THE CHROMOSOME 18 REGISTRY & RESEARCH SOCIETY

UT Health San Antonio Chromosome 18 Clinical Research Center

How to create a personalized syndrome description

This tutorial has 3 parts:

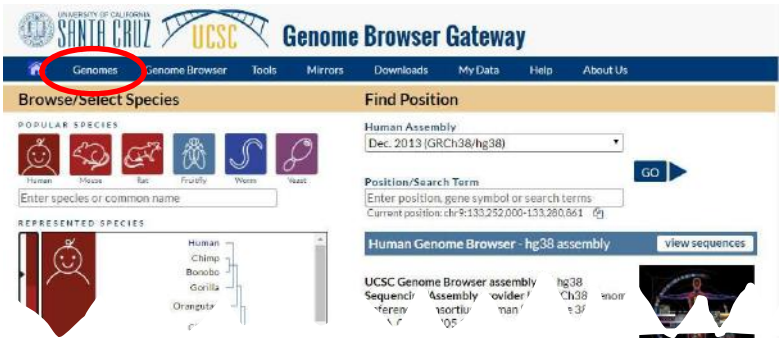
1. *How to use the UCSC Genome Browser*
2. *How to look up individual genes or phenotypes*
3. *How to compile gene dosage information for a region of interest*

How to use the UCSC Genome Browser

1. Go to the website for the University of California at Santa Cruz Genome Browser at: genome.ucsc.edu

2. You will see the home page that looks like this.

3. Click on "Genomes" and select : Human GRCh37/hg19

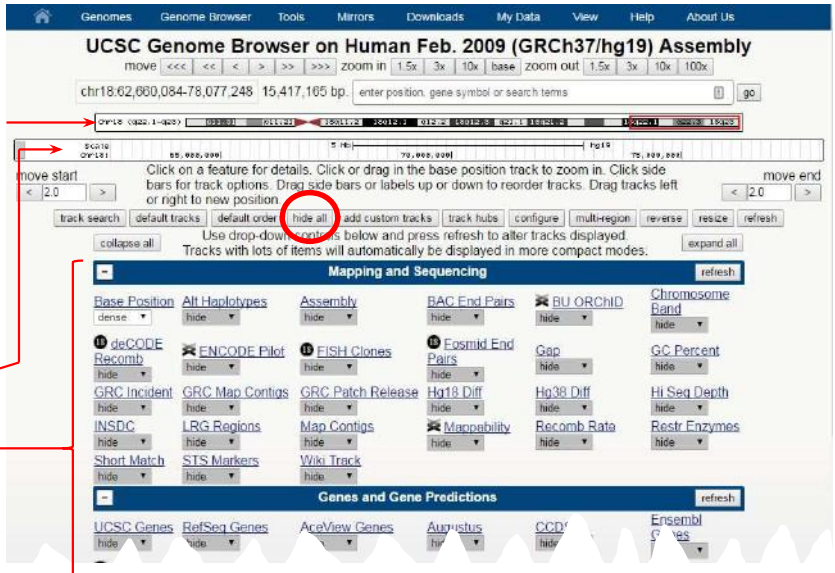


4. Under "assembly" select the assembly used in the genomic lab report that diagnosed the chromosome 18 abnormality; hg18 or hg19.

5. Under "search term" type the coordinates of the persons' deletion or duplication. For example, someone with 18q- and a breakpoint within the Reference Group region might have a breakpoint such as this: chr18:62,660,084-78,077,248
Then click "submit"

7. The next screen may not look exactly like this, so click on "hide all." This step will remove all the information you don't need. In the next steps you can add just the information you want to see.

