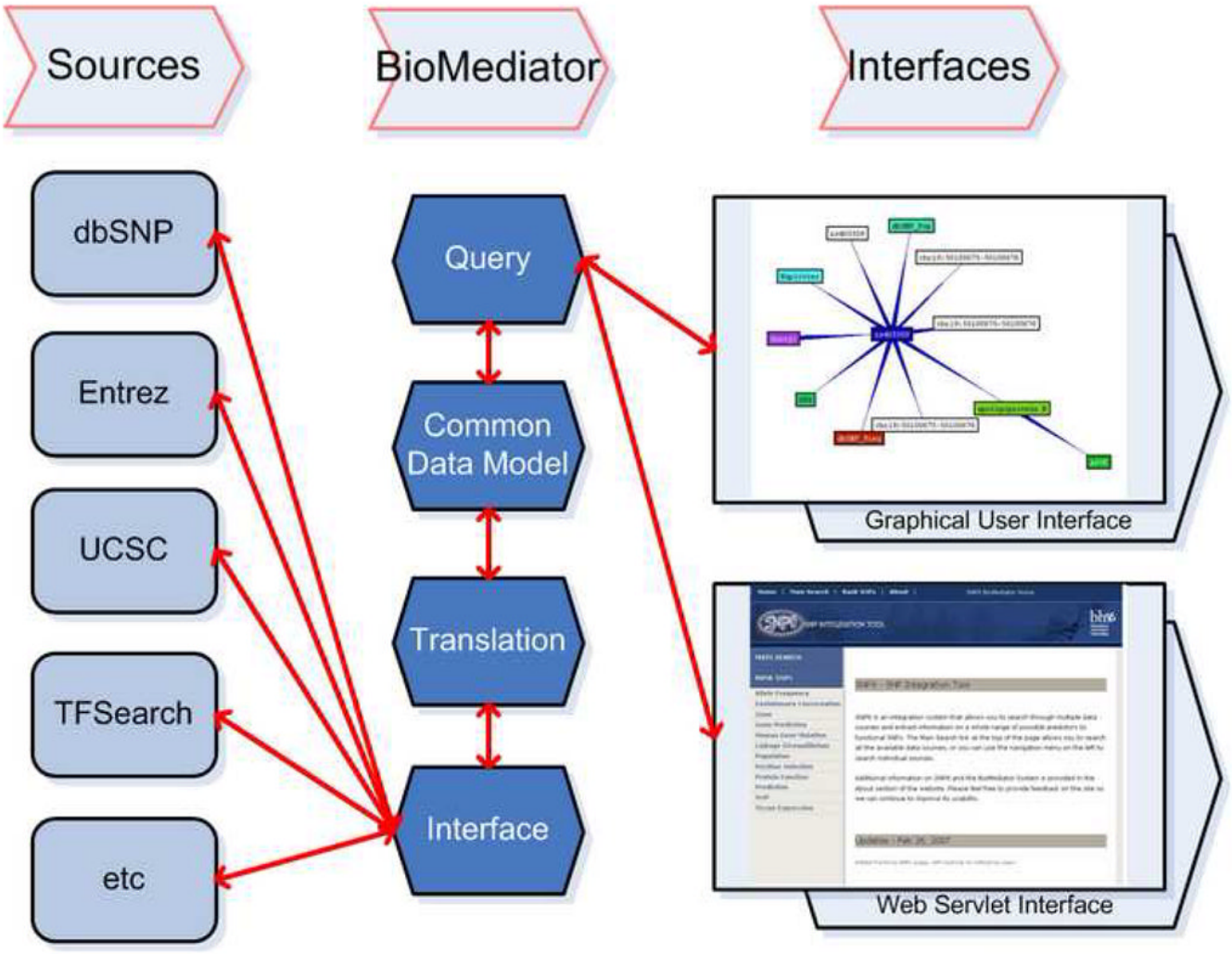


Figure 2. SNPit diagram of the various system components

SNPit's various components, including the query layer, common data model, translation and interface between the different data sources and interfaces of SNPit.

