



Genome-wide Linkage Mapping Continued: Surveying Candidate Genes

Genome-wide linkage mapping of the gene for atrial septal defect (ASD) revealed that the gene lies between two markers on Chromosome 5, **D5S635** and **D5S807**. Is there a gene associated with ASD in this region of chromosome 5? If so, no one has identified it yet. Are there potential genes in that region with no known function? If so, they might be associated with ASD? Where does a researcher go searching for answers to these questions?

Online databases:

A good place to start is one of several extensive, online, public databases of biological information. The information stored in these databases includes sequences and locations of known genes, sequences and 3-D structures of known proteins, and even whole genomes – ours included.

National Center for Biotechnology Information

One of the more extensive collections of databases is maintained by NCBI, the National Center for Biotechnology Information. NCBI was established in 1988 and is funded by the National Institutes of Health. It hosts GenBank, a public database of gene sequences. It also provides free public access to the PubMed literature database. One of its most useful tools is called Entrez, which searches several linked databases.

You can access the NCBI Web Site at:

<http://www.ncbi.nlm.nih.gov/>

We will now use the resources at NCBI to answer our questions about whether any genes or putative genes lie in the region determined to be associated with ASD by our genome-wide linkage analysis.

- 1.) Open to URL for the NCBI web site in your browser.
<http://www.ncbi.nlm.nih.gov/>
- 2.) From Homepage, click on “Map viewer” in the right column. You may view any of the genomes listed on the tree diagram.
- 3.) Click on *Homo sapiens*. You will see all 23 chromosomes displayed along with the mitochondrial genome (MT).

- 4.) Click on Chromosome 5 to see an enlarged view. On the left, you will see an enlarged view of the chromosome divided into regions that are numbered. You will note that some numbers contain a “p” or “q”. These refer to the p and q arms of the chromosome. The next column to the right shows the contigs (stretches of sequenced clones that overlap with one another and have been assembled)
- 5.) Enter the marker name “D5S635” in the search window in the upper left. Click “Find in this view”. A red dot will appear in the contig column where that marker is located.
- 6.) Enlarge the view by 8X with the view centered on D5S635. To do this, click the vertical blue line just to the left of the red dot that represents D5S635. A pulldown menu will appear. Choose “Zoom in 8X”.
- 7.) Remember the position of the D5S635 marker and enter the marker name “D5S807” in the search window in the upper left. Click “Find in this view”.
- 8.) At approximately the midpoint between the two markers, click and choose “Recenter”.
- 9.) Enlarge by 4X.
- 10.) In the column labeled “symbol”, you will see the abbreviations for genes and lines pointing to their exact location on the chromosome. Note that there are 10 genes shown in map viewer between D5S635 and D5S807 . They are:

LOC285689
LOC285690
MGC5309
LOC134111
FLJ20303
SRD5A1
POLS
ADCY2
MGC5297
MTRR

- 11.) Click on one of these to see more information about the gene. The entry that will appear sometimes contains a great deal of information, most often in abbreviated form. Some useful places to focus your attention are:
 - **Summary:** tells the function of the gene, if known
 - **Locus type:** There are about five options, and they are not always worded the same way, but they are – gene that encodes protein, gene that encodes untranslated RNA, mapped phenotype, anonymous DNA segment, and model

- **pm:** Anywhere you see this abbreviation as a link, you can click on it to see a relevant journal article
- **BL:** Anywhere you see this abbreviation as a link it means you can click it to see every sequence in the database that has any homology to this locus. Sequences closer to the top have more homology.
- **OMIM:** At the bottom of the report, you may see a link next to the acronym OMIM, which stands for Online Mendelian Inheritance in Man. If you click here, it will give you a nice summary of what is known about this locus, though definitely not in plain English. Not all loci will have an OMIM link.

12.) Of the loci between D5S635 and D5S809, which are potential candidate genes for atrial septal defect in this family?

13.) Atrial septal defect may be caused by other genes in different families. To see if there are any known genes that are associated with atrial septal defect, use the search option at the top of the page in map viewer. Return to the map viewer for the human genome http://www.ncbi.nlm.nih.gov/mapview/map_search.cgi. In the search box at the top of the page, type “atrial septal defect”. You do not need to fill anything in the other boxes. Click “Find”. If you get any results, click on the number in the “map element” column. You will see a view of the location on the chromosome. The gene that matched your search will be highlighted in light pink. Click on the number in the far right column for more information about this gene.