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The impact of genetic variations in bipolar disorder

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The Impact of Genetic Variations in Bipolar Disorder

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ABSTRACT

Bipolar disorder is a devastating illness that affects the quality of life for millions of Americans. The current diagnostic system depends on an extremely subjective interview and can frequently result in an incorrect diagnosis and ineffective treatment. An improved, biologically based, classification system requires a thorough understanding of the genetic basis of bipolar disorder. This understanding has been hampered by the difficulty in diagnosing patients and by the heterogeneity of the illness. The number of linkage analysis studies and lack of organization have also added to the challenges involved in understanding the biological basis of the disorder.

The Bipolar Disorder Genetics Database web application, located at http://www.bipolardisordergenetics.com, resolves the issue of organization, allowing researchers to quickly identify promising chromosomal regions that merit further investigation which will lead to understanding the functions of the affected genes and the impact of the various mutations. Understanding these functions will lead to significant advances in the areas of diagnosis and treatment.

The intuitive web-based interface is a novel approach to creating a big picture view of our existing knowledge. The application will become the premiere resource for researchers and will assist them as they make significant advances in treating this illness.

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INTRODUCTION

Background

Bipolar disorder, an illness that affects an estimated 2.3 million American adults,[1] has been characterized in many different ways. The original diagnosis of "manic-depressive insanity,"[2] described by Emil Kraepelin in his 1899 edition of *Clinical Psychiatry*, has evolved through the years to the current classification system of four subtypes: Bipolar I Disorder, Bipolar II Disorder, Cyclothymic Disorder and Bipolar Disorder Not Otherwise Specified.[3] This evolution and elucidation of subtypes rests on the realization that not all cases of the illness are the same. These subtypes are not based on the underlying biology of the illness but rather on the consensus opinion of mental health professionals and have changed significantly over the years. These subtypes will continue to change until there is a biological basis for the diagnoses.

The primary mood disturbance in Bipolar I Disorder is either mania or a mixed episode and it is usually accompanied by episodes of depression.[3] The primary mood disturbance in Bipolar II disorder is depression and it is accompanied by at least one episode of a mild form of mania called hypomania.[3] An individual with Cyclothymic Disorder cycles between periods of hypomanic symptoms and periods of depressive symptoms.[3] The hypomanic symptoms are never severe enough to be considered a manic episode and the depressive symptoms are never severe enough to be considered a depressive episode.[3] Bipolar Disorder Not Otherwise Specified captures all of the other variants of the disease that do not fit neatly into one of the above categories.[3]

A major depressive episode lasts at least two weeks.[3] The major symptom is either

a depressed mood or a loss of enjoyment in activities nearly every day.[3] An individual also needs to have at least four other symptoms.[3] Three of the possible symptoms involve either an increase or a decrease in normal functioning. They are a change in appetite, a change in sleeping patterns and a change in the speed of physical movements.[3] Other possible symptoms include fatigue, feeling guilty or worthless, poor concentration and thoughts of death or suicide.[3]

A hypothetical example of someone suffering from a major depressive episode is a college student named Frieda. She constantly feels exhausted even though she sleeps for nearly 14 hours every day. She skips her classes more times than she attends them and spends most of her time staring out her dorm room window because nothing seems interesting anymore. She rarely goes to the dining hall to eat since she has almost no appetite. Her homework assignments have piled up and she can never seem to get more than a few pages of reading done before her mind wanders. When her friends ask her what's wrong all she can say is she feels down because she doesn't know any other way to explain it.

A manic episode lasts at least one week and consists of an abnormally elevated mood with at least three other symptoms.[3] Probably the most noticeable symptoms are a decreased need for sleep, being unusually talkative and having an inflated self-esteem.[3] The other possible symptoms are racing thoughts, being easily distracted, an increase in activity and an excessive involvement in activities that are enjoyable but could result in serious consequences.[3]

A hypothetical example of someone suffering from a manic episode is a grocery store cashier named Fred. Fred feels like he is on top of the world and can do anything. Ever since he realized he needs only four hours of sleep a night he's been incredibly

productive. He started writing three different novels, partially assembled six jigsaw puzzles and redesigned the layout of the grocery store. He showed the plans to the store manager who seemed annoyed rather than interested. Fred decided the manager was missing a golden opportunity so he quit his job to open his own store. He then went on a large shopping spree to celebrate the success he knew was just around the corner.

A hypomanic episode lasts at least four days and, with the exception of the mood disturbance, has the same possible symptoms as a manic episode.[3] Whereas in a manic episode the mood is abnormally elevated, in a hypomanic episode the mood is only persistently elevated.[3] A mixed episode occurs when an individual has symptoms of both a major depressive episode and a manic episode nearly every day for at least a week.[3]

Currently, a patient afflicted with bipolar disorder is diagnosed based on the displayed symptoms. While blood tests and physical exams can be used to rule out other illnesses with similar symptoms, there are no medical tests that can diagnose bipolar disorder. The diagnosis is based on an interview with the patient and, if possible, input from the patient's friends and family members. The focus of the interview is to review the list of possible symptoms with the diagnosis dependent on the answers. Although this subjective method of diagnosis is inherently flawed, unfortunately it is the best method available.

An accurate diagnosis depends on the patient's recognition and recollection of symptoms along with the physician's knowledge and experience. Communication issues, especially if the patient and the physician do not speak the same primary language, can lead to confusion about the symptoms. One of the biggest challenges

is a direct result of the cyclic nature of the illness. If a patient with bipolar disorder has symptoms of depression and either hasn't experienced a manic or hypomanic episode, or doesn't recall having experienced one, an incorrect diagnosis of unipolar depression can be made.

Treatment decisions are equally difficult with medication choices largely dependent on the physician's knowledge and experience. In many cases, the choice of medication is based on what works for other people. A small number of very fortunate patients will respond to the first medication tried and start to experience relief from symptoms within two months. For many of the patients, this trial and error method of medication selection will last much longer since most of the medications take up to two months to be effective. For some patients, the choice of medication can make the illness worse. Some individuals experience a manic episode as a result of taking certain antidepressants. While this information might be widely known among researchers and psychiatrists, it's possible that primary care physicians are unaware of the danger. This risk to patients will continue to increase as more and more of them seek treatment from a primary care physician instead of a psychiatrist. A primary care physician is also unlikely to be able to provide the same level of follow-up care as a psychiatrist.

Years of research, most notably homozygous twin studies, have lead to the conclusion that there are genetic and environmental components to bipolar disorder. The search for the genes involved has been both encouraging and discouraging with replication studies failing to validate earlier promising results. Bipolar disorder is a complex disease that results from interactions between an unknown number of genes and the environment. How many mutations are needed? Are there some mutations more potent than others? How much of an influence does the

environment have? Does the amount of environmental impact required vary depending on the genes affected? Is there a simple "on or off" threshold or does the severity of the illness increase as the number of mutations increase? Questions like these need to be answered in order to aid the research but can't be answered without the results of the research.

Linkage analysis studies, the best method for understanding the biological causes of bipolar disorder, are used to isolate chromosomal regions of susceptibility and the genes those regions contain. The primary result of a linkage analysis study is a set of LOD scores. LOD scores, short for “logarithm of odds”, are a ratio of the likelihood that two sections of a chromosome are inherited together.[4] If two sections of a chromosome appear together more often in people with a particular disease compared to people without that disease then it’s possible those chromosomal locations contain susceptibility genes. Larger scores indicate a higher likelihood with values greater than three considered significant[5].

There are three commonly used types of linkage analysis studies. A Parametric Analysis study type requires that researchers specify parameters regarding mode of inheritance, allele frequency and penetrance. [4] Penetrance is the probability that a particular mutation will result in a person having bipolar disorder. [4] A Parametric Analysis study is powerful but incorrectly specifying a parameter could result in flawed results.[4] An Affected Sibling Pair study calculates the number of alleles shared between two siblings that have a particular disorder and compares that to the number that would result from a completely random assortment.[4] One of the biggest advantages of the Affected Sibling Pair study type is that researchers don’t have to specify the parameters required by a Parametric Analysis study type. Nonparametric Analysis is another study type that doesn’t require researchers to

specify parameters. The primary disadvantage of a Nonparametric Analysis is the lack of power to detect linkage compared to the other study types.

Schizophrenia, another devastating mental illness, is also believed to have genetic and environmental causes. Currently classified as two separate disorders, schizophrenia and bipolar disorder have a common set of symptoms such as hallucinations, a change in sleeping patterns and diminished concentration.[3] In fact, diagnosis of one subtype of schizophrenia, schizoaffective disorder, requires that the individual have an episode of mania or depression.[3] Linkage analysis studies of schizophrenia have identified chromosomal regions of susceptibility that have also been identified as regions of susceptibility for bipolar disorder. Furthermore, many of the linkage analysis studies of bipolar disorder include individuals who have been diagnosed as having schizophrenia. The common set of symptoms, combined with the overlapping regions of susceptibility, have led some researchers to believe that the illnesses are part of one broader spectrum rather than two distinct disorders.

Future Research and Benefits

Conducting linkage analysis studies to identify the genes responsible for bipolar disorder is the first step in finding improved methods of diagnosis and treatment. Linkage analysis studies are currently indexed in PubMed, a repository of articles from all of the sciences. The articles are not organized and the search functionality is not robust enough to meet the needs of psychiatric genetics researchers. The Bipolar Disorder Genetics Database web application, located at http://www.bipolardisordergenetics.com, focuses solely on linkage analysis studies and intelligently organizes them. A researcher can use the application to identify studies in a matter of minutes instead of spending days reading abstracts in PubMed.

The next, and perhaps most critical, step is to understand the functions of the affected genes and the impact of the various mutations. Understanding these functions will lead to significant advances in the areas of diagnosis and treatment. Do certain mutations affect different copies of the same genes? Are certain mutations silent with no biological impact? What is the impact of a different set of genes being mutated in different individuals? Do the different genes all perform the same function or are they different functions? Is this difference in function the reason why the symptoms vary so much from individual to individual?

Understanding the functions will allow for a more granular classification system and a decrease in the amount of heterogeneity in the illness and symptoms. Patients will be more easily diagnosed and the accuracy of the initial diagnosis will improve. The long term ambitious goal is an objective diagnostic tool that does not rely on the symptoms, patient or physician. The importance of an early accurate diagnosis can't be overstated since "the correct treatment at the first onset of symptoms may reduce the patient's degree of lifelong suffering."[6]

An improved classification system will increase the effectiveness of the genetic research by eliminating much of the statistical noise that results from including a heterogeneous mix of illnesses. These advances in genetic research will further improve classification, continuing the cycle of advances in one area fueling advances in another.