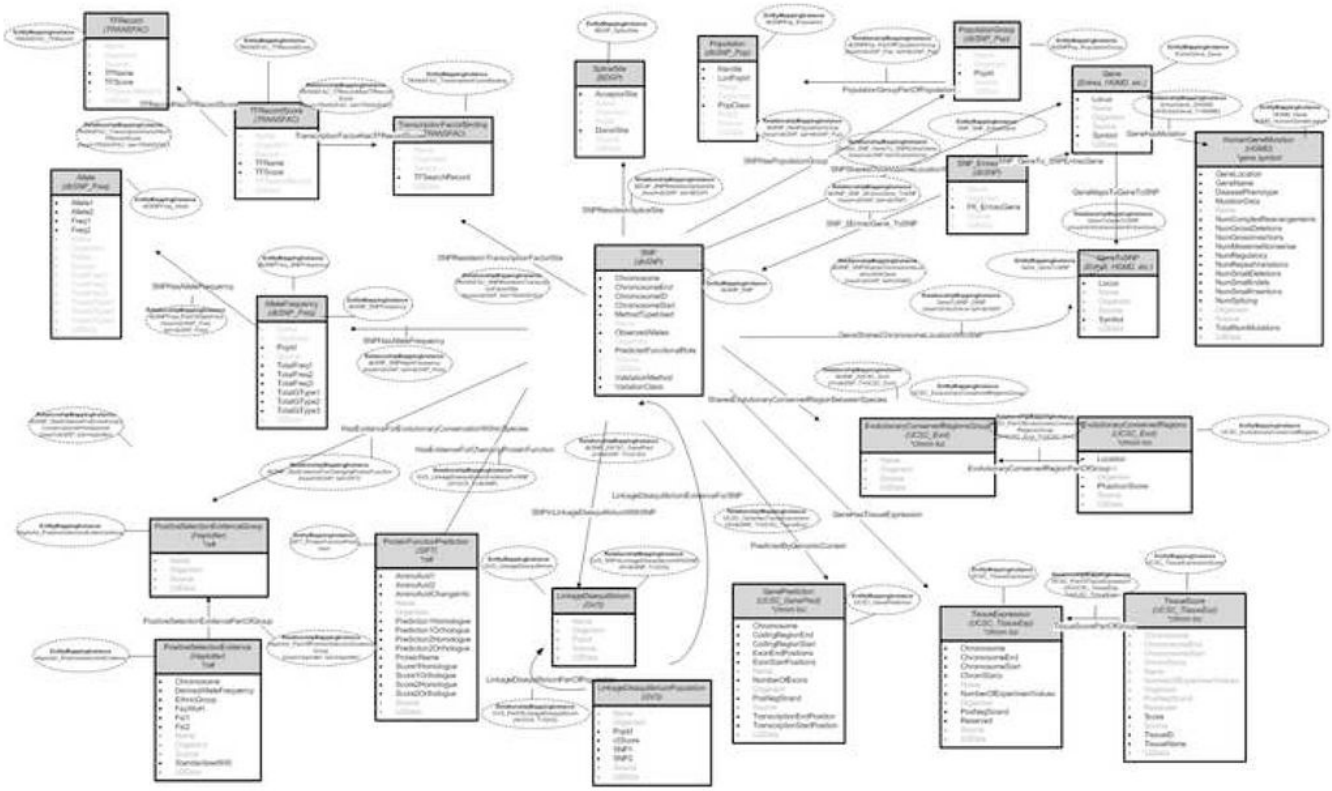


Figure 3. Visio diagram of the mediated schema

Subset of the mediated schema, demonstrating the entities, relationships, and attributes of the entities: SNP, gene, evolutionary conservation, splice site, and human gene mutations.

