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GeneSeeker: extraction and integration of human disease-related information from web-based genetic databases

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ABSTRACT

The identification of genes underlying human genetic disorders requires the combination of data related to cytogenetic localization, phenotypes and expression patterns, to generate a list of candidate genes. In the field of human genetics, it is normal to perform this combination analysis by hand. We report on GeneSeeker (http://www.cmbi.ru.nl/GeneSeeker/), a web server that gathers and combines data from a series of databases. All database searches are performed via the web interfaces provided with the original databases, guaranteeing that the most recent data are queried, and obviating data warehousing. GeneSeeker makes the same selection of candidate genes as the human geneticists would have performed, and thus reducing the time-consuming process to a few minutes. GeneSeeker is particularly well suited for syndromes in which the disease gene displays altered expression patterns in the affected tissue(s).

INTRODUCTION

The identification of causative genes in human genetic disorders will be accelerated by the wealth of ‘omics’ information being generated. Geneticists consult a number databases to search for these genes. Each database concentrates on a different (molecular) aspect. In addition, databases have their own user interface, different formats to present the data and sometimes even their own ontologies. Data, such as gene localization and expression patterns, may be distributed over multiple databases.

Material and methods

Databases used

Table 1 lists the databases that GeneSeeker queries. These are divided over database groups (DB-groups). All databases are accessed through their standard WWW interfaces except MIMMAP and OXFORD. MIMMAP is a reformatted version of the OMIM (6) gene mapping information. OXFORD is used to translate human to mouse chromosomal locations, and is described in more detail in the pre-processing section. We use SRS (Sequence Retrieval System, Lion Biosciences, Cambridge, UK) to access these two databases (7). The SRS parser was modified to allow searches for chromosomal ranges.

Data processing

The layout of the GeneSeeker web server is shown in Figure 1. The user query consists of a chromosomal band range using...
standard nomenclature (e.g. 7p15–p21). This cytogenetic localization is passed through DB-group 1. Syntenic regions in the mouse are sought in DB-group 2 using an Oxford-grid. Tissues of interest or phenotypic features of a syndrome can be specified by the user as a Boolean expression that is split up and processed by DB-group 3. This modular set-up makes it easy to add extra DB-groups in the future. For every database, a plug-in was designed to perform all tasks from user-query pre-processing to query-result post-processing. These plug-ins deal with a series of technical topics, such as query reformatting, generating the correct URL, filling in the form on that database’s web interface, requesting all hits rather than in chunks, parsing the database HTML output and so on.

The name of a gene can vary from database to database. The gene for the multi-drug resistance-associated protein 1, for example, is stored as \textit{ABCC1}, \textit{MRP} or \textit{MRP1}, depending on the database used. These gene nomenclature problems have to be solved because GeneSeeker depends on the gene names in the combination steps. For each DB-group the results are integrated with a Boolean OR. The resulting gene lists of the three DB-groups are combined according to the Boolean logic specified in the user query.

**Implementation issues**

\textit{Parallelization}. The database plug-ins run in parallel to minimize the waiting time. A queuing system prevents excessive loads on remote servers. The plug-ins return the results of the queries to GeneSeeker as a list containing the gene names and corresponding database hyperlinks.

\textit{Mouse–human synteny}. An Oxford grid (8) is used to find the homologous genes and gene regions in the mouse genome for all human chromosome locations entered by the user. A human chromosomal band range is translated into the corresponding mouse chromosome locations. Two mouse locations are combined if the genetic distance is shorter than a user-specified value (defaults to 10 cM). We regenerate this Oxford grid