Pharmaceutical researchers will also benefit and be able to more narrowly focus on the affected functions when creating the next generation of medications. These new medications will be more targeted and have fewer side effects, resulting in an

improved quality of life for patients. It will also decrease the number of patients who don't take medication because they feel the side effects are worse than the illness.

The Role of the Bipolar Disorder Genetics Database

The human curated Bipolar Disorder Genetics Database includes only the papers containing linkage analysis studies. The details extracted from these papers and included in the database will assist a researcher in deciding whether a study is relevant to his or her research. If it is then the paper can be obtained from the publisher's website. If it isn't then the researcher can set it aside and focus on the studies that are.

This application will become a primary resource for researchers studying the genetics of bipolar disorder. Database population will be a continuous endeavor and future enhancements will include incorporating gene and function information, a full-text search, a glossary and a reference section with recommendations about books and tutorials.

METHODS

PubMed Search

The first phase of the thesis involved searching through PubMed for all papers that include linkage analysis studies of bipolar disorder (see Figure 1). The search criteria were all papers that contained the term “Bipolar Disorder” or the term “Manic Depression”. This search was initially performed on November 28, 2005 and resulted in 20,008 records ordered chronologically. The search was performed multiple times over the course of the next few weeks with an increasing number of records. The final search was performed on January 6, 2006 and resulted in 21,016 records. Of those records, 16,006 were from papers published between 1980 and the present. I read the abstracts of those papers and identified 1,178 that referred to linkage analysis studies.

I then re-reviewed the abstracts published from 2000 to the present and identified 175 papers that were either reviews or positive findings of a linkage analysis study. Publication dates from 2000 to the present were selected partly to limit the results to a reasonable number and partly because that is when the current classification system was approved. Of those 175 papers, I identified five to serve as a pilot project by highlighting the range of features available in the web application.

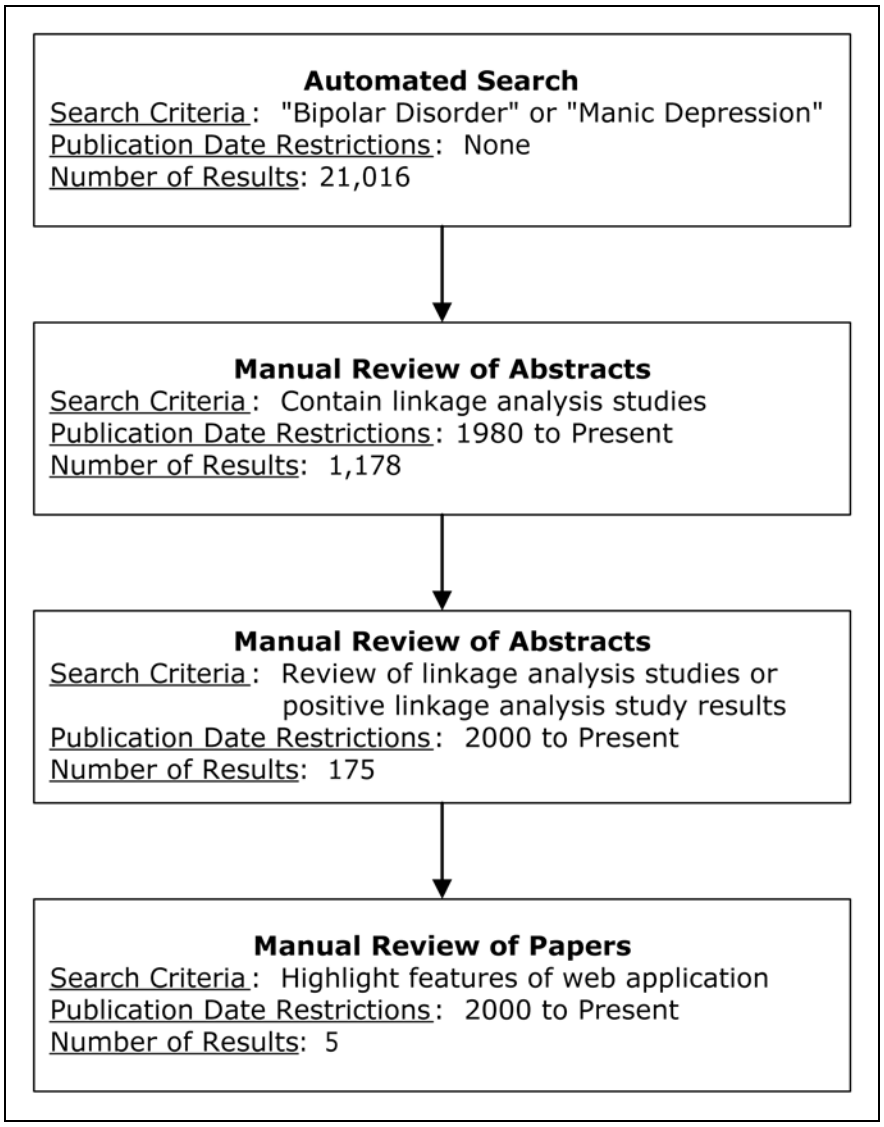

Figure 1 - PubMed Search Process

Database Development

The database was originally developed in MySQL on a Unix server located in the Bioinformatics department. The database is comprised of 31 normalized tables as shown in Figure 2 and described in Appendix A.

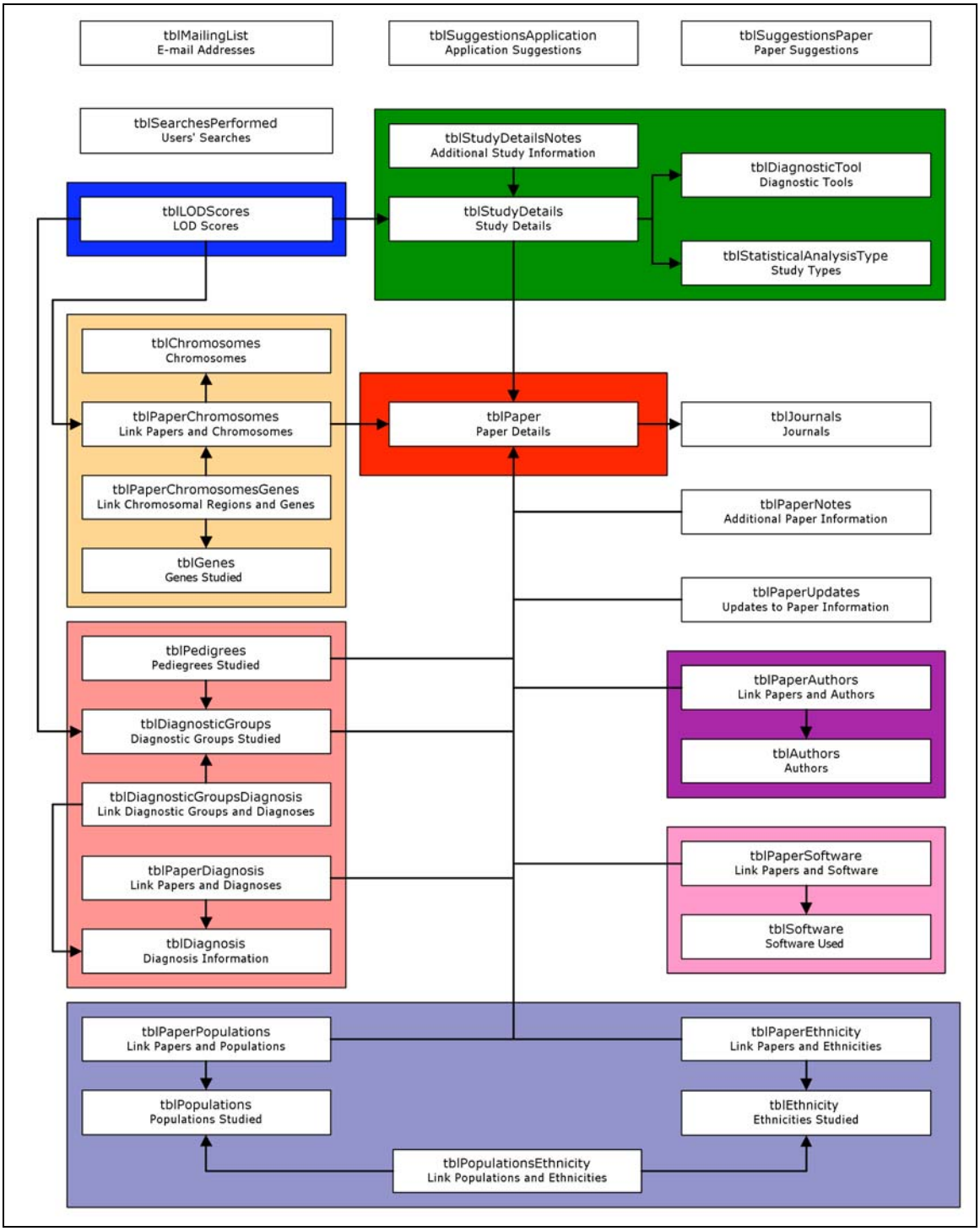

Figure 2 - Database Schema

There are three main tables used by the application. tblPaper (in red in Figure 2) contains details about the paper, tblStudyDetails (in green in Figure 2) contains details about the studies and tblLODScores (in blue in Figure 2) contains details about the linkage analysis LOD scores. A study was defined as a set of parameters under which the LOD scores were calculated. Since multiple studies can be discussed in one paper, the decision was made to create one table to contain study details and one table to contain paper details.

Tables tblChromosomes and tblPaperChromosomes contain details about the chromosomes studied. Tables tblGenes and tblPaperChromosomesGenes contain details about the genes studied.

Tables tblAuthors and tblPaperAuthors contain details about the authors of the papers. Tables tblSoftware and tblPaperSoftware contain details about the software packages used by the authors. Details about the journals in which the papers were published are contained in tblJournals.

Details about the populations being studied are contained in tables tblPopulations and tblPaperPopulations. Details about the ethnicities being studied are contained in tables tblEthnicity, tblPaperEthnicity and tblPopulationsEthnicity.

