GIST: A web tool for collecting gene information

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A COMMON PROBLEM in studies of complex disease is the difficulty in acquiring the relevant genetic data for rational choice of candidate genes. This has led to the use of only some of the many relevant genes and markers in genetic studies of association and linkage. A primary explanation for the noncomprehensive nature of candidate gene compilations is the lack of easy availability of informatics tools to identify all relevant candidate genes. Although pertinent information such as nucleotide sequence and chromosomal map location for genes can be found in a host of genomic databases, there is no simple way to tailor this information for each candidate gene. To this end, we have created a web tool (http://genome.cwru.edu/gist/gist.html) to allow the rapid cataloging of currently available genetic data. This tool, called GIST (or “Gene Information Search Tool”), allows an investigator to search the major genomic databases containing gene and marker information from a single query point. To prove the utility of GIST, a catalog of 150 hypertension candidate genes was created. This resource collates all available nucleotide and amino acid sequence data, expression data, chromosomal map location, and genetic marker interval for each gene, collected from on-line databases. These data can be used to guide genetic studies of hypertension.

A web tool for collecting gene information.
Acquiring and assembling genomic data for a large number of genes from the many different databases is not a trivial task. To ease this process, we have created a web-based search tool called GIST, the Gene Information Search Tool (Fig. 1). This web page is a one-site query tool for multiple databases. Its frames format has been designed to allow the quick assembly of information from a variety of databases (Table 1). It allows searching both by genes and by microsatellite markers from multiple information sources. To test the utility of this tool, we built an on-line candidate gene list for hypertension containing 150 genes.

Fig. 1. Entry view for GIST, Gene Information Search Tool (http://genome.cwru.edu/gist/gist.html).

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Essential hypertension is a leading cause of morbidity and mortality in the United States and is an important target of contemporary biomedical research. Hypertension is clinically defined as a systolic blood pressure greater than 140 mmHg and/or a diastolic blood pressure greater than 90 mmHg (17), and it shows familiality with estimates of heritability ranging from 60% in twin studies to 25% in family studies (29). The familial resemblance of hypertension fits a model in which no single locus contributes overwhelmingly to the trait but, rather, multiple genes and environmental factors, each with a small cumulative effect, contribute to the hypertensive state (15, 25).

A variety of biological/biochemical pathways, composed of potentially hundreds of genes, including the renin-angiotensin system, hypothalamus-pituitary axis, and hormonal regulation, control an individual's blood pressure via homeostatic mechanisms. Some genes in these pathways, such as that encoding angiotensinogen, are well described; some, such as that encoding chymase, have not been well studied; and many, if not most, are yet to be discovered. However, it is clear that some of these genes must be involved in hypertension given their unequivocal role from physiological studies. Evidence for a genetic role in hypertension has arisen from the study of several genes, including angiotensinogen, α-adducin, and the β3 subunit of G protein (4, 16, 28), through candidate gene association studies. Although the biological implication that interindividual genetic variation in these genes leads to variation in blood pressure is not complete (6, 18, 19), this small collection of genes implicates remarkably different pathways. Therefore, to responsibly characterize hypertension candidate genes, we have “cast a wide net” for identifying a variety of genes from diverse pathways that work directly or indirectly to control blood pressure.

http://physiolgenomics.physiology.org
Table 1. Databases that can be searched by GIST

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<thead>
<tr>
<th>Gene searches</th>
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<tr>
<td>NCBI—PubMed</td>
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<td>NCBI—GenBank</td>
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<td>NCBI—UniGene</td>
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<td>ExPASy—SwissProt</td>
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<tr>
<td>GDB—Genome Data Base</td>
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<td>NCBI—Entrez Protein Division</td>
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<td>Weizmann Institute—GeneCard</td>
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<td>HUGO Nomenclature Committee</td>
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<td>NCBI—Entrez Nucleotide Division</td>
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<td>HGMD—Human Gene Mutation Database</td>
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<td>OMIM—Online Mendelian Inheritance in Man</td>
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<td>GeneMap’98—International RH Mapping Consortium</td>
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<th>Marker searches</th>
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<td>CEPH—D</td>
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<td>CEPH—AFM</td>
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<td>NCBI—PubMed</td>
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<td>CEPH—YAC Maps</td>
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<tr>
<td>WI-MIT—Whitehead/MIT</td>
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<td>GDB—Genome Data Base</td>
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<td>SHGC—Stanford Human Genome Center</td>
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<td>CHLC—Cooperative Human Linkage Center</td>
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<td>dbSTS—Database of Sequence Tagged Sites</td>
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GIST, gene information search tool; NCBI, National Center for Biotechnology Information; HUGO, Human Genome Organization; RH, radiation hybrid; CEPH, Centre d'Etudes Polymorphismes Humains; AFM, Association Française contre les Myopathies; YAC, yeast artificial chromosome; MIT, Massachusetts Institute of Technology.

