Michigan Molecular Interactions

Module 1

Finding Literature Based on Relevant Interactions and Pathways

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Biological Problem

GAB2 is located at 11q14.1, a chromosomal region that has not been implicated before in Alzheimer's Disease (AD) in genome-wide linkage or association studies. GAB2 is a scaffolding protein in numerous growth and differentiation signaling pathways, including MAPK/Akt and PI3K, and may be involved in inversely modulating the hyperphosphorylation of tau, a core pathological feature of AD. In fact, reduction of GAB2 expression was shown to increase tau phosphorylation in vitro [Reiman et al., 2007].

Interestingly, in peripherally related articles two other key proteins in the pathological cascade leading to AD (amyloid precursor protein (APP, also called APOE) and presenilin 1 (PSEN1)) interact with the GRB2 adaptor protein to modulate ERK1,2 signaling [Nizzari et al., 2007; Russo et al., 2002].

GRB2 is important because it binds to the proline rich domain in GAB2 and is thought to mediate recruitment of GAB2 to receptor tyrosine kinases [Li et al, 2004].

Chapuis et al (2008), however, claim little if any association of GAB2 alleles with Alzheimer's disease regardless of APOE allele status [Chapuis, J et al, 2008].

Analysis Purpose and Task

You want to see if you find anything else in the research literature linking GAB2 to AD or suggesting a credible and plausible biological story for the association.

The main question driving this exploration is:
What other papers beside the ones cited above are available that suggest or refute an association between GAB2 and Alzheimer's disease in humans?

Ideally, you want to find literature you would not find with your usual means of searching
You will follow leads to articles suggested by interactions that GAB2, GRB2 and other relevant genes are known to have.
You may find articles published earlier than you usually examine.
You may find articles from other subspecialties than your own.
You may find articles from other organisms.