Tables tblDiagnosis and tblPaperDiagnosis contain details about the diagnoses studied in the papers. Tables tblDiagnosticGroups, tblDiagnosticGroupsDiagnosis and tblPedigrees contain details about the diagnostic groups used in the studies.

Table tblStatisticalAnalysisType contains the possible study types. Table tblDiagnosticTool contains the possible diagnostic tools.

Feedback from site visitors is contained in two tables. tblSuggestionsApplication contains suggestions about the application and tblSuggestionsPaper contains suggestions for papers to index.

Tables tblStudyDetailsNotes and tblPaperNotes contain miscellaneous information about the study and the paper respectively.

Three tables are used for administrative purposes. Table tblPaperUpdates is used to record changes to any of the information contained in the database. Table tblSearchesPerformed is used to capture details about searches performed by users. Table tblMailingList is used to store the e-mail addresses of all users who want to receive notification when new papers are indexed.

After creating the database, I read the five papers identified during the PubMed search, extracted the relevant details and entered them into the database using the command-line MySQL client.

Hosting

I purchased the domain www.bipolardisordergenetics.com through the GoDaddy domain name registration company. I am using GoDaddy's Windows servers to host the MySQL database and the website. The website uses Microsoft's Active Server Pages technology and therefore must reside on a Windows server. I moved the database from the Bioinformatics server to the GoDaddy server in order to keep response time at an acceptable level.

Site Development

The web pages are primarily a combination of the HyperText Markup Language (HTML) and Active Server Pages (ASP) programming languages. The ASP code

controls searching the data, processing forms and sending e-mail messages. The HTML code controls the presentation of the data and the display of user input forms. A Cascading Style Sheet (CSS) was used to easily manage the formatting of the pages. All of the pages that contain user input forms include scripts written in the JavaScript programming language. The code for the images at the top of the pages, the navigation links on the left, the links on the bottom and the disclaimer text is located in two include files. A third include file is used to store the database connection string. The include files have an “inc” prefix in their names.

The DNA image was purchased from Corbis Corporation under their royalty-free license agreement (contained in Appendix B) that allows for unrestricted use of the image. The image is used in the main content on the home page, in the heading on all pages and as the icon that appears when users bookmark the site.

All of the code files are stored in the main directory and all of the images are located in a subdirectory named “images”. The pages for the simple searches are named “SimpleSearch*x*.asp” where *x* is a number from one to nine. Pages that process a form, such as a simple search, have names that are similar to the names of their respective form pages. The only difference is the word “Process” appended to the processing page. For example, the page SimpleSearch2Process.asp processes the SimpleSearch2.asp page.

The code was developed using a text editor (TextEdit from Apple Computer, Inc) on an Apple iBook G4. Image manipulation was done using a graphics program (Adobe Photoshop CS from Adobe Systems Incorporated). The files were transferred to the Windows server using an FTP client (CuteFTP Mac by GlobalSCAPE Texas, LP). The pages were viewed with the Firefox Internet browser on the iBook.

User Testing

The site was tested on multiple browser and platform combinations to ensure compatibility. The testing found that the site works well on all of the common browser and platform configurations. Users with a screen resolution of 800 x 600 will find it necessary to scroll from left to right. The online tool Dr. HTML (by Imagiware, Inc., http://www2.imagiware.com/RxHTML/) was used to check the code for errors. Six individuals, two of whom have psychiatric research experience, performed additional testing. Their feedback, combined with the results of the testing and Dr. HTML analysis, was incorporated into the site.

Site Promotion

The website was submitted to the Google search engine as part of a search engine optimization plan. The plan also includes adding a listing in Yahoo!, MSN and several other popular search engines. Additionally, a manuscript is being written for submission to the peer-reviewed journal Neuropsychiatric Genetics.

RESULTS

The primary result of this thesis is a database driven web application that will be a central repository of linkage analysis studies. The user-friendly interface will allow researchers to quickly and easily find relevant studies without having to read through thousands of abstracts.

Phil is a hypothetical researcher investigating possible bipolar disorder susceptibility regions on chromosome 8. Figure 3 shows how he uses the Bipolar Disorder Genetics Database web application to quickly identify papers that contain positive results of linkage analysis studies on chromosome 8. He uses the "Search By Chromosome" feature and retrieves four results. For each result, he views the study and paper details. On the study details page he sees the chromosomal regions, number of subjects, subjects' diagnoses, population and ethnicity. He then goes to the paper details page and reads the abstract. Two of the papers are relevant to his research so, using the citation information and the link from the paper details page, he goes to the publishers' websites and purchases them.

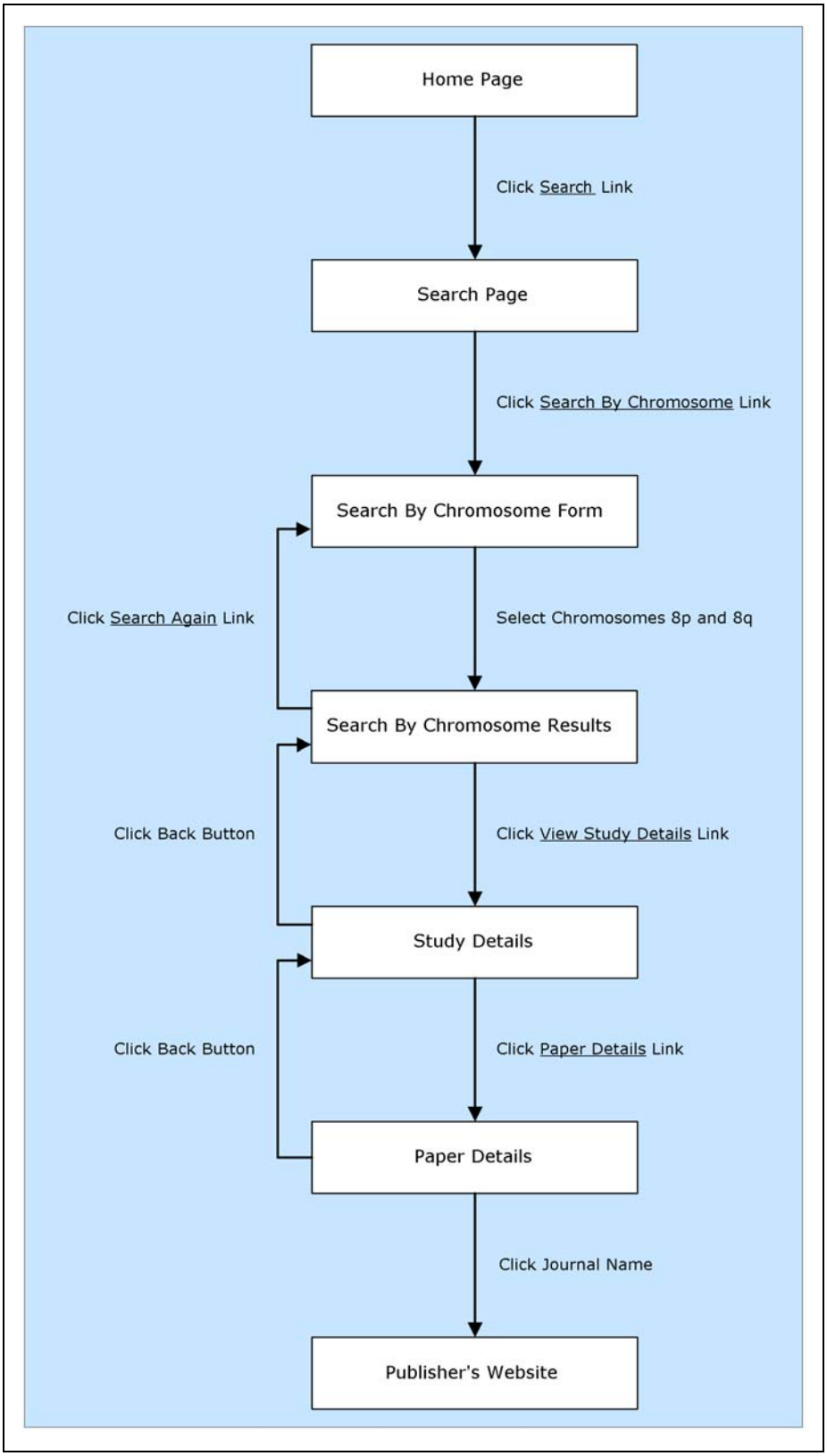

Figure 3 - Searching By Chromosome

Target Audience

The example of Phil searching by chromosome 8 is not merely hypothetical but is also indicative of the types of searches that will be performed. The primary users of the Bipolar Disorder Genetics Database web application will be researchers in the field of psychiatric genetics studying bipolar disorder. Researchers studying the genetics of schizophrenia will also benefit from using the application because they will be able to search for studies that included individuals with schizophrenia. Researchers can use the site to identify chromosomal regions to investigate prior to undertaking initial linkage analysis studies. Researchers can also identify studies they want to try and replicate in order to verify results. Researchers who have already completed a linkage analysis study can use the application to identify similar studies for comparison of results.

Site Layout and Page Structure

The site is divided into seven main sections and three minor sections. The main sections are listed in the navigation pane as shown in Figure 4. The minor sections are listed in the footer pane (see Figure 4). The page structure is divided into four panes using include files and tables (see Figure 4). The header, navigation and footer are identical on every page.