8. This is the main page you will work from. The layout of this page includes an ideogram of the selected chromosome with a red box around the part of the chromosome shown in the viewing area. The bottom portion of the screen includes about 150 drop-down boxes for selecting "tracks" that include different types of genome annotation data. You will not need to use the majority of these tracks



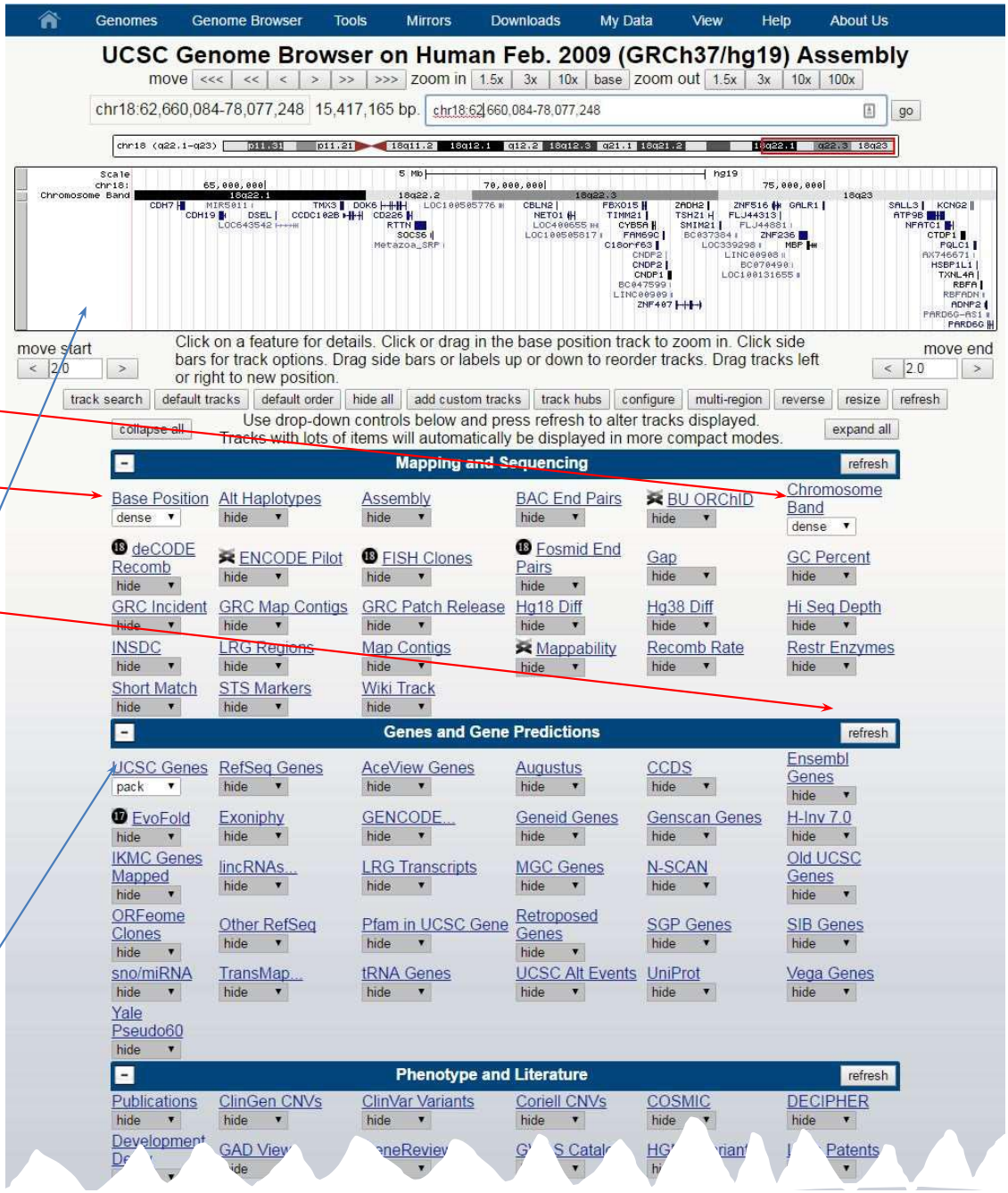
9. The next step is to select only the genome annotation tracks that you want to see. By clicking on any of the track names you will go to a page with an explanation of the data in that track.