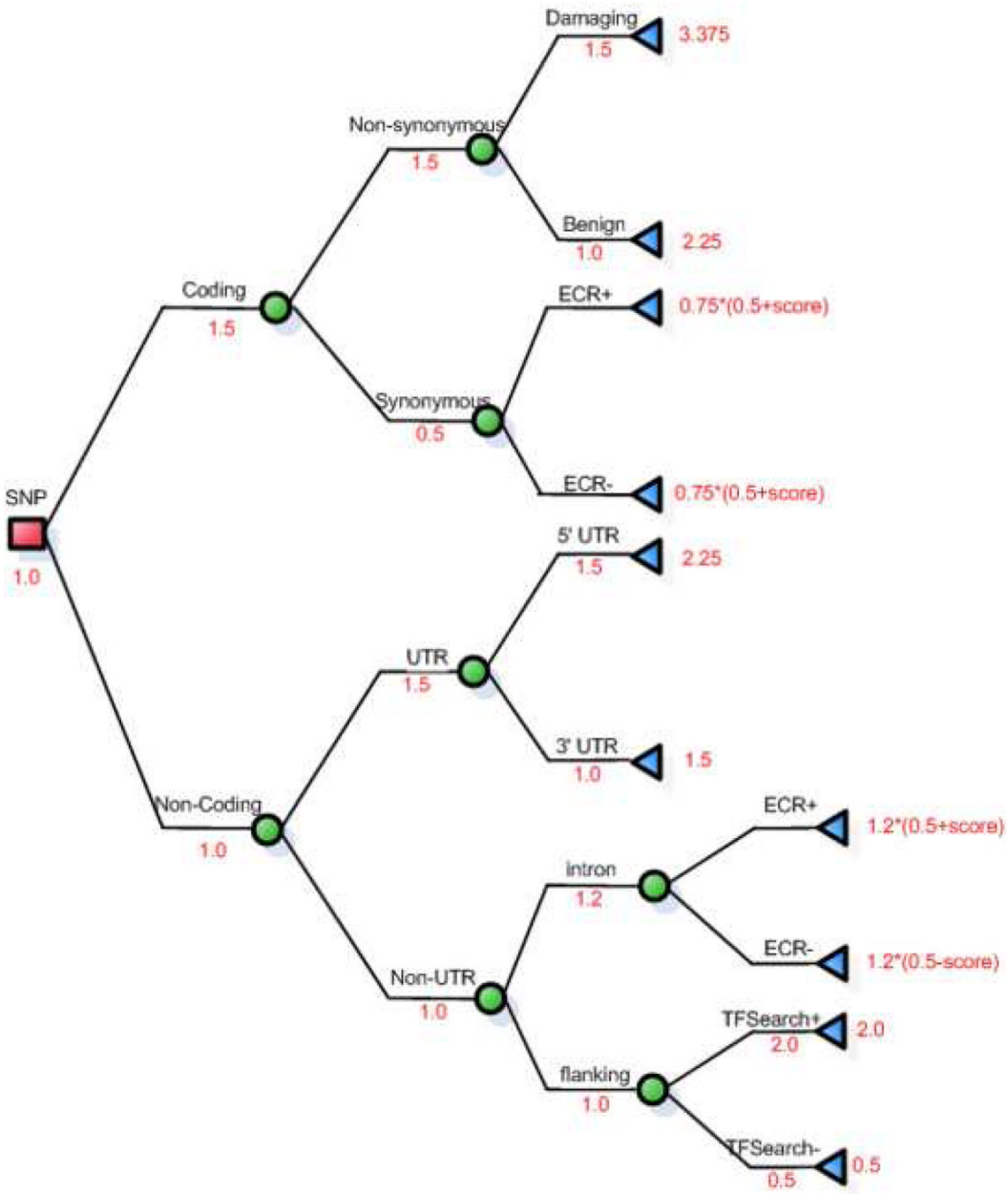


Figure 4. Decision tree with heuristic weights

Decision tree with paths and weights, heuristic weights were assigned to each node in the decision tree to reflect the prioritization of SNPs based on functional annotation. TFSearch refers to transcription factor binding and ECR refers to evolutionary conservation.