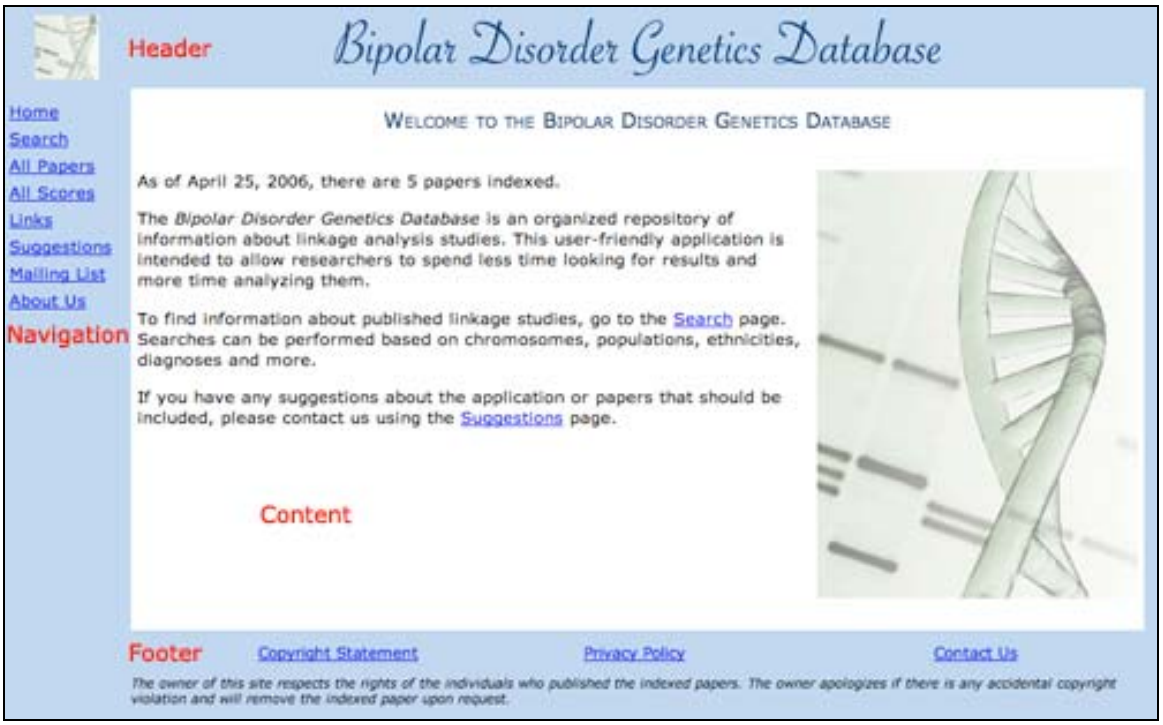

Figure 4 - Page Structure

Search Functionality

The main Search page, accessed by clicking the Search link in the navigation pane, displays links to ten search forms, as shown in Figure 5. Nine of the forms allow the user to search by only one characteristic and are categorized as “simple searches”. The results page for each form displays the search terms, number of results, chromosomal region, LOD score range and a link to the study details (see Figure 6). The tenth form allows a user to search by a combination of chromosome, population, ethnicity and diagnosis. The results page displays the search terms, number of results, population, ethnicity, diagnosis, chromosomal region, LOD score range and a link to the study details (see Figure 7).

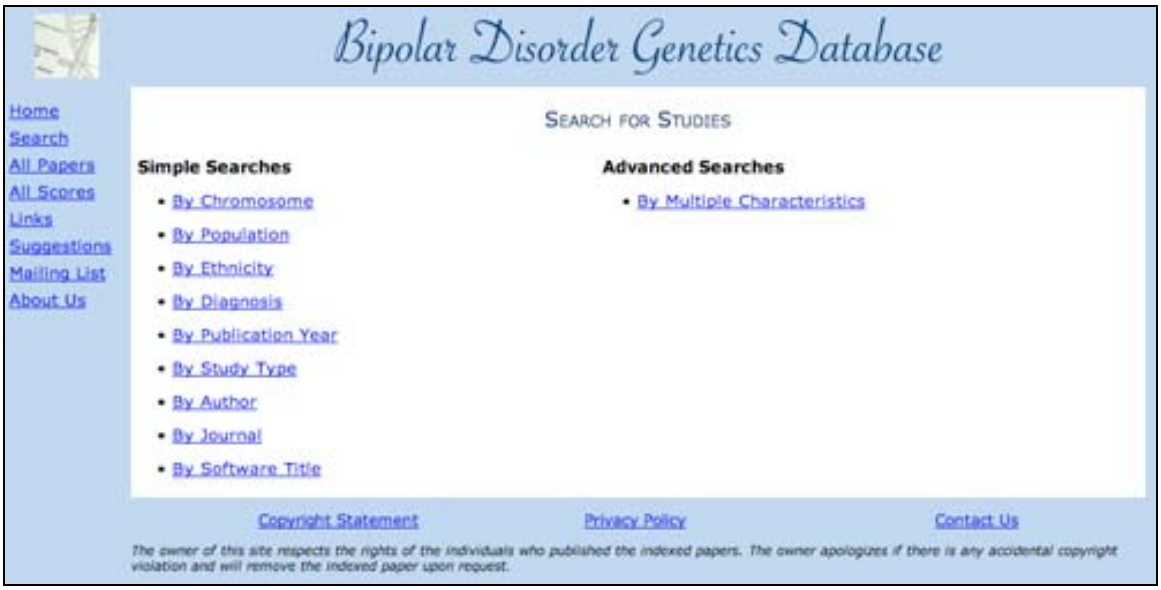

Figure 5 - Main Search Page

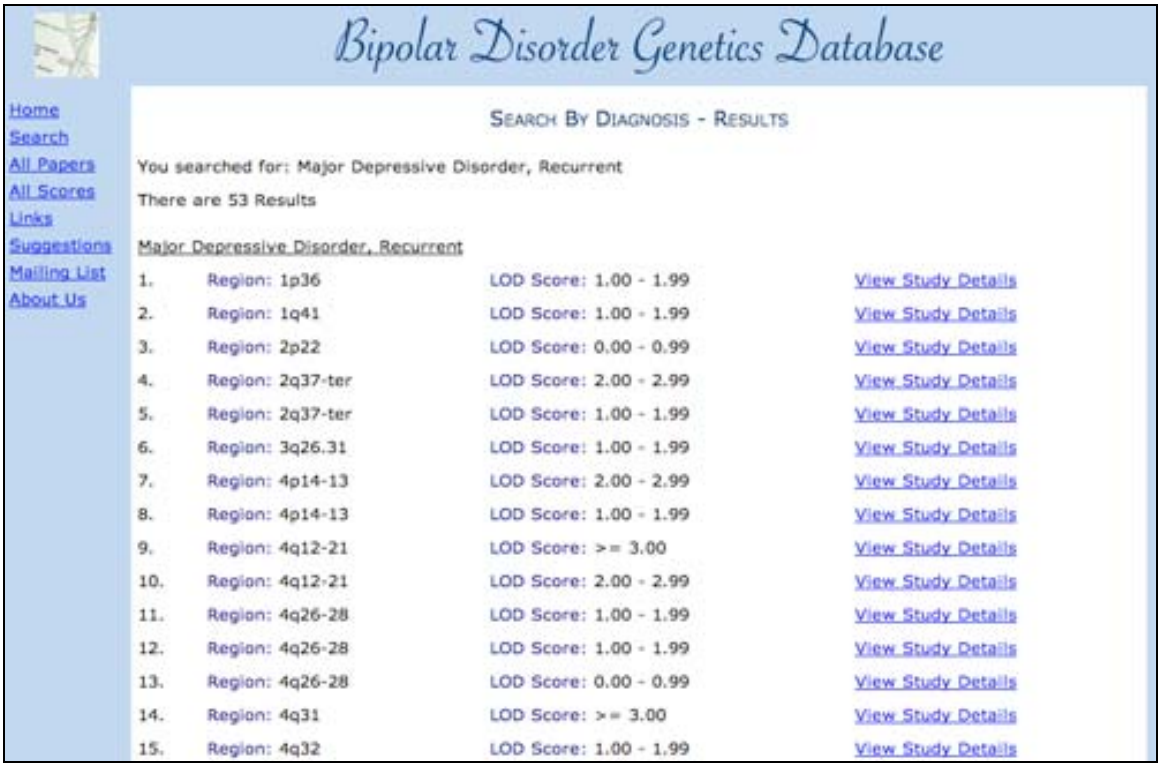

Figure 6 - Simple Search Results

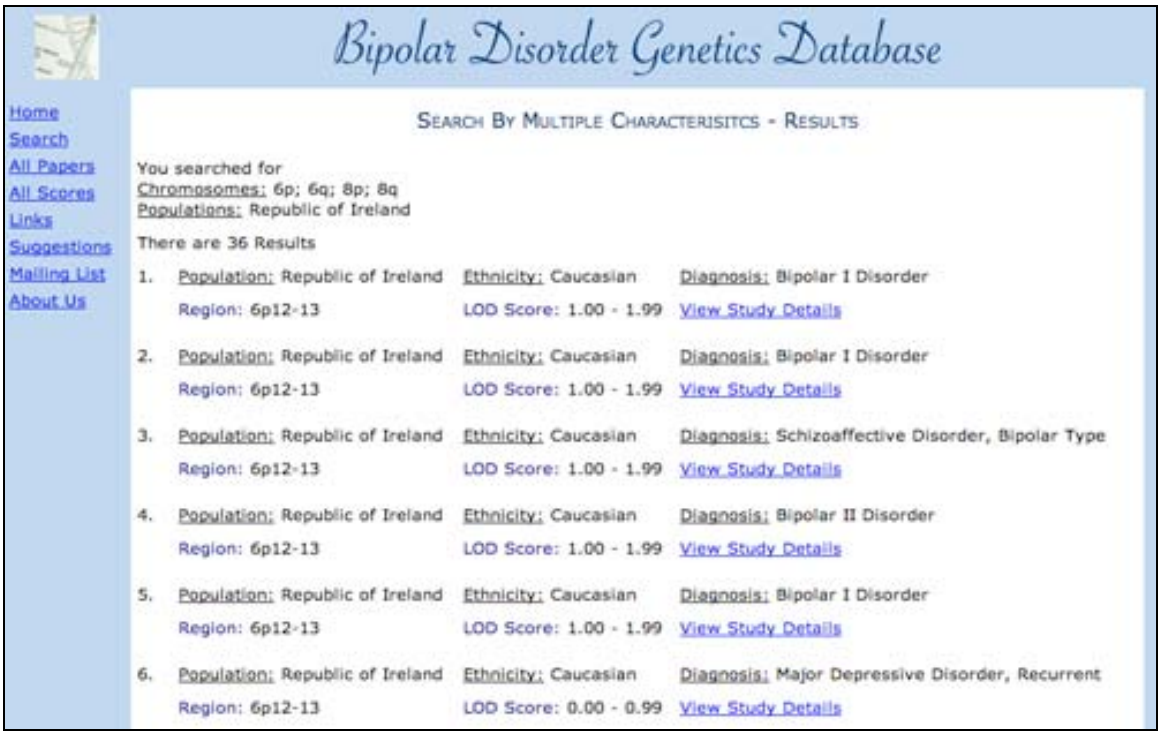

Figure 7 - Advanced Search Results

All Papers and All Scores Pages

The All Papers and All Scores pages allow users to quickly see an overview of the information contained in the database. The All Papers page displays the paper title, publication year and a link to the paper details (see Figure 8). The All Scores page displays the population, ethnicity, diagnosis, chromosomal region, LOD score range and a link to the study details (see Figure 9).