10. Select under "Chromosome band" "dense".

11. Select under "UCSC Genes" "pack."

12. Click on any "refresh" button on the right.

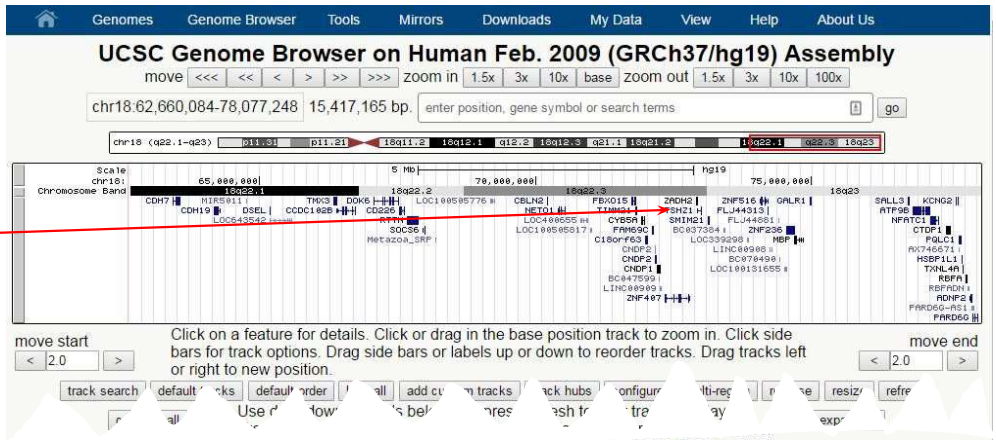
13. Your genome viewing window should look like the one pictured here – with the scale bar and base position at the top. The chromosome bands shown in the next row and the genes shown beneath. In this particular view I have clicked on the "UCSC Genes" and on the subsidiary page de-selected "splice variants" because I do not want to see all the possible variations for each gene.



14. Now you are ready to explore the genetic content of a deletion or duplication. Click on any gene in the viewing window to learn more.

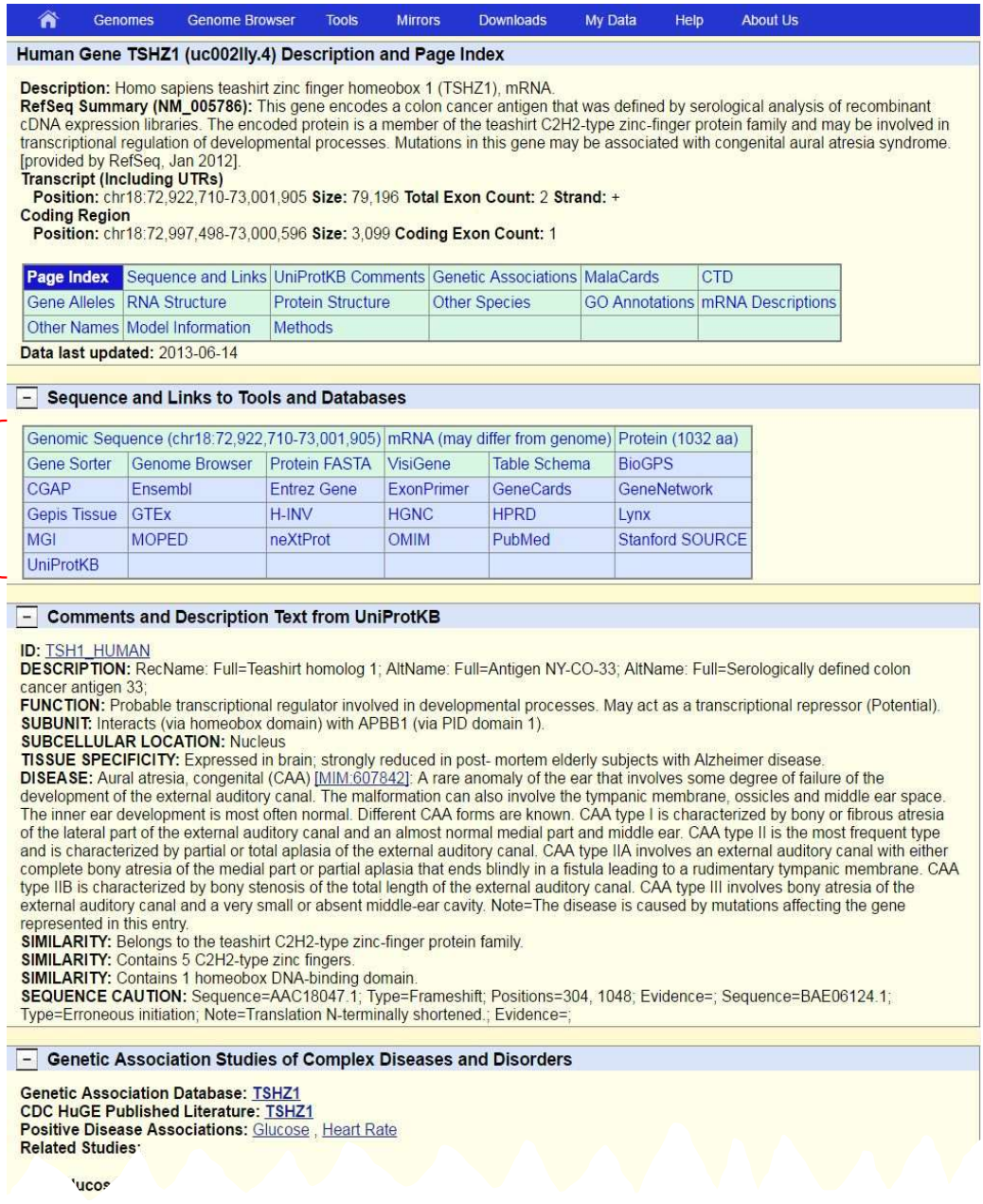
15. In addition you can determine if particular genes are duplicated or deleted in a control population. Such a gene is unlikely to be a cause of disability. These data are collated by the Database of Genomic Variation and can be found by scrolling down to the section of genome annotation tracks labeled "Variation" and then selecting the drop-down box labeled "DGV Struct Var." Then click on a "refresh" button and areas of structural variation will be displayed in the viewing window.