\begin{table}
\caption{Databases accessed by the GeneSeeker} 
\begin{tabular}{ll}
\hline Database & URL \\
\hline DB-group 1: localization databases (human) & \\
OXFORD (15) & srs.bioasp.nl:4080 \\
MIMMAP (6) & srs.bioasp.nl:4080 \\
GDB (16) & www.gdb.org \\
DB-group 2: localization databases (mouse) & \\
MGD (15) & www.informatics.jax.org \\
Datasets used in the interface & \\
GXD thesaurus & Van Steensel \textit{et al.} (10) \\
Zuerich dataset & Brewer \textit{et al.} (11,12) \\
DB-group 3: expression/phenotype databases & \\
PubMed (Nature Library of Medicine, Bethesda, MD) & www.ncbi.nlm.nih.gov/pubmed \\
OMIM (6) & srs.bioasp.nl:4080 \\
UniProt (9) (Swiss-Prot, TyEMBL, etc.) & srs.bioasp.nl:4080 \\
GXD (17) & www.informatics.jax.org \\
MLC (15) & www.informatics.jax.org \\
TBASE (18) & (was thaise, merged January 2005) \\
’Link out’ database & \\
GeneCards (14) & bioinfo.weizmann.ac.il/cards/
\hline
\end{tabular}
\end{table}

\begin{figure}
\caption{Overview of GeneSeeker. The query, which consists of a cytogenetic localization, a phenotypic description and expression data, is divided over the three DB-groups that use the database-specific plug-ins to deal with all topics ranging from user-query pre-processing to post-processing of the query output. Results from each DB-group are merged with a Boolean OR. The results of the three DB-groups are combined as specified in the user query.}
\end{figure}
weekly to ensure that the latest synteny information is used in each query.

**Gene nomenclature.** Inconsistent gene nomenclature is resolved using gene synonym information from UniProt database (9). We use the MGD human homologues information to interconvert mouse and human gene names. We maintain local copies of these conversion tables because nearly all queries require that gene nomenclature problems be solved.

**User interface**

The GeneSeeker interface consists of the query form shown in Figure 2 and an options form that usually requires no user input. A genetic localization and the phenotypic/expression terms should be entered for a meaningful search. Databases that generate more noise than signal can be removed from the query. The user can also suppress the display of housekeeping genes or a specified list of genes. The options form contains a

The GeneSeeker v2.0

![GeneSeeker interface screen shot](image)

**Figure 2.** An example of a GeneSeeker query. Analyses of Trismus-Pseudocamptodactyly syndrome (TPC; MIM 158 300) has been linked to 17p12–p13.1 (13). TPC is characterized by defects in muscle tissue mainly in limb and/or mouth. The options form is data not shown.

**Figure 3.** The output of GeneSeeker for the Trismus-Pseudocamptodactyly syndrome query (see Figure 2). It has been shown that mutations in the MYH8 gene can cause TPC (13). Top left table: genes that agree perfectly with the user query. Top right table: genes found in mouse syntenic regions that cannot be mapped automatically on the human genome, but match the expression pattern. Bottom left table: genes found in mouse syntenic regions that match the expression pattern, but map on the human genome outside the candidate cytogenetic region. Bottom right table: human genes in the candidate cytogenetic region that do not match the phenotype/expression pattern. All genes are hyperlinked to the underlying database, and, when possible, to GeneCards (14).
RESULTS AND DISCUSSION

The GeneSeeker offers a user-friendly quick scan of several databases that are commonly used by geneticists to identify candidate genes for specific Mendelian diseases. As such, GeneSeeker uses those databases that are most appropriate for the questions asked. Several aspects are likely to change in the near future as genomics and genetics develop. For example, our usage of an Oxford grid can be improved or replaced as soon as consensus is reached about the localization of genes on the mouse and human genomes among the various databases. Expression pattern information (e.g. microarray data) is growing rapidly, and is expected to become useful for GeneSeeker in the near future.

In its present form, GeneSeeker is best suited for syndromes in which one can assume aberrant or absent gene expression in the affected tissues. GeneSeeker allows the user to query heterogeneous databases and obtain good candidate genes for the disease of interest based on positional, expression and model data (5). With the present hardware set-up GeneSeeker can perform ~1000 searches per day.

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Conflict of interest statement. None declared.