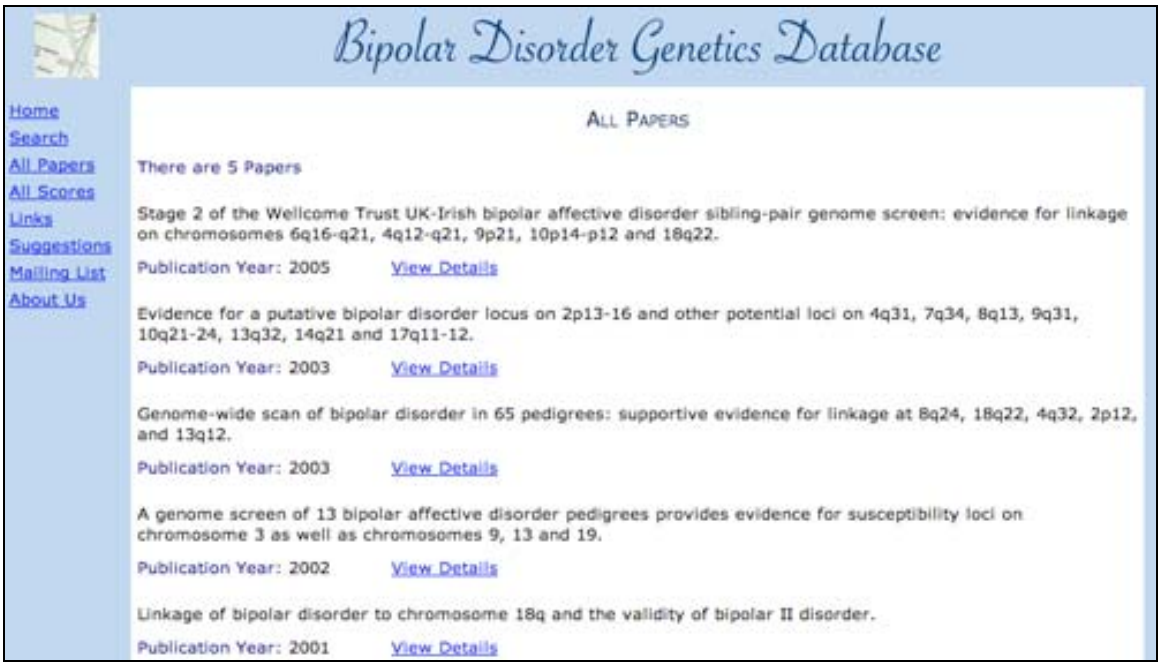

Figure 8 - All Papers

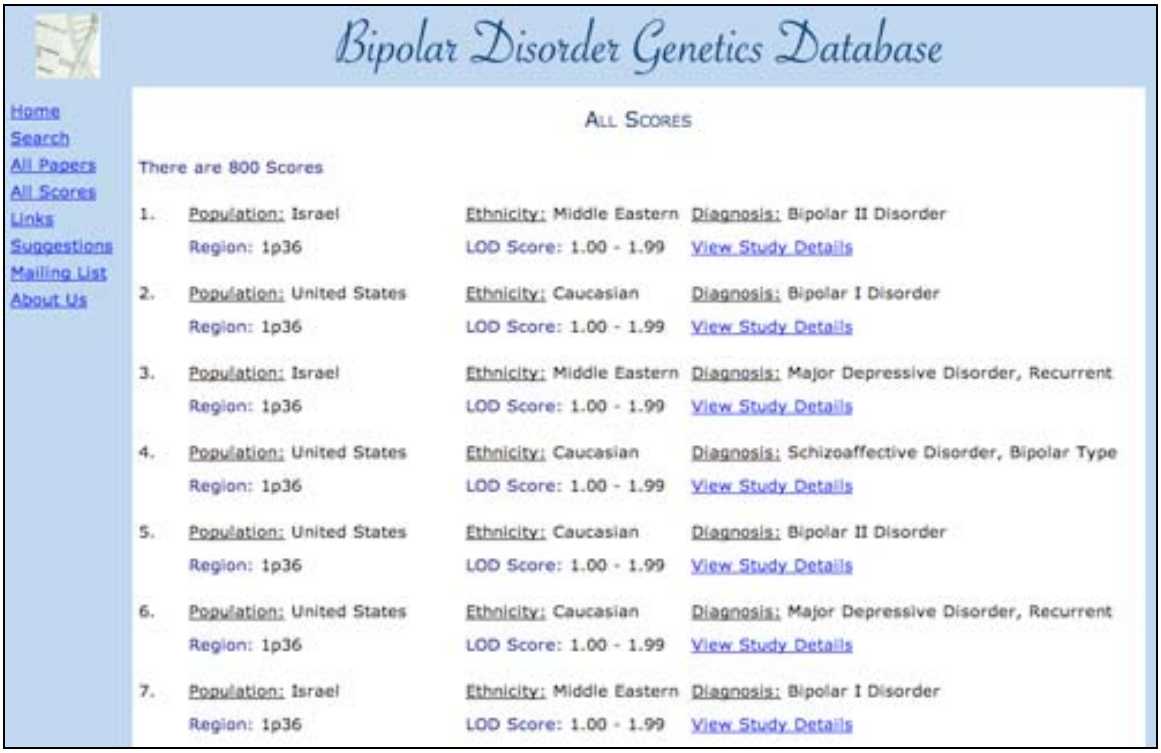

Figure 9 - All Scores

Study and Paper Details

Every search result page and the All Scores page contain links to the study details page. The study details page is divided into categories about the study, the subjects, the genotyping and additional information (see Figure 10). The page also contains the paper's citation and a link to the paper details.

The study category contains the type of study and the chromosomal regions investigated. The rest of the information in the study category depends on the type of study. For an Affected Sibling Pair (ASP) study, the number of ASPs is displayed. For a Parametric Analysis study, the allele frequencies and penetrance values are displayed.

The subjects category displays the diagnostic tool used, the kappa score, onset age, interview age, number of pedigrees, ethnicities and populations. The kappa score is a measure of how well multiple doctors agree on the diagnoses of the subjects in the study. The values range from zero to one with higher scores better than lower ones. The category also contains information about the diagnoses and diagnostic groups being studied.

The genotyping category contains the number of individuals, number of markers and marker density.

The additional information category contains the names of the software programs used and all miscellaneous notes. Clicking on the name of a software program will load the program's website in a separate browser window.

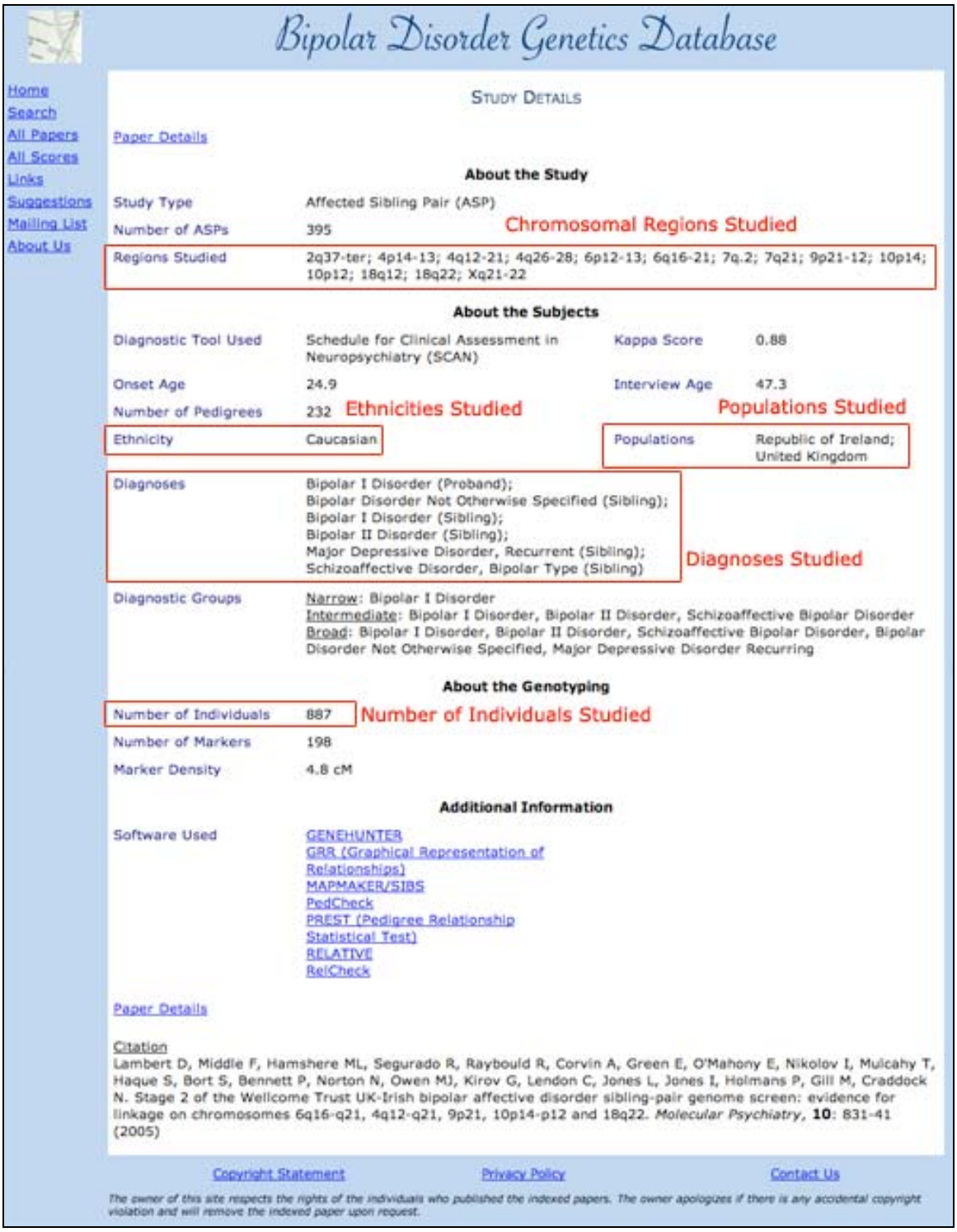

Figure 10 - Study Details

The study details page and the All Papers page link to the paper details page. The paper details page displays the paper title, publication year, journal, PubMed ID, authors, abstract and citation (see Figure 11). The page also contains links to the study details. Clicking on the journal name will open the journal's website in a new browser window. Clicking on the PubMed ID will open the PubMed entry in a new browser window.