16. Information on individual genes can be investigated by clicking on the gene of interest. For example, click on *TSHZ1*.



17. Clicking on the gene takes you to this page. From this page you can access many databases with information on the gene. A short summary is also included here.

18. The databases with potential clinical significance are OMIM (Online Mendelian Inheritance in Man), PubMed and MGI (Mouse Genome Institute).



In addition, The Chromosome 18 Clinical Research Center continuously curates emerging data as it relates to potential gene dosage effects, for all the genes on chromosome 18. These data are accessible through custom tracks on the UCSC Genome Browser.

How to compile gene dosage information for a region of interest

Custom tracks created for investigating chromosome 18 gene dosage effects and visualized using the UCSC Genome Browser are explained on our website at:
http://www.pediatrics.uthscsa.edu/centers/chromosome18/dosage.asp

There are 2 reasons for using our Gene Dosage Maps:

1. To **investigate individual genes or phenotypes** to determine what is known related to the gene dosage effects of that gene or phenotype.
2. To **investigate the clinical consequences of a chromosome deletion or duplication** region. This is the most straightforward approach to investigate a patient's deletion.

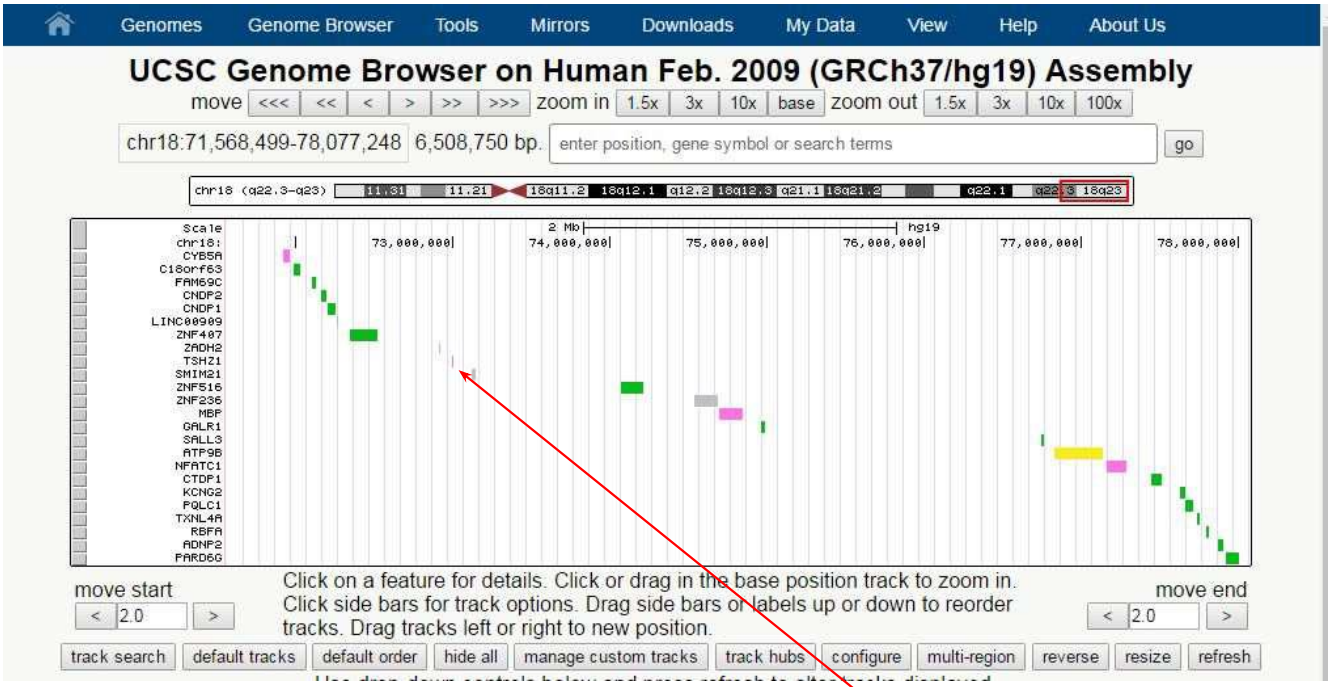
Investigating individual genes and phenotypes:

There are 2 types of data and therefore 2 custom track data sets;

1. The annotated genes (Gene Dosage Map) includes information related to the gene dosage effects for each gene on chromosome 18 and are color codes as shown below.