RESULTS

To test the usefulness of GIST, we built a hypertension candidate gene database that could be made available through the Internet. We performed a search of the hypertension literature, selecting genes based on prior genetic, animal, or physiological studies, and identified 150 of the most common and likely candidate genes. Although there are certainly scores of other genes that might be deemed as candidates, our discovery was limited to these 150 genes, as explained in discussion. A complete listing of these 150 genes and the information gathered on each is available at the web site http://genome.cwru.edu/candidates/candidates.html (Fig. 2). These 150 hypertension genes have been sorted by gene name, gene symbol, and functional group and have been hyperlinked to separate web pages for each gene. Figure 3 shows the available data for each gene and the databases queried to obtain the information. Using GIST, we were successful in quickly acquiring and collating the necessary genomic information from a variety of databases. The types of information and relative success rates for collection of each type of information are discussed below.

The full gene name, the official gene nomenclature symbol, and possibly a common gene symbol(s) were identified for each gene. Using the gene name or symbol, we queried seven genomic databases. OMIM records were obtained for 147 of the 150 genes. OMIM accession numbers on the individual gene web pages were hyperlinked to provide direct access to the OMIM record. For all 150 genes, two or three GenBank records were obtained for each gene: the first represents DNA sequence from the gene itself, either as a whole or partial genomic segment or as a cDNA; the second accession number is for a nucleotide-sequenced large-insert clone, generally not annotated, on which part, or all, of a gene resides; the third represents a protein record for the gene. These records are also hyperlinked by the accession number to the full GenBank sequence record.

The available GenBank sequence was next parsed into the categories of 5′ (promoter and 5′-UTR), exonic, intronic, and 3′ (3′-UTR and flanking 3′) sequence to represent how much DNA information was known for
each gene. DNA sequence totaling over 3.6-megabases was obtained for the 150 genes. The most significant variable determining the amount of sequence available for a gene was whether it is contained in a large-insert clone [bacterial artificial chromosome (BAC), P1-derived artificial chromosome (PAC), cosmid, etc.] that has been sequenced as part of the Human Genome Project: parts of 37 genes were contained on large-insert clones, representing 80% of all sequence data available. At the time the list was generated (the data set was frozen as of January 9, 1999), many of these sequences were on unordered “phase 1” clones. Phase 1 sequencing indicates the sequencing record is incomplete and that multiple unordered “contigs” of the larger clone exist. Therefore, approximations of available sequence length, to the nearest 10 kb, for 5′-UTR, introns, and 3′-UTR were made. Approximately one-fourth of the 150 genes (i.e., 36 genes) have been sequenced as cDNAs with no genomic structure information. The remaining 77 genes have various amounts of genomic sequence available.

Tissue expression data were available for 118 candidate genes from the UniGene database, based on the specific library from which the gene, or an expressed sequence tag (EST), was sequenced (13). A gene is assumed to be expressed in a tissue if its cDNA can be sequenced from a specific library derived from that tissue. This method clearly underestimates expression patterns of genes, due to limitations in the depth of sequencing from many tissue-specific EST libraries. This information can be used to identify tissues and cell lines that could produce the transcribed mRNA product. Many candidate genes appear to have ubiquitous expression, as 27 of the candidate genes were found to be transcribed in 10 or more tissues.