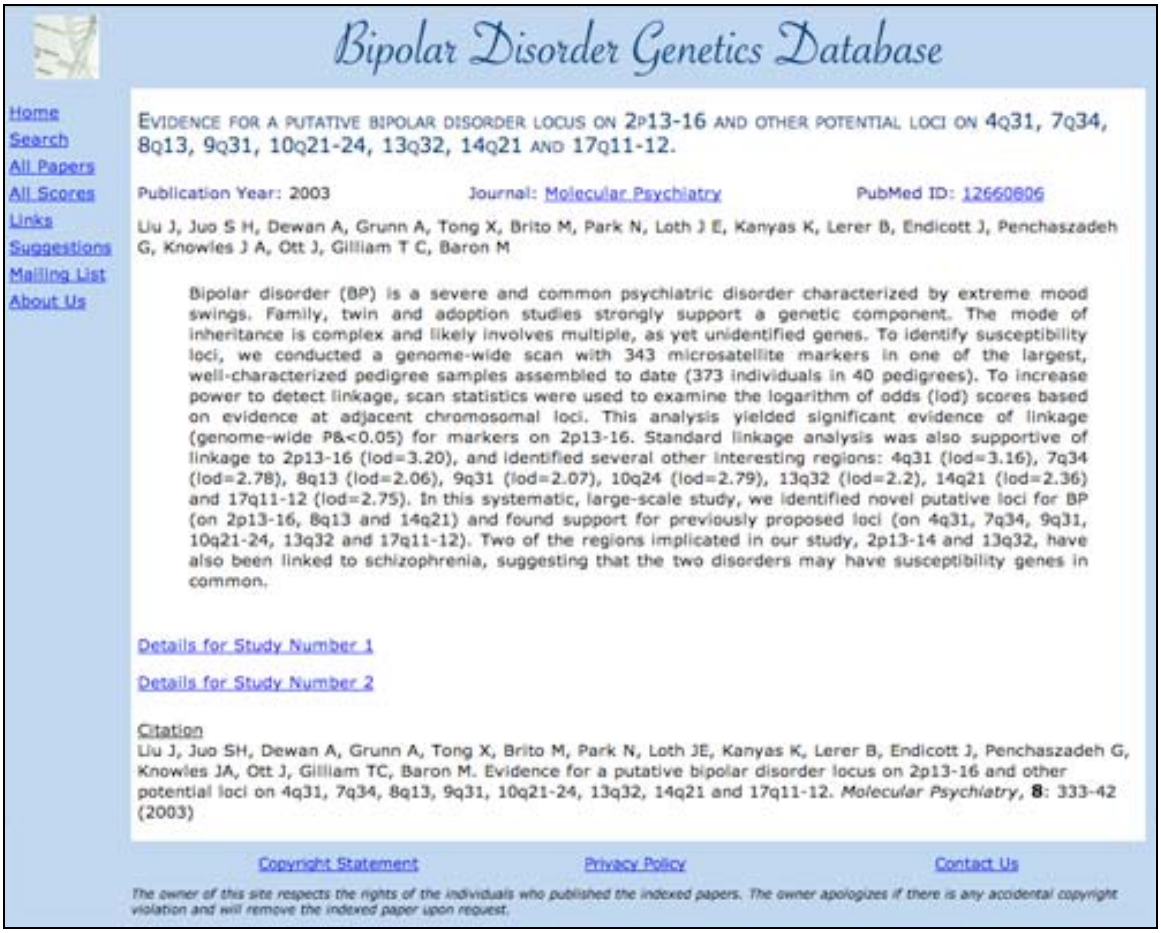

Figure 11 - Paper Details

User Feedback

There are three forms that allow users to provide feedback and two forms relating to a mailing list. Two forms allow users to make suggestions regarding the application and papers to index. The two mailing list forms allow users to subscribe and unsubscribe. When new papers are indexed in the database a notification message is sent to all users on the mailing list. A general-purpose contact form is provided for all other types of comments and inquiries.

The Bipolar Disorder Genetics Database is a fully functional research tool. The application allows users to search for information in many different ways. The interface is intuitive and, because it is web-based, requires no installation or maintenance by the user.

DISCUSSION

The proposal for this thesis outlined several goals including identifying all papers containing linkage study information published since 2000 and developing an application publicly available to the research community. Both of those goals were met and provide a valuable tool for psychiatric researchers as well as a strong foundation for future application enhancements.

Prior to the development of this application there were no tools available to provide a high-level overview of linkage analysis study results. Analysis of the studies required a lengthy and cumbersome manual review of the literature. This laborious process had to be repeated by every researcher interested in the results. The human curated Bipolar Disorder Genetics Database eliminates that duplication of effort.

The identification of all relevant papers allows researchers to focus on the most promising chromosomal regions and proceed to the next phase of understanding the biological basis of bipolar disorder, the identification of genes. Once the genes have been identified, their functions can be determined, a significant step in finding improved methods of diagnosis and treatment.

As one indicator of how the community views the importance of a user-friendly application, more than one journal agreed to publish a manuscript describing it. As a second indicator, a presentation to the researchers at the Centre for Addiction and Mental Health in Toronto was enthusiastically received.

Content Considerations

During user testing the amount of content provided by the application was reviewed to ensure that it does not infringe on the copyright of the authors and publishers of the papers. The content was also reviewed to ensure that users would not be able to obtain enough information from the database to make reading the paper unnecessary. Since most of the articles are published in journals that require a subscription, allowing users to circumvent the subscription process would be unfair to the publishers. After consulting with several sources, including psychiatric researchers and members of Rochester Institute of Technology's Publishing and Scholarship Support Center, several changes were made to the application.

The main concern was that displaying all of the LOD scores, a major component of the study, could be interpreted as plagiarizing proprietary information. Originally the specific values were displayed and because these were actual data it could be copyright infringement. Two changes were made to address this concern. The first was to change the way LOD scores are displayed in the search results. Instead of displaying the actual data, the scores are now displayed as one of the following ranges: 0.00 – 0.99, 1.00 – 1.99, 2.00 – 2.99 and >= 3.00. These ranges provide enough information to allow the user to determine if the scores are significant enough to warrant further review. Displaying ranges instead of actual data protects the author's work without reducing the user experience. The second change was the removal of the page allowing users explicit access to all of the LOD scores published in a particular paper.

In addition, the paper's citation was included in the study details page and the paper details page. Furthermore, a disclaimer at the bottom of every page states "*The owner of this site respects the rights of the individuals who published the indexed*

papers. The owner apologizes if there is any accidental copyright violation and will remove the indexed paper upon request." These changes resulted in an application that protects the rights of authors and publishers while still providing a venue for highlighting relevant peer reviewed literature without revealing proprietary information.

Future Enhancements

There are several enhancements planned for the application. Inclusion of a full-text search will allow a researcher to easily search all of the content in the database for specific items not listed on any of the current search forms. A glossary and recommendations on books and tutorials will help researchers who are new to the field. Creation of an administrative interface will simplify entering paper information, allowing that function to be turned over to other individuals. The last planned enhancement will benefit individuals with bipolar disorder and their family members. Since it is likely that non-researchers may be directed to the site by a search engine, a section will be added that focuses on their needs. The section will contain information about online resources, mental health organizations and book recommendations. These enhancements, an ongoing project over the next few years, will add to the application's importance and make it one of the premiere tools in the field. The application is fully functional and will be a valuable resource to the community.

The focus of this thesis was to create a user-friendly web application that would serve as an organized repository of linkage analysis study information. By identifying relevant research, creating a database and developing the application, I created a tool to allow researchers to spend less time getting linkage analysis study results and more time interpreting them.

CONCLUSIONS

Bipolar Disorder is a devastating mental illness that affects an estimated 2.3 million American adults[1]. Interpretation of linkage analysis studies of the illness is the best hope for improved diagnosis and treatment by allowing researchers to identify the biological causes. This interpretation has suffered from the lack of organization of linkage analysis studies because there is no central repository specifically designed for linkage analysis studies of bipolar disorder. Without a central repository, researchers are unable to quickly and easily locate relevant papers.

The Bipolar Disorder Genetics Database web application, located at http://www.bipolardisordergenetics.com, is an intuitive user-friendly central repository that will allow researchers to quickly and easily search peer-reviewed literature for relevant studies. Using the application will allow researchers to spend less time getting the results and more time interpreting them.

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APPENDIX A – DATABASE DEFINITION

tblStudyDetails	
Table comments: Contains details about the studies	
Field	**Description**
tblStudyDetails_pk	Primary Key
tblStudyDetails_fk_tblPaper	Foreign Key - tblPaper
tblStudyDetails_fk_tblDiagnosticTool	Foreign Key - tblDiagnosticTool
tblStudyDetails_fk_tblStatisticalAnalysisType	Foreign Key - tblStatisticalAnalysisType
tblStudyDetails_onsetAge	Onset Age
tblStudyDetails_interviewAge	Interview Age
tblStudyDetails_kappaScore	Kappa Score
tblStudyDetails_markerDensity	Genotype Marker Density
tblStudyDetails_numberOfMarkersGenotyped	Number of Markers Genotyped
tblStudyDetails_numberOfIndividualsGenotyped	Number of Individuals Genotyped
tblStudyDetails_numberOfPedigrees	Number of Pedigrees Studied
tblStudyDetails_numberOfASPs	Number of Affected Sibling Pairs Studied
tblStudyDetails_dominantAlleleFrequency	Allele Frequency in the Dominant Model
tblStudyDetails_dominantPenetranceCarriers	Penetrance of Carriers in the Dominant Model
tblStudyDetails_dominantPenetranceNoncarriers	Penetrance of Noncarriers in the Dominant Model
tblStudyDetails_recessiveAlleleFrequency	Allele Frequency in the Recessive Model
tblStudyDetails_recessivePenetranceCarriers	Penetrance of Carriers in the Recessive Model
tblStudyDetails_recessivePenetranceNoncarriers	Penetrance of Noncarriers in the Recessive Model

tblDiagnosticTool	
Table comments: Contains diagnostic tools used to diagnose subjects	
Field	**Description**
tblDiagnosticTool_pk	Primary Key
tblDiagnosticTool_name	Name of the Diagnostic Tool

tblStatisticalAnalysisType	
Table comments: Contains the study types used	
Field	**Description**
tblStatisticalAnalysisType_pk	Primary Key
tblStatisticalAnalysisType_name	Name of the Study Type