2. The annotated phenotype regions (Phenotype Map) indicates the region of chromosome 18 linked to a specific phenotype for which a gene has not yet been attributed. When these data come from linkage or GWAS studies they are agnostic with regard to mechanism. This means they may or may not be relevant in a gene dosage context. Phenotype regions are also derived from critical regions data identified by genotype / phenotype mapping of people with copy number changes which are of by definition relevant to an abnormal gene dosage mechanism. The phenotype regions are color coded with regard to mechanism as shown below.

Green	This gene is unlikely to cause a phenotype when there is a copy number change.
Pink	This gene is dosage sensitive. There can be either high or low penetrance of the abnormal phenotype.
Yellow	A copy number change in this gene ONLY results in a phenotype in the presence of a second event (eg. drug exposure or a second genetic change).
Red	This gene is thought to be haplolethal.
Grey	The consequences of a copy number change in this gene are unknown.

On our website: (http://www.pediatrics.uthscsa.edu/centers/chromosome18/dosage.asp) if you click on the link to the "Gene Dosage Map" and select the region "chr18:71,568,499-78,077,248" you will se a screen that looks like this:



Here all the genes are color coded as described above. To learn more about a specific gene with regard to gene dosage, click on that gene. For example, *TSHZ1.*

In addition, you can add any of the other standard data tracks to you browser window as explained previously.

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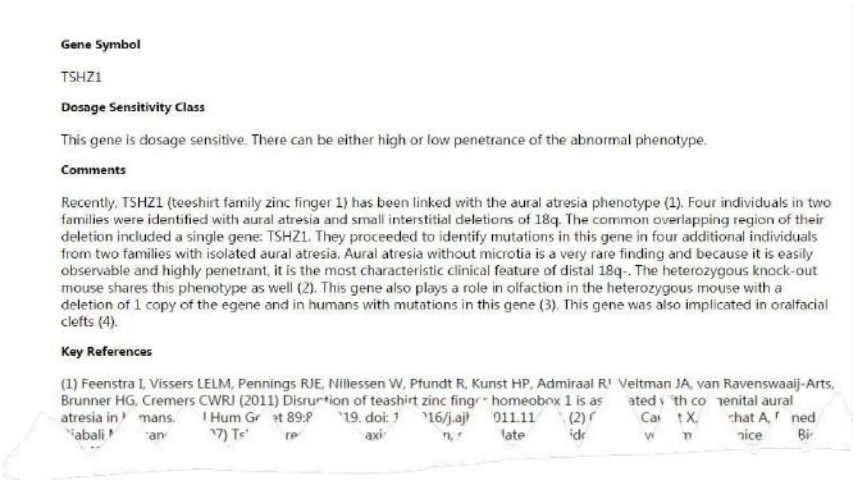
clicking on the *TSHZ1* gene in the Gene Dosage Map takes you to this page.