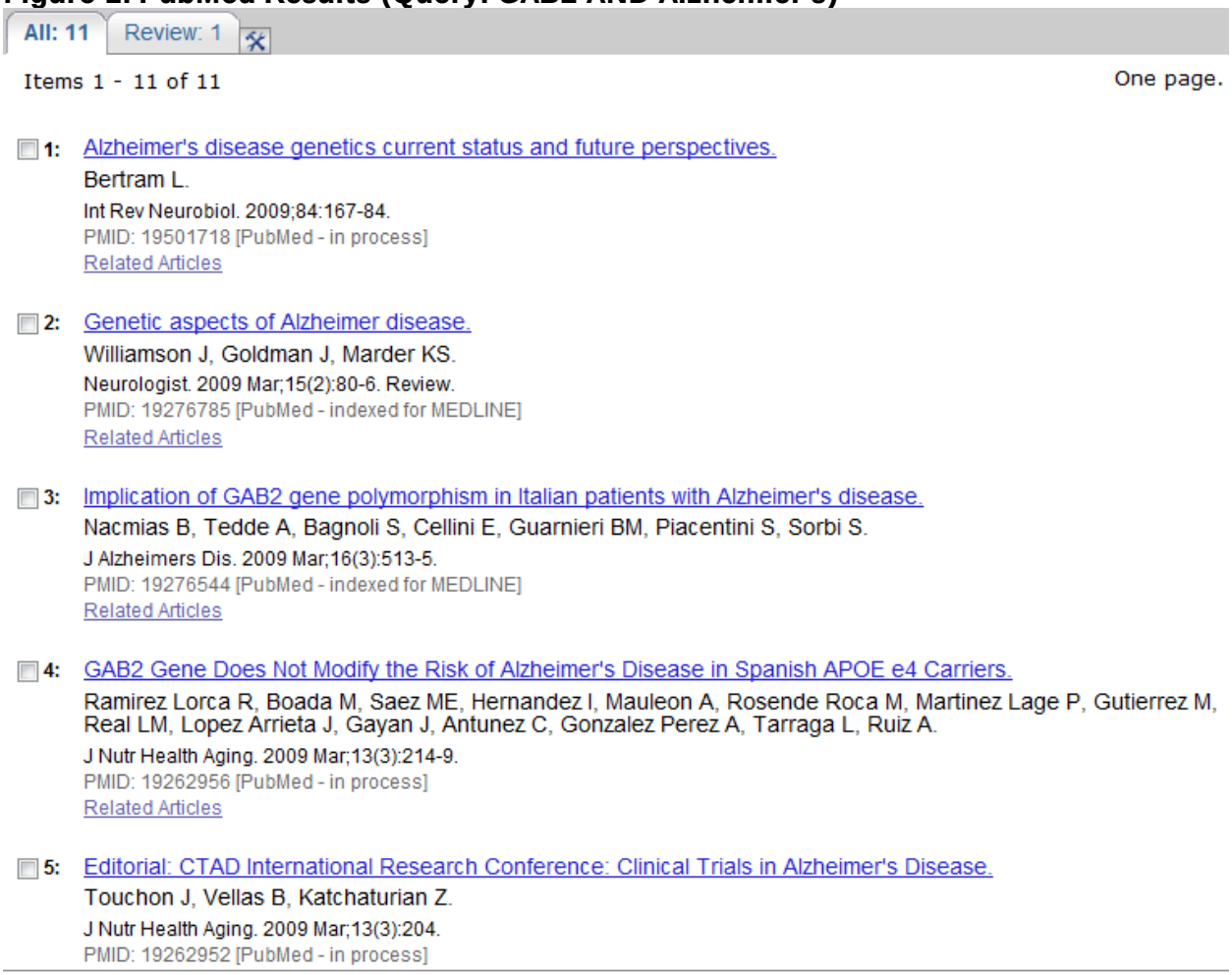
Steps

1. Go to PubMed, either in your usual way to access articles or at http://www.pubmed.gov/.

2. Type the query that you'd like to do for the problem in this case: GAB2 AND Alzheimer's disease. You get 11 results, one of which is a 2009 review article (See Figure 1).

3. Scan the articles. Then click the Review tab and read the abstract of the article. The authors refer to GAB2 as a very recent proposed gene and connect it to associations with sortilin-related receptor (SORL1 – synonym, LR11).

Figure 1. PubMed Results (Query: GAB2 AND Alzheimer's)



Ordinarily, following through on this and other PubMed queries would be the approach you would take for a question like the one you are exploring in this tutorial.

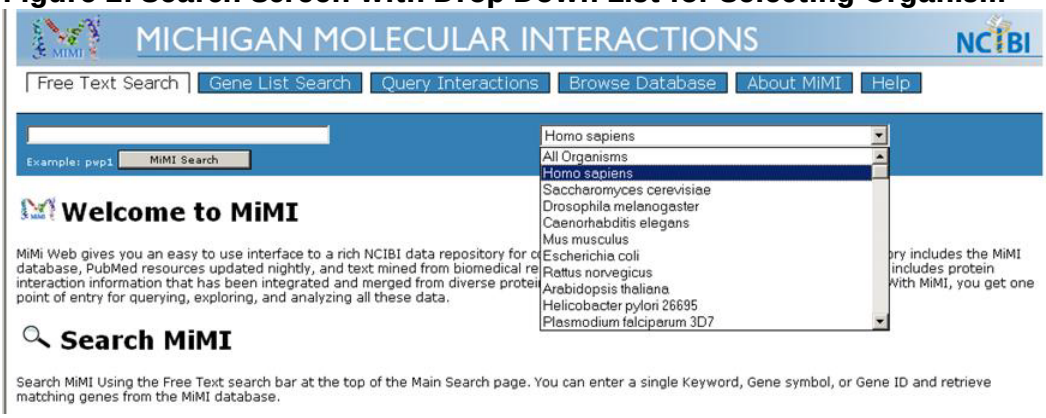
Now take an alternate approach and turn to the MiMI-based set of NCIBI tools. This set of integrated tools enables you to shape your search around conceptual relationships and gene interactions.

Steps

1. Go to MiMI Web: mimi.ncibi.org

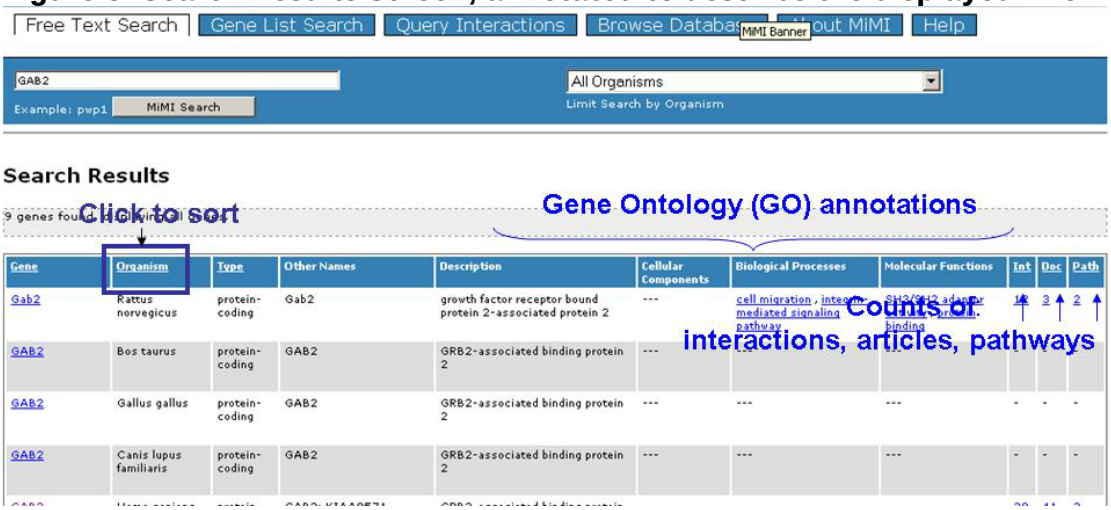
2. Type GAB2 in the Search box. Change the filter to All Organisms (from Homo Sapiens) as shown in Figure 2.