Table tblStudyDetails contains fields for a foreign key to the tblPaper table and for 16 parameters. Three of the fields relate to genotyping and contain the number of individuals genotyped, the number of markers genotyped and the marker density. Five fields relate to the subjects and contain the age of onset, age at the interview,

number of pedigrees, the kappa score and a foreign key to tblDiagnosticTool. Table tblDiagnosticTool contains the different possible diagnostic tools, such as the Diagnostic Interview for Genetic Studies (DIGS). The remaining eight fields contain details about the study model. The first field is a foreign key to tblStatisticalAnalysisType, a table that contains the different possible study types. The second field, used only when the study type is Affected Sibling Pair, contains the number of Affected Sibling Pairs. Six fields are used only for the Parametric Analysis study type. There are two fields for allele frequency, one for a dominant model of inheritance and one for a recessive model. The penetrance values are contained in four fields and are carrier penetrance in the dominant model, noncarrier penetrance in the dominant model, carrier penetrance in the recessive model and noncarrier penetrance in the recessive model.

tblPaper	
Table comments: Contains details about the papers	
Field	**Description**
tblPaper_pk	Primary Key
tblPaper_fk_tblJournals	Foreign Key - tblJournals
tblPaper_publicationYear	Year Published
tblPaper_pages	Page Numbers
tblPaper_PMID	PubMed ID
tblPaper_abstract	Abstract
tblPaper_enteredBy	Entered By
tblPaper_dateEntered	Date Entered
tblPaper_title	Paper Title
tblPaper_citation	Paper Citation

Table tblPaper contains seven fields for details about the paper, a field for the name of the person who entered the information and a field for the date the information was entered. The paper details include the title, abstract, PubMed ID, citation and publication year. The table also contains the paper's page numbers and a foreign key to tblJournals, a table that contains information about journals.

tblLODScores	
Table comments: Contains details about the LOD scores	
Field	**Description**
tblLODScores_pk	Primary Key
tblLODScores_fk_tblStudyDetails	Foreign Key - tblStudyDetails
tblLODScores_fk_tblDiagnosticGroups	Foreign Key - tblDiagnosticGroups
tblLODScores_fk_tblPaperChromosomes	Foreign Key - tblPaperChromosomes
tblLODScores_gender	Gender of the subjects - Male, Female or Both
tblLODScores_multipointOrTwoPoint	Type of Comparison - Two Point or Multipoint
tblLODScores_geneticModel	Type of Genetic Model Used
tblLODScores_LODScore	LOD Score
tblLODScores_NPLScore	NPL Score
tblLODScores_pValue	p Value for the Score
tblLODScores_marker	Chromosomal Marker
tblLODScores_positionCM	Position in centiMorgans
tblLODScores_positionMB	Position in Megabases

Table tblLODScores contains 12 fields for details about the linkage analysis study results. One field is the foreign key to tblStudyDetails to link the score information with the appropriate study. Three fields contain the score information. One contains the LOD score value, one contains the Nonparametric Linkage (NPL) value and one contains the probability value (p value). The NPL value is entered only if the study type is Nonparametric Linkage. Four fields are used to contain details about the location within the genome. The first is a foreign key to tblPaperChromosomes, a table that contains the chromosomal regions being studied. The other three contain the marker name, the position measured in centiMorgans and the position measured in megabases. Two of the fields contain additional details about the type of analysis. The first one indicates whether the analysis is two point, comparing two markers, or multipoint, comparing multiple markers. The second, used only if the study type is Parametric Analysis, contains the type of genetic model. The remaining two fields contain details about the subjects. One is for the gender of the subjects and the other is a foreign key to tblDiagnosticGroups, a table that contains details about the diagnostic groups studied by the authors.

tblChromosomes	
Table comments: Contains number and arm for all Chromosomes	
Field	**Description**
tblChromosomes_pk	Primary Key
tblChromosomes_number	Chromosome Number
tblChromosomes_arm	Chromosome Arm - p or q

tblPaperChromosomes	
Table comments: Link the Paper and Chromosomes tables	
Field	**Description**
tblPaperChromosomes_pk	Primary Key
tblPaperChromosomes_fk_tblPaper	Foreign Key - tblPaper
tblPaperChromosomes_fk_tblChromosomes	Foreign Key - tblChromosomes
tblPaperChromosomes_region	Chromosomal Region

Table tblChromosomes contains details about all of the human chromosomes. There is a field for the number and a field for the arm. Table tblPaperChromosomes is used to associate the chromosomes to the papers that study them. The table also contains a field for the region being studied.

tblAuthors	
Table comments: Contains the names of the authors	
Field	**Description**
tblAuthors_pk	Primary Key
tblAuthors_lastName	Author's Last Name
tblAuthors_firstName	Author's First Name
tblAuthors_middleName	Author's Middle Name

tblPaperAuthors	
Table comments: Link the Paper and Authors tables	
Field	**Description**
tblPaperAuthors_pk	Primary Key
tblPaperAuthors_fk_tblPaper	Foreign Key - tblPaper
tblPaperAuthors_fk_tblAuthors	Foreign Key - tblAuthors

Table tblAuthors contains all of the authors that contributed to at least one of the indexed papers. Each individual is listed only once, regardless of how many papers he or she authored. Table tblPaperAuthors is used to associate the authors with their papers.

tblPopulations	
Table comments: Contains the populations studied	
Field	**Description**
tblPopulations_pk	Primary Key
tblPopulations_name	Name of the Population

tblPaperPopulations	
Table comments: Link the Paper and Populations tables	
Field	**Description**
tblPaperPopulations_pk	Primary Key
tblPaperPopulations_fk_tblPaper	Foreign Key - tblPaper
tblPaperPopulations_fk_tblPopulations	Foreign Key - tblPopulations

Table tblPopulations contains all of the populations studied in the papers, with each population listed only once. Table tblPaperPopulations is used to associate the papers with the populations.

tblEthnicity	
Table comments: Contains ethnicities of subjects	
Field	**Description**
tblEthnicity_pk	Primary Key
tblEthnicity_name	Name of the Ethnicity

tblPaperEthnicity	
Table comments: Link the Paper and Ethnicity tables	
Field	**Description**
tblPaperEthnicity_pk	Primary Key
tblPaperEthnicity_fk_tblPaper	Foreign Key - tblPaper
tblPaperEthnicity_fk_tblEthnicity	Foreign Key - tblEthnicity

tblPopulationsEthnicity	
Table comments: Link the Populations and Ethnicity tables	
Field	**Description**
tblPopulationsEthnicity_pk	Primary Key
tblPopulationsEthnicity_fk_tblPopulations	Foreign Key - tblPopulations
tblPopulationsethnicity_fk_tblEthnicity	Foreign Key - tblEthnicity

Table tblEthnicity contains all of the ethnicities studied in the papers, with each ethnicity listed only once. Table tblPaperEthnicity is used to associate the papers with the ethnicities. Table tblPopulationsEthnicity associates a population with its ethnicity.

tblSoftware	
Table comments: Contains the software used in the studies	
Field	**Description**
tblSoftware_pk	Primary Key
tblSoftware_name	Software Name
tblSoftware_link	URL to the Software's Website

tblPaperSoftware	
Table comments: Link the Paper and Software tables	
Field	**Description**
tblPaperSoftware_pk	Primary Key
tblPaperSoftware_fk_tblPaper	Foreign Key - tblPaper
tblPaperSoftware_fk_tblSoftware	Foreign Key - tblSoftware

Table tblSoftware contains details about software mentioned in the papers. It contains a field for the software title and a field for the URL to the software's website. Table tblPaperSoftware associates the papers with the software.

tblJournals	
Table comments: Contains information about the journals	
Field	**Description**
tblJournals_pk	Primary Key
tblJournals_name	The Journal's Name
tblJournals_publisher	The Journal's Publisher
tblJournals_link	URL to the Journal's Website

Table tblJournals contains details about the journals in which the papers are published. One field contains the journal's name, one contains the publisher's name and one contains the URL for the journal's website.

tblDiagnosis	
Table comments: Contains diagnoses from the DSM	
Field	**Description**
tblDiagnosis_pk	Primary Key
tblDiagnosis_name	Diagnosis Name
tblDiagnosis_code	Diagnosis Code
tblDiagnosis_DSMEdition	DSM Edition

tblPaperDiagnosis	
Table comments: Link the Paper and Diagnosis tables	
Field	**Description**
tblPaperDiagnosis_pk	Primary Key
tblPaperDiagnosis_fk_tblPaper	Foreign Key - tblPaper
tblPaperDiagnosis_fk_tblDiagnosis	Foreign Key - tblDiagnosis
tblPaperDiagnosis_probandOrRelative	Whether the Diagnosis is for the Proband or a Relative

Table tblDiagnosis contains information about mood and psychotic disorder diagnoses. The table contains the name, diagnostic code and version of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) in which it appears. Table tblPaperDiagnosis associates a paper with the diagnoses studied by the authors. The table also contains a field to indicate whether it's the proband or a relative that needs to have the diagnosis.

tblDiagnosticGroups	
Table comments: Contains diagnostic groups mentioned in papers	
Field	**Description**
tblDiagnosticGroups_pk	Primary Key
tblDiagnosticGroups_fk_tblPaper	Foreign Key - tblPaper
tblDiagnosticGroups_name	Name of the Group
tblDiagnosticGroups_description	Diagnoses Contained in the Group

tblDiagnosticGroupsDiagnosis	
Table comments: Maps Diagnostic Groups to the DSM Diagnoses	
Field	**Description**
tblDiagnosticGroupsDiagnosis_pk	Primary Key
tblDiagnosticGroupsDiagnosis_fk_tblDiagnosticGroups	Foreign Key - tblDiagnosticGroups
tblDiagnosticGroupsDiagnosis_fk_tblDiagnosis	Foreign Key - tblDiagnosis

Table tblDiagnosticGroups contains information about the diagnostic groups studied in the papers. Table tblDiagnosticGroupsDiagnosis associates these diagnostic groups with the DSM diagnoses that are contained in them.