Next click on TSHZ1 Outside Link.

You are then directed to this details page with a brief description of the data and the references.

By collating the data on the pink and yellow coded genes within a region of an individual's deletion a genetic basis can be compiled. In addition. Determining which critical regions and dosage sensitive genes are NOT within a person's deletion can eliminate certain phenotypes as irrelevant to this individual.



Gene Symbol

TSHZ1

Dosage Sensitivity Class

This gene is dosage sensitive. There can be either high or low penetrance of the abnormal phenotype.

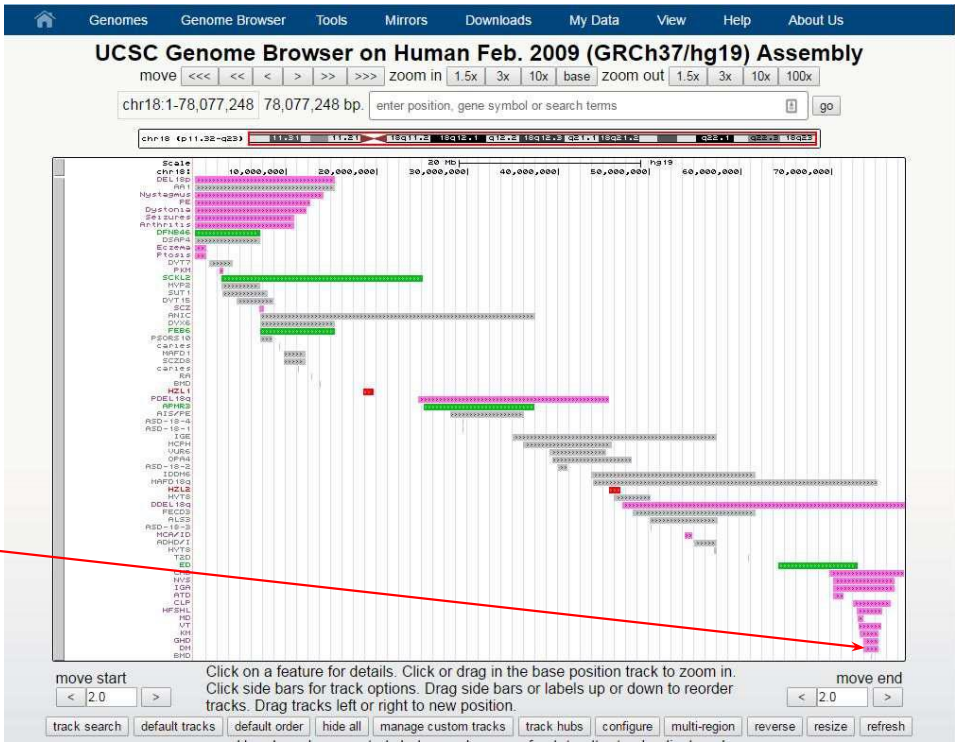
Comments

Recently, TSHZ1 (teeshirt family zinc finger 1) has been linked with the aural atresia phenotype (1). Four individuals in two families were identified with aural atresia and small interstitial deletions of 18q. The common overlapping region of their deletion included a single gene: TSHZ1. They proceeded to identify mutations in this gene in four additional individuals from two families with isolated aural atresia. Aural atresia without microtia is a very rare finding and because it is easily observable and highly penetrant, it is the most characteristic clinical feature of distal 18q-. The heterozygous knock-out mouse shares this phenotype as well (2). This gene also plays a role in olfaction in the heterozygous mouse with a deletion of 1 copy of the egene and in humans with mutations in this gene (3). This gene was also implicated in oralfacial clefts (4).