IF the SNP has a predicted functional role of coding-nonsynonymous,
THEN categorize this SNP as nonsynonymous and assign it a score.

```
(defrule check_cSNP_nonsyn
    (SNP (SourceID ?snp_id) (PredictedFunctionalRole ?a&:(regex ?a "coding-nonsynonymous")))
    (not(ProteinFunctionPrediction (SourceID ?snp_id) (Prediction1Homologue ?b)))
                =>
    (printout t "cSNP nonsyn" crlf)
    (assert (RankingSNP (rsnumber ?snp_id) (score (format nil "%.3f" 2.25)) (category "coding SNP,
nonsynonymous")))
)
```

Figure 5. Example of Jess inference rule

Pseudo-code demonstrating how Jess rules can be used to filter out SNPs that are nonsynonymous, (top) shows the pseudo-code and (bottom) demonstrates the actual Jess syntax.

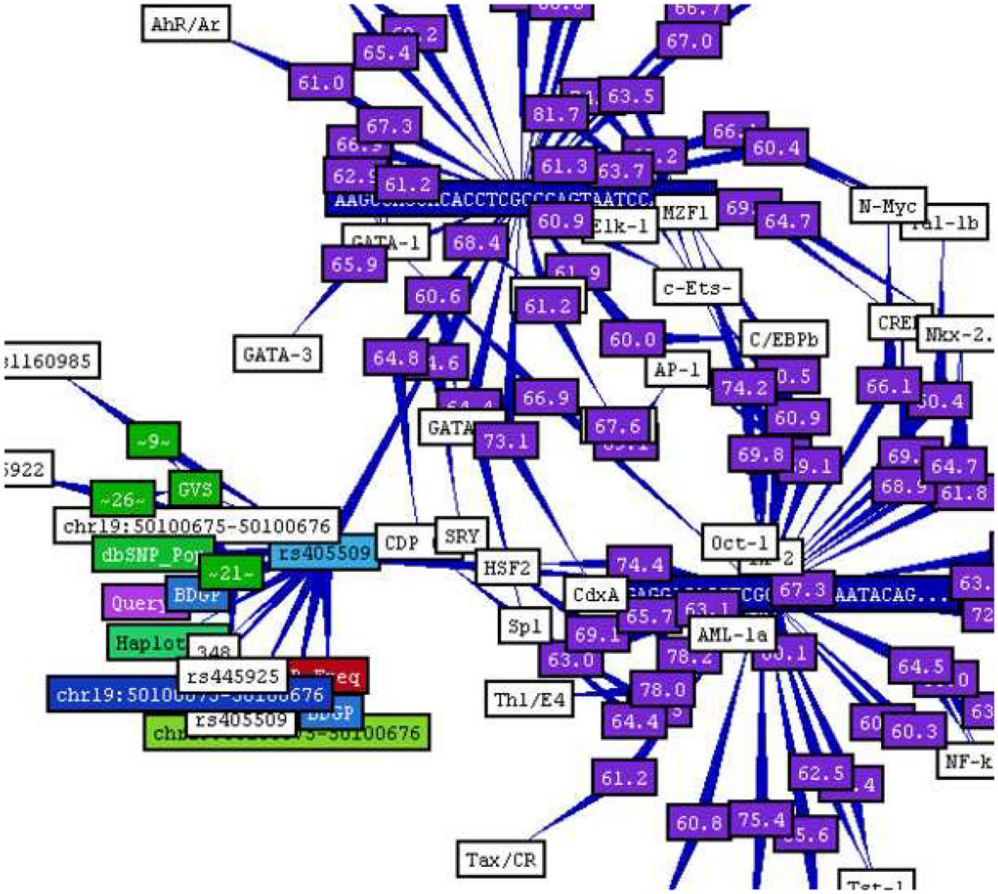


Figure 6. Touchgraph interface for SNPit

Touchgraph demonstrating how two expansions out from the central SNP leads to numerous SNPs being in linkage disequilibrium with the queried SNP.