Figure 2. Search Screen with Drop Down List for Selecting Organism



3. Click Search. Results appear (see Figure 3).

Figure 3. Search Results Screen, annotated to describe the displayed information



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You are interested in mammals – mouse, rat and human – and will look first at GAB2 Homo Sapiens and literature about it.

Steps

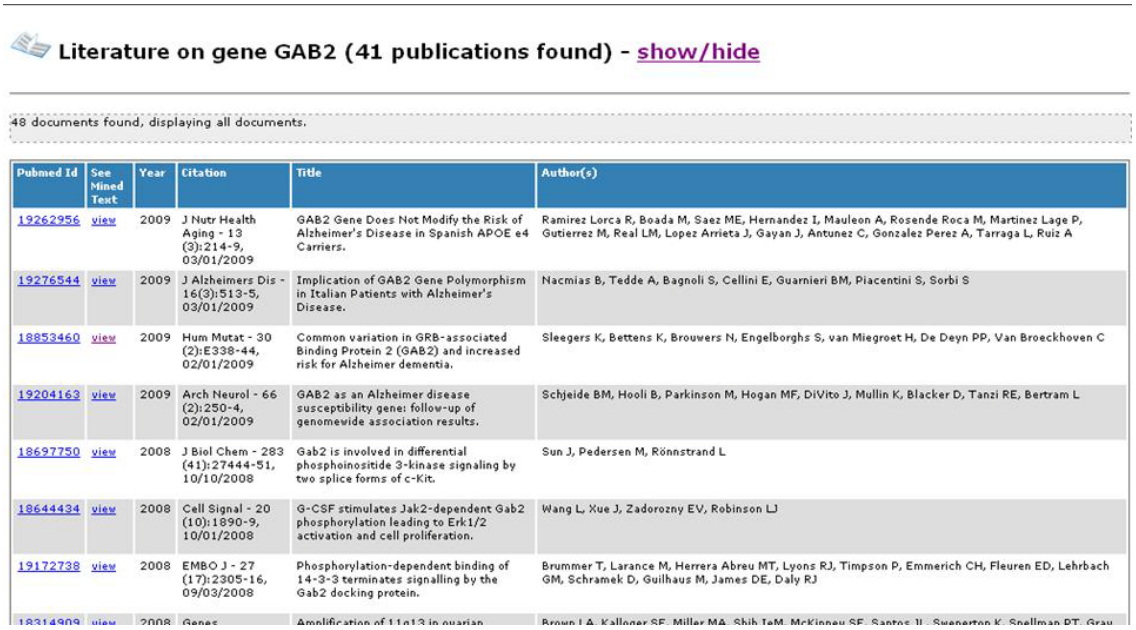
1. Click on "GAB2" in the Homo sapiens row. The **GAB2 Gene Details** page appears (see Figure 4).

Figure 4. Gene Details Page for GAB2

2. Scroll down the page to "Literature on gene" and click "show/hide." A list of articles having to do with GAB2 appears.

3. Scan the titles (See Figure 5).

Figure 5. Literature on GAB2



Literature on gene GAB2 (41 publications found) - show/hide

48 documents found, displaying all documents.