Key References

(1) Feenstra I, Vissers LELM, Pennings RJE, Nillessen W, Pfundt R, Kunst HP, Admiraal RJ, Veltman JA, van Ravenswaaij-Arts, Brunner HG, Cremers CWRJ (2011) Disruption of teashirt zinc finger homeobox 1 is as ated with co enital aural atresia in mans. Hum Gr et 89:P 19. doi: 16/j.aj 011.11 (2) Ca t X, chat A, ned abali an 7) Ts re axi n, late idr w n nice Bi

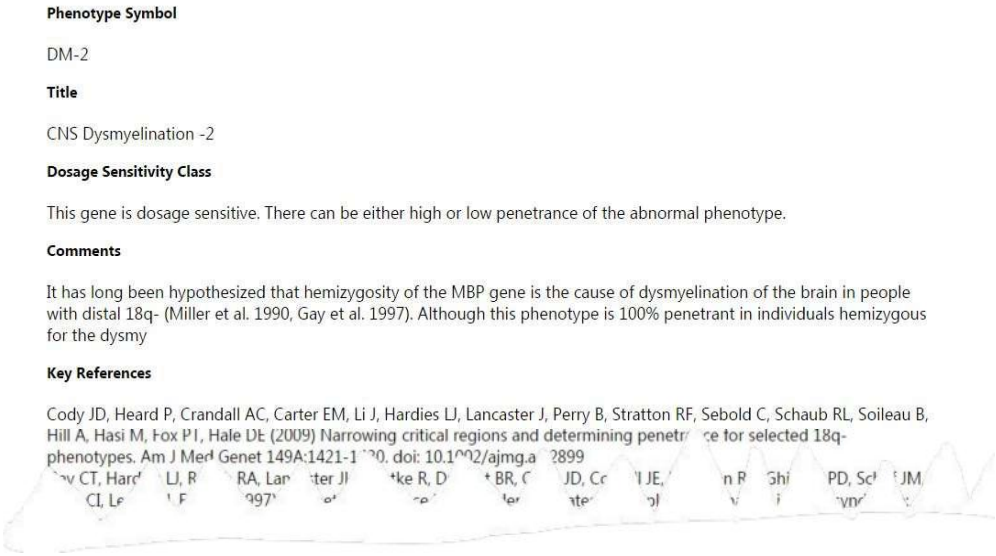
To look up a specific phenotype the process is similar. Go to our website and click on the “Phenotype Map.” To the right is the phenotype map for the entire chromosome. To learn more about the data used to identify the region, click on a region of interest. For example, DM (dysmyelination).



This will take you to a browser details page on which you have to click on the “Outside Link”

You are then directed to this details page with a brief description of the data and the references.

By collating the data on the pink coded phenotypes within a region of an individual’s deletion a list of potential phenotypes can be compiled. In addition. determining which phenotype regions are NOT within a person's deletion can eliminate certain phenotypes as relevant to this individual.



Phenotype Symbol

DM-2

Title

CNS Dysmyelination -2

Dosage Sensitivity Class

This gene is dosage sensitive. There can be either high or low penetrance of the abnormal phenotype.