The chromosomal location of each gene was also determined. All but two genes had been assigned to at least a specific chromosome, but most genes have detailed cytogenetic map locations. The use of GenMap 98 allowed the placement of 77% of genes (116) within a radiation hybrid mapped interval between two polymorphic microsatellite markers (9). Genes were located on all chromosomes except on chromosome 15 and the Y chromosome. We found that the pattern of distribution of these genes on the chromosomes differs from that expected for the distribution of a random set of 148 genes ($\chi^2 = 53.5, 22$ df, $P < 0.0002$). To determine if this was an effect of gene family clustering, all
clusters were reduced to a single representative in the analysis; the distribution remained nonrandom ($\chi^2 = 44.6, 22$ df, $P < 0.003$), albeit less significant, after the removal of 10 genes. This nonrandom distribution may be the result of a selection bias for these 150 genes arising from human or model organism blood pressure QTL studies, which in turn have encouraged increased study of genes located in these areas. Indeed, we found 17% percent of all genes were located within a linkage group from a human or model organism QTL for blood pressure or a blood pressure intermediate phenotype (12, 15, 21).

**DISCUSSION**

**GIST.** GIST was designed to reduce the tedious process of consulting multiple on-line databases for information regarding a specific gene (Fig. 1). GIST is a simple JavaScript and HTML application that allows queries of all major genetic databases from a single site. Three types of searches can be performed with GIST: a gene search, a human-only gene search, and a marker search. To use GIST, the name of the gene or marker of interest is entered, followed by selection of an appropriate database (listed in Table 1) to send an Internet query to the database for the gene entered. For human-only queries, the query will be sent with a tag to return human data only, where such data exists. Twelve different databases are accessible from the query window, including several specific for microsatellite marker-based searches.

GIST is not meant to replace more thorough searches that can be performed at specific web sites. More importantly, GIST is not a database. It is simply a one-site query tool for multiple databases, having been designed to allow quick surveys of information available about a gene of interest and to get the “gist” of what is known about a gene or marker. GIST can be used for a variety of additional applications beyond building candidate gene lists, including performing simple searches of genes of interest in multiple databases and identifying microsatellite marker information such as heterozygosity and a marker’s prior use in genetic studies.

**Candidate gene list.** Using GIST, we have rapidly created an on-line resource for hypertension candidate genes. In preparing this resource, two aspects of list construction were important: the genes themselves and the information obtained for each. To build this list, genes were selected from a literature search based on several different lines of evidence. The strongest criteria used were human genetic studies (linkage and association analyses) and gene-specific transgenic or other animal models that have associated blood pressure-altering phenotypes. These two criteria account for only 30–40 genes (7, 15). We next selected genes from pathways regulating vasculature remodeling/repair, glucose homeostasis, cardiac function, kidney small molecule/ion transport, and neural and hormonal blood pressure pathways. The list we generated represents only a subset of all hypertension candidate genes, but as such it is the largest publicly available resource of genetic information focused on a specific complex genetic disease.

Nearly all of the information displayed at the web site was obtained from on-line databases. The one exception is the inclusion of hyperlinks to papers describing genetic studies of linkage or association for those genes in which studies have been attempted, obtained from a recent hypertension review article (15). The pace at which new gene information becomes available is remarkable. The data for this list were updated twice in an 18-month period after the initial list was created. Each time, ~20% more sequence, mapping, or expression information became available. Currently, 80% of all the data fields have been filled, and this percentage will certainly improve over the next several months because of the continuing ramp-up of the Human Genome Project sequencing effort (8). The information compiled for each gene is sufficient for projects designed to find polymorphic markers (SNPs) in gene regions and to compare genes relative to QTLs based on map position. However, none of this information allows hierarchical ranking of these genes as being more or less likely candidate genes for hypertension. That is, very little biologically relevant information relating to disease is available in genomic databases; but this is likely to change in the future. We predict that the information available from alternative expression pattern studies of these genes in hypertensive and normotensive subjects as determined by microarray systems (10) will allow the ranking of genes based on
the observed extent of difference between the two groups, as is currently being performed in the cancer community with the Cancer Genome Anatomy Project initiative.

We expect this on-line resource to be beneficial to both the hypertension research community and other complex genetic disease research communities. We believe this resource initiates a common starting point for gene discovery in hypertension. For other communities, this resource can serve as a template for additional candidate gene lists.

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REFERENCES