tblPedigrees	
Table comments: Contains details about the pedigrees used in a study	
Field	**Description**
tblPedigrees_pk	Primary Key
tblPedigrees_fk_tblPaper	Foreign Key - tblPaper
tblPedigrees_fk_tblDiagnosticGroups	Foreign Key - tblDiagnosticGroups
tblPedigrees_numberOfPedigrees	Number of Pedigrees
tblPedigrees_totalNumberOfIndividuals	Total Number of Individuals
tblPedigrees_meanNumberOfIndividuals	Mean Number of Individuals in a Pedigree

Table tblPedigrees contains additional details about the diagnostic groups. The table contains foreign keys to tblDiagnosticGroups and to tblPaper. There are also fields for the number of pedigrees in a diagnostic group, the total number of individuals and the mean number of individuals.

tblGenes	
Table comments: Contains the names of genes	
Field	**Description**
tblGenes_pk	Primary Key
tblGenes_name	Name of the Gene

tblPaperChromosomesGenes	
Table comments: Link the PaperChromosomes and Gene tables	
Field	**Description**
tblPaperChromosomesGenes_pk	Primary Key
tblPaperChromosomesGenes_fk_tblPaperChromosomes	Foreign Key - tblPaperChromosomes
tblPaperChromosomesGenes_fk_tblGenes	Foreign Key - tblGenes

Table tblGenes contains names of genes. Table tblPaperChromosomesGenes associates the gene with a chromosomal region studied in one of the papers.

tblSuggestionsPaper	
Table comments: Contains details about suggestions for papers to index	
Field	**Description**
tblSuggestionsPaper_pk	Primary Key
tblSuggestionsPaper_title	Paper Title
tblSuggestionsPaper_author	Paper Author
tblSuggestionsPaper_year	Publication Year
tblSuggestionsPaper_dateEntered	Date Entered

tblSuggestionsApplication	
Table comments: Contains suggestions about the application	
Field	**Description**
tblSuggestionsApplication_pk	Primary Key
tblSuggestionsApplication_suggestion	Suggestion
tblSuggestionsApplication_email	Suggester's E-mail Address
tblSuggestionsApplication_dateEntered	Date Entered
tblSuggestionsApplication_referringPage	Referring Page

Table tblSuggestionsPaper contains suggestions for papers to index with three fields for details provided by the user. The fields are title, author and year. The table also contains the date the suggestion was made. Table tblSuggestionsApplication contains suggestions about the application itself. This table contains fields for the suggestion and the user's e-mail address. There are also fields to contain the date the suggestion was entered and the page the user was on prior to filling out the suggestion form.

tblStudyDetailsNotes	
Table comments: Contains miscellaneous notes about the studies	
Field	**Description**
tblStudyDetailsNotes_pk	Primary Key
tblStudyDetailsNotes_fk_tblStudyDetails	Foreign Key - tblStudy Details
tblStudyDetailsNotes_enteredBy	Entered By
tblStudyDetailsNotes_dateEntered	Date Entered
tblStudyDetailsNotes_note	Note

tblPaperNotes	
Table comments: Contains miscellaneous notes from the papers	
Field	**Description**
tblPaperNotes_pk	Primary Key
tblPaperNotes_fk_tblPaper	Foreign Key - tblPaper
tblPaperNotes_enteredBy	Entered By
tblPaperNotes_dateEntered	Date Entered
tblPaperNotes_note	Note

Table tblStudyDetailsNotes contains additional information about the study. Table tblPaperNotes contains additional information about the paper. Both tables contain fields for the note, the name of the person who entered it and the date it was entered. Table tblStudyDetailsNotes includes a foreign key to the tblStudyDetails table. Table tblPaperNotes includes a foreign key to the tblPaper table.

tblPaperUpdates	
Table comments: Contains details about updates to the paper information	
Field	**Description**
tblPaperUpdates_pk	Primary Key
tblPaperUpdates_fk_tblPaper	Foreign Key - tblPaper
tblPaperUpdates_updatedBy	Updated By
tblPaperUpdates_dateUpdated	Date Updated
tblPaperUpdates_note	Note About the Update

tblSearchesPerformed	
Table comments: Contains details about the searches performed	
Field	**Description**
tblSearchesPerformed_pk	Primary Key
tblSearchesPerformed_page	Search Page
tblSearchesPerformed_resultCount	Number of Results
tblSearchesPerformed_date	Date Search was Performed
tblSearchesPerformed_SQLStatement	The SQL Statement Executed

tblMailingList	
Table comments: Contains e-mail addresses for the mailing list	
Field	**Description**
tblMailingList_pk	Primary Key
tblMailingList_email	E-mail Address
tblMailingList_dateEntered	Date Entered

Table tblPaperUpdates is used to record changes to any of the information contained in the database. The table contains fields for the name of the person who made the change, the date the change was made and a note about the nature of the change. The table also contains a field for a foreign key to the tblPaper table. Table tblSearchesPerformed contains information about the searches executed by users. One of the fields contains the type of search, such as by chromosome or by diagnosis. The table also has fields to contain the date the search was performed and the number of results returned. The last field contains the SQL command that was executed. Table tblMailingList is used to store the e-mail addresses of all users who want to receive notification when new papers are indexed. The table contains a field for the e-mail address and a field for the date the address was entered.

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13. Footage-Specific Content (Footage Type): All Footage is licensed by the "cut" unless specifically noted. A "cut" shall be defined as one continuous scene from camera start to camera stop. All "cuts" are licensed at a per second charge with a ten second minimum charge per "cut". Any multiple uses of any "cut", splitting of any "cut"; or speeding, slowing or freezing of any "cut" is subject to additional charges. If the Footage is licensed by the "second" instead of by the "cut", You shall pay for the actual running time of the Footage. Any duplicate usage of the Footage, freeze frames, or slow motion shall be calculated at the actual on-screen running time of the Footage. All Footage licensed by the "second" may be subject to minimums based upon the agreed per second rate.

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15. Cancellation/Termination:

(a) By You: If You cancel rights granted in the Invoice within seven (7) days from the date of the Invoice, You will be charged a fifty dollar (US$50) transaction fee per Image or Footage Clip. If the cancellation notice is received more than seven (7) days, but less than thirty (30) days after the Invoice date, a cancellation fee equal to fifty percent (50%) of the amount of the Invoice will be charged. After thirty (30) days, no cancellations will be accepted and You are responsible for and must pay the full amount of the Invoice. For any cancellations, You must also pay any and all service charges, production fees, processing and handling fees and shipping fees. All licenses applicable to the cancellation shall immediate terminate upon cancellation. All cancellations are final.

(b) By Corbis: Corbis may, without further obligation or any liability to You or any other person or entity, terminate this Agreement and Your license to use the Content by written notice in the event You fail to comply with any provision of this Agreement. Upon any termination, cancellation or expiration of this Agreement, neither You nor any other person or entity covered by the license granted to You under this Agreement shall have any further right to make any use of the Content.

16. Copies: At Corbis' reasonable request, You shall provide to Corbis free of charge one (1) copy of any use made of the Content as authorized hereunder.

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21. Choice of Law / Jurisdiction / Attorneys' Fees: Any dispute regarding this Agreement shall be governed by the laws of the State of New York, and by Titles 15, 17 and 35 of the U.S.C., as amended, and the parties agree to accept the exclusive jurisdiction of the state and federal courts located in New York, New York, regardless of conflicts of laws. This Agreement shall not be governed by the United Nations Convention on Contracts for the International Sale of Goods, the application of which is expressly disclaimed. The parties hereto confirm that it is their wish that this Agreement as well as any other documents relating hereto, including notices, has been and shall be written in the English language. In any dispute between Corbis and You for breach of this Agreement where Corbis prevails, Corbis shall be entitled to recover its reasonable attorneys' fees, legal expert fees, court costs, and other legal expenses.

22. Confidentiality: During this Agreement, Corbis may provide You with certain pricing, technical, marketing and other confidential information. You acknowledge that such confidential information encompasses valuable trade secrets and is proprietary to Corbis. You agree that You will maintain the confidentiality of any "confidential information" that Corbis may provide to You, and You shall not use or disclose the same without the prior written consent of Corbis. "Confidential information" includes any information that is either designated as confidential by Corbis or that, under the circumstances surrounding the disclosure, ought in good faith to be treated as confidential by You.

23. Survival: Sections 2, 3(a), 4, 5, 8, 10, 11, 12, and 14 - 25 shall survive termination or expiration of the Agreement.

24. Defined Terms:

(a) "Agreement" means, collectively, the terms and conditions (i) herein, (ii) in the Invoice(s) and (iii) in the Specific Content Web Page(s) applicable to the Content licensed hereunder, all of which are incorporated into this Agreement by this reference.

(b) "Comps" means Content licensed without a fee solely for Your internal evaluation to determine whether the Content is appropriate for Your intended use as either Rights Managed Content or Royalty-Free Content.

(c) "End Use" means the final work product created with the Content as authorized hereunder and excluding Comp uses.

(d) "Images" and "Footage" mean all images and footage clips, respectively, and related informational materials in any medium obtained from or furnished by Corbis hereunder, including without limitation related metadata, text, captions, or information.

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(g) "Term" means: (1) with respect to each license granted hereunder, the term specified herein or in the applicable Invoice and/or Specific Content Web Page, unless earlier terminated as provided herein and, (2) with respect to this Agreement, the term shall end on the earlier to occur of (i) termination or cancellation of this Agreement as provided herein or (ii) the expiration of all licenses issued under this Agreement.

25. Miscellaneous: This Agreement and any listed restrictions constitute the entire agreement between the parties with respect to the subject matter hereof and merge all prior and contemporaneous communications. This Agreement shall not be modified except by a written agreement signed by duly authorized representatives of Corbis, provided that no purchase order or similar document issued by You shall modify this Agreement even if signed by Corbis. If Corbis' performance of any of its obligations hereunder is delayed by labor dispute, war, governmental action, acts of terrorism, flood, fire, explosion, other act of nature, the public enemy, or any other matter not within Corbis' reasonable control, then the date for performance shall be extended by the time of such delay. If any provision of this Agreement is found invalid or unenforceable, the remainder of this Agreement shall remain valid and enforceable according to its terms. Accordingly, the parties agree that if any provisions are deemed not enforceable, they shall be deemed modified to the extent necessary to make them enforceable and in such manner as comes closest to the intentions of the parties to this Agreement as is possible. This Agreement will inure to the benefit of and be binding upon the parties, their successors and assigns, except that You may not assign or transfer this Agreement without Corbis' prior written consent.