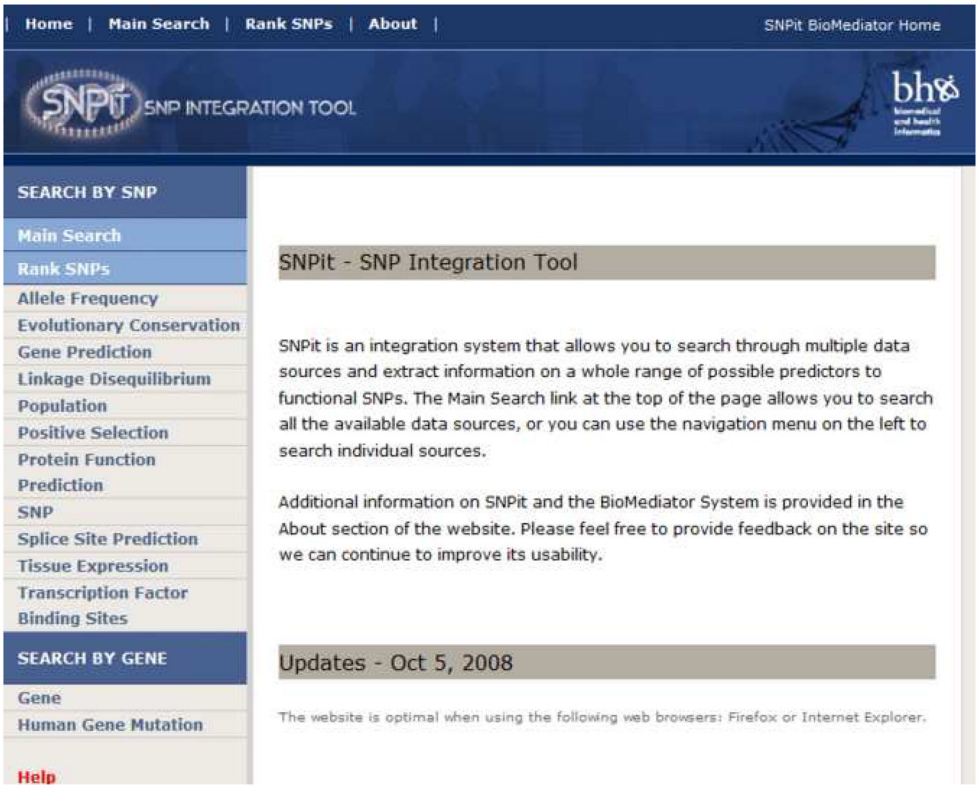


Figure 7. SNPit Web Interface

SNPit web servlet, left menu includes links to various data sources.