REFERENCES

1. Blackshaw,S., Fraioli,R.E., Furukawa,T. and Cepko,C.L. (2001) Comprehensive analysis of photoreceptor gene expression and the identification of candidate retinal disease genes. Cell, 107, 579–589.
2. den Hollander,A.I., van Driel,M.A., de Kok,Y.J., van de Pol,D.J., Hoyng,C.B., Brunner,H.G., Deutman,A.F. and Cremers,F.P. (1999) Isolation and mapping of novel candidate genes for retinal disorders using suppression subtractive hybridization. Genomics, 58, 240–249.
3. Dryja,T.P. (1997) Gene-based approach to human gene–phenotype correlations. Proc. Natl Acad. Sci. USA, 94, 12117–12121.
4. Chiang,A.P., Nishimura,D., Searby,C., Elbedour,K., Carmi,R., Ferguson,A.L., Secrist,J., Braun,T., Casavant,T., Stone,E.M. et al. (2004) Comparative genomic analysis identifies an ADP-ribosylation factor-like gene as the cause of Barde–Biedl syndrome (BBBS). Am. J. Hum. Genet., 75, 475–484.
5. van Driel,M.A., Cuelenaere,K., Kemmeren,P.P., Leunissen,J.A. and Brunner,H.G. (2003) A new web-based data mining tool for the identification of candidate genes for human genetic disorders. Eur. J. Hum. Genet., 11, 57–63.
6. Hamosh,A., Scott,A.F., Amberger,J., Bocchini,C., Valle,D. and McKusick,V.A. (2002) Online Mendelian Inheritance in Man (OMIM), a knowledgebase of human genes and genetic disorders. Nucleic Acids Res., 30, 52–55.
7. Eizold,T., Ulyanov,A. and Argos,P. (1996) SRS: information retrieval system for molecular biology data banks. Methods Enzymol., 266, 114–128.
8. Edwards,J.H. (1991) The Oxford Grid. Ann. Hum. Genet., 55, 17–31.
9. Apweiler,R., Bairoch,A., Wu,C.H., Barker,W.C., Boeckmann,B., Ferro,S., Gasteiger,E., Huang,H., Lopez,R., Magrane,M. et al. (2004) UniProt: the Universal Protein knowledgebase. Nucleic Acids Res., 32, D115–D119.
10. van Steensel,M.A., Celli,J., van Bokhoven,J. and Brunner,H.G. (1999) Probing the gene expression database for candidate genes. Eur. J. Hum. Genet., 7, 910–919.
11. Brewer,C., Holloway,S., Zawalnyski,P., Schinzel,A. and FitzPatrick,D. (1998) A chromosomal deletion map of human malformations. Am. J. Hum. Genet., 63, 1153–1159.
12. Brewer,C., Holloway,S., Zawalnyski,P., Schinzel,A. and FitzPatrick,D. (1999) A chromosomal duplication map of malformations: regions of suspected haplo- and triplolethality—and tolerance of segmental aneuploidy—in humans. Am. J. Hum. Genet., 64, 1702–1708.
13. Veuveling,M., Bressan,M., McDermott,D.A., Weremowicz,S., Morton,C.C., Mabry,C.C., Lefaivre,J.F., Zunamon,A., Destree,A., Chaudron,J.M. et al. (2004) Mutation of perinatal myosin heavy chain associated with a Campomelic complex variant. N. Engl. J. Med., 351, 460–469.
14. Safran,M., Chalifa-Caspi,V., Shmueli,O., Olender,T., Lapidot,M., Rosen,N., Shnoish,M., Peter,Y., Glusman,G., Feldmesser,E. et al. (2003) Human Gene-Centric Databases at the Weizmann Institute of Science: GeneCards, UDB, CroW 21 and HORDE. Nucleic Acids Res., 31, 142–146.
15. Blake,J.A., Richardson,J.E., Bult,C.J., Kadin,J.A. and Eppig,J.T. (2003) MGD: the Mouse Genome Database. Nucleic Acids Res., 31, 193–195.
16. Letovsky,S.I., Cottingham,R.W., Porter,C.J. and Li,P.W. (1998) GDB: the Human Genome Database. Nucleic Acids Res., 26, 94–99.
17. Ringwald,M., Eppig,J.T., Begley,D.A., Corradi,J.P., McCright,J.J., Hayamizu,T.F., Hill,D.P., Kadin,J.A. and Richardson,J.E. (2001) The Mouse Gene Expression Database (GXD). Nucleic Acids Res., 29, 98–101.
18. Woychik,R.P., Wassom,J.S., Kingsbury,D. and Jacobson,D.A. (1993) TBASE: a computerized database for transgenic animals and targeted mutations. Nature, 363, 375–376.