Comments

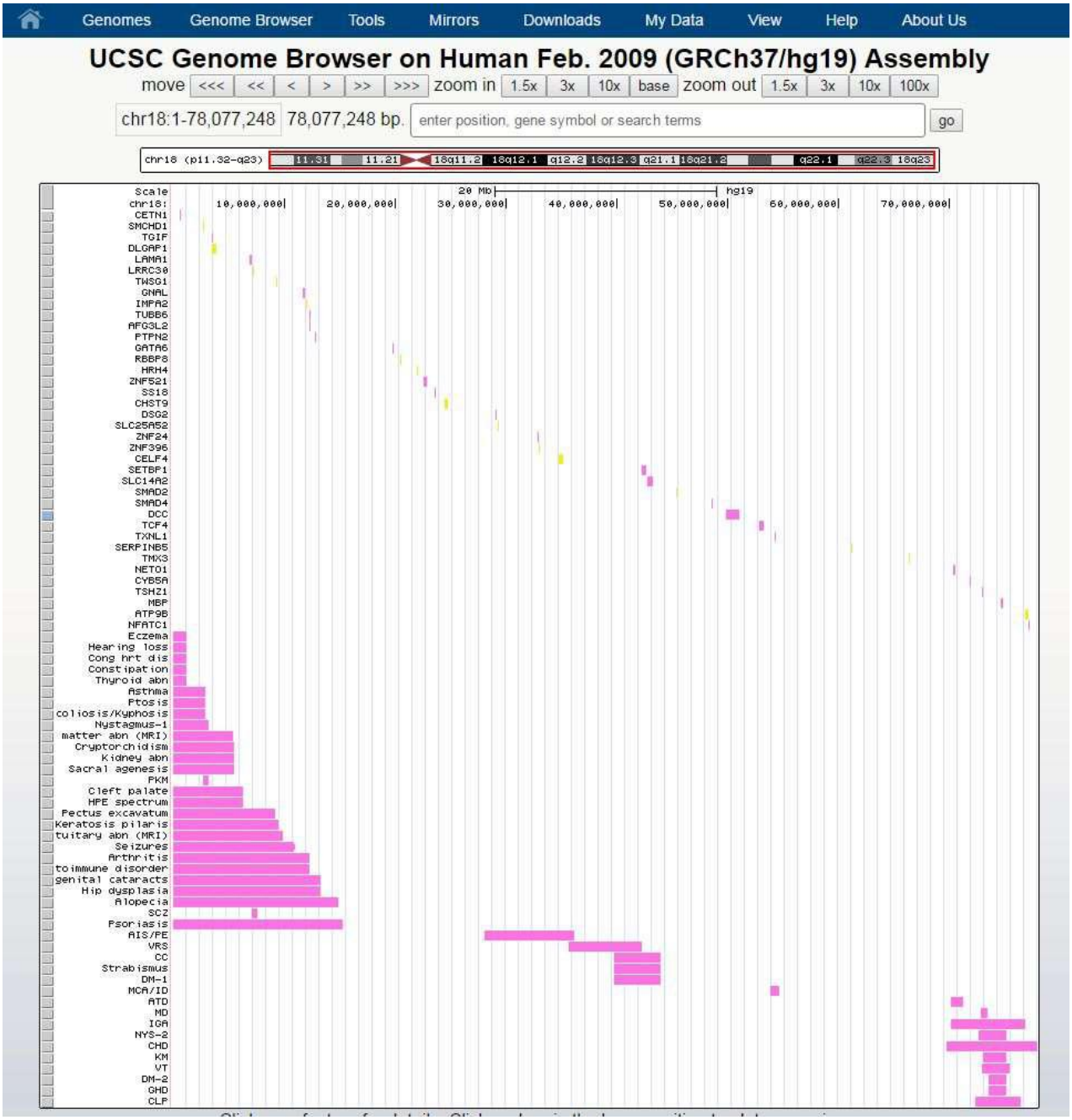
It has long been hypothesized that hemizygosity of the MBP gene is the cause of dysmyelination of the brain in people with distal 18q- (Miller et al. 1990, Gay et al. 1997). Although this phenotype is 100% penetrant in individuals hemizygous for the dysmy

Key References

Cody JD, Heard P, Crandall AC, Carter EM, Li J, Hardies LJ, Lancaster J, Perry B, Stratton RF, Sebold C, Schaub RL, Soileau B, Hill A, Hasi M, Fox PT, Hale DE (2009) Narrowing critical regions and determining penetr ce for selected 18q- phenotypes. Am J Med Genet 149A:1421-1 0. doi: 10.1002/ajmg.a 2899

Investigating the clinical consequences of a chromosome deletion or duplication

The Gene Dosage Map and the Phenotype map just described include the information on all the genes on chromosome 18 and all of the chromosome 18 localized phenotypes . Since most of the genes and many of the phenotypes are not thought to be dosage relevant, we have created a combined custom track with only the dosage relevant information. These versions of the gene dosage maps only include information on genes that have known clinical relevance (a small proportion of the genes) and those phenotypes known to be caused by gene dosage abnormalities. These are the genes and phenotypes color coded pink or yellow in the tracks described above . This is therefore is a condensed version allowing a focus only on clinically relevant information. It can be used/viewed in the same way as the other custom tracks; select the region of interest, then click on the gene or phenotypes in order to get to more detailed information.



Note: When you are viewing these custom tracks within the Genome Browser you can also navigate within the browser and you can add additional tracks in the same way as in the previous set of directions