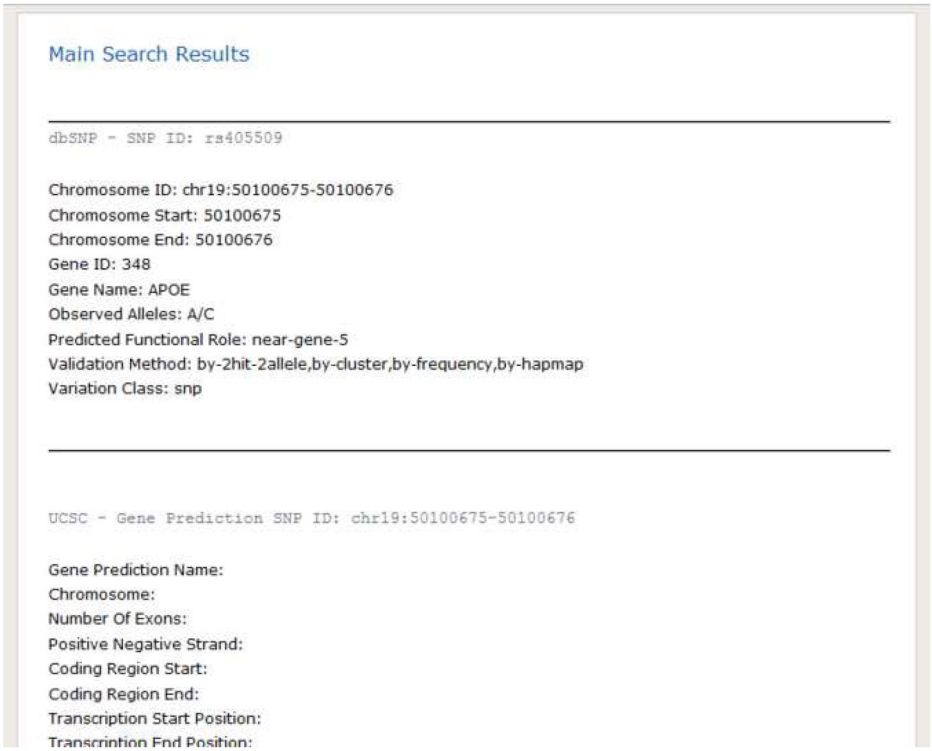
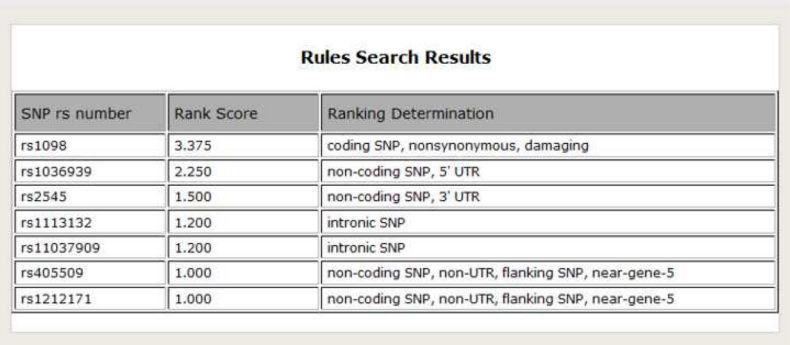


Figure 8. Results from SNPit web interface
Subset of results returned when the user queries on rs405509.



Rules Search Results

SNP rs number	Rank Score	Ranking Determination
rs1098	3.375	coding SNP, nonsynonymous, damaging
rs1036939	2.250	non-coding SNP, 5' UTR
rs2545	1.500	non-coding SNP, 3' UTR
rs1113132	1.200	intronic SNP
rs11037909	1.200	intronic SNP
rs405509	1.000	non-coding SNP, non-UTR, flanking SNP, near-gene-5
rs1212171	1.000	non-coding SNP, non-UTR, flanking SNP, near-gene-5

Figure 9. Decision tree with heuristic weights
Ranked SNPs based on decision tree.

Table 1

Data sources that are integrated into SNPit

Different data sources that are being included in SNPit.

dbSNP	central repository database for both single base nucleotide substitutions and short deletion and insertion polymorphisms [18]
EntrezGene	gene-centric database that includes information on nomenclature, chromosomal localization, gene products and their attributes [19]
HGMD	provides publication evidence to genes responsible for human inherited diseases [20]
Haplotter	web tool that includes evidence for positive selection within the human genome, two statistical measures that look at the linkage disequilibrium of positively selected alleles and frequencies of polymorphisms are provided [21]
GVS	local database that provides access to information in dbSNP and includes tag SNP and linkage disequilibrium analysis [22]
SIFT	resource for predicting the functional impact of nonsynonymous coding SNPs, algorithm sorts tolerant from intolerant polymorphisms [23]
UCSC Phastcons	predicts evolutionary conservation of noncoding SNPs based on aligning genomic sequences of different species [26]
UCSC Genscan	predicts whether the SNP lies in a region that is likely to be gene region, based on transcriptional, translational, and donor/acceptor splicing signals [24]
UCSC GNFAtlas2	displays gene-centric expression of polymorphisms over 79 human tissues [25]