Pubmed Id	See Mined Text	Year	Citation	Title	Author(s)
19262956	view	2009	J Nutr Health Aging - 13 (3):214-9, 03/01/2009	GAB2 Gene Does Not Modify the Risk of Alzheimer's Disease in Spanish APOE e4 Carriers.	Ramirez Lorca R, Boada M, Saez ME, Hernandez I, Mauleon A, Rosende Roca M, Martinez Lage P, Gutierrez M, Real LM, Lopez Arrieta J, Gayan J, Antunez C, Gonzalez Perez A, Tarraga L, Ruiz A
19276544	view	2009	J Alzheimers Dis - 16(3):513-5, 03/01/2009	Implication of GAB2 Gene Polymorphism in Italian Patients with Alzheimer's Disease.	Nacmias B, Tedde A, Bagnoli S, Cellini E, Guarnieri BM, Piacentini S, Sorbi S
18853460	view	2009	Hum Mutat - 30 (2):E338-44, 02/01/2009	Common variation in GRB-associated Binding Protein 2 (GAB2) and increased risk for Alzheimer dementia.	Sleegers K, Bettens K, Brouwers N, Engelborghs S, van Miegroet H, De Deyn PP, Van Broeckhoven C
19204163	view	2009	Arch Neurol - 66 (2):250-4, 02/01/2009	GAB2 as an Alzheimer disease susceptibility gene: follow-up of genomewide association results.	Schjeide BM, Hooli B, Parkinson M, Hogan MF, DiVito J, Mullin K, Blacker D, Tanzi RE, Bertram L
18697750	view	2008	J Biol Chem - 283 (41):27444-51, 10/10/2008	Gab2 is involved in differential phosphoinositide 3-kinase signaling by two splice forms of c-Kit.	Sun J, Pedersen M, Rönnstrand L
18644434	view	2008	Cell Signal - 20 (10):1890-9, 10/01/2008	G-CSF stimulates Jak2-dependent Gab2 phosphorylation leading to Erk1/2 activation and cell proliferation.	Wang L, Xue J, Zadorozny EV, Robinson LJ
19172738	view	2008	EMBO J - 27 (17):2305-16, 09/03/2008	Phosphorylation-dependent binding of 14-3-3 terminates signalling by the Gab2 docking protein.	Brummer T, Larance M, Herrera Abreu MT, Lyons RJ, Timpson P, Emmerich CH, Fleuren ED, Lehrbach GM, Schramek D, Guilhaus M, James DE, Daly RJ
18314909	view	2008	Genes	Amplification of 11q13 in ovarian	Brown LA, Kalloger SE, Miller MA, Shih IeM, McKinney SE, Santos JL, Swenerton K, Spellman PT, Gray

You see many of the same articles that you retrieved in PubMed, such as the 2009 article by Schjeide et al. It looks relevant and you look at it more closely.

4. In that article's row, click "view" in the See Mined Text column. The abstract appears. You see that of 4 previously implicated genes for Alzheimer's disease (AD), variants of GAB2 alone have been found to have some – albeit modest – influence in the risk of AD. The recent publication data of this article suggests that evidence about the relationship of GAB2 and AD may be growing.

5. Click the browser's Back Arrow to return to the Literature table on the Gene Details page. You realize that not all of the articles listed will be directly related to your focus on AD but some of them may indirectly reveal a plausible link to the disease.

   There are 48 citations – a more manageable number to scan later in comparison to the 100+ you imagine you would find if you just entered GAB2 in PubMed.

6. Save the table for later reference by scrolling to the bottom of the table and clicking on the Excel spreadsheet icon. In the dialogue box that appears, Open the file. You can subsequently name and save it to your computer.

Steps

1. Still on the Gene Details page for GAB2, scroll to “Protein Interactions” and click “show/hide.” A table of Interactors appears (See Figure 6).

2. Scroll the list of interacting gene products. You see GRB2 and want to see articles about this interaction.

3. In the GRB2 row, click “3” in the Lit Count column. Three citations appear.

4. For each citation, click “See Text” under See Mined Text. None seems to relate to AD. None of this is encouraging for supporting the hypothesis that some relationship between GAB2 and GRB2 may be tied to risk of AD.

5. Since research has targeted GRB2, you don’t want to give up on this interaction just yet.

Figure 6. GAB2 Protein Interactions (39 interactors)

GRB2 is boxed. Click the number 3 in that row to see articles about GAB2 and GRB2 interactions.

Gene1	Gene2	Source Provenance	Lit. Count	Interaction Info	Experiments
GAB2	E2F2	BIND	0	bidirectional	
GAB2	E2F3	BIND	0	bidirectional	
GAB2	EGFR	IntAct	0	bidirectional	
GAB2	EPOR	GRID; HPRD	1	in vivo, bidirectional	
GAB2	ETV6	GRID	1		
GAB2	FYN	KEGG	0		
GAB2	GRAP2	GRID; HPRD	1	bidirectional, in vitro	
GAB2	GRB2	GRID; HPRD; KEGG	3	Invitro, in vitro, bidirectional	
GAB2	INPP5D	HPRD	1	in vivo, bidirectional	
GAB2	LAT	GRID; HPRD	1	bidirectional, in vivo	
GAB2	LCK	HPRD	1		

Find More on GRB2 interactions Based on Articles from Integrated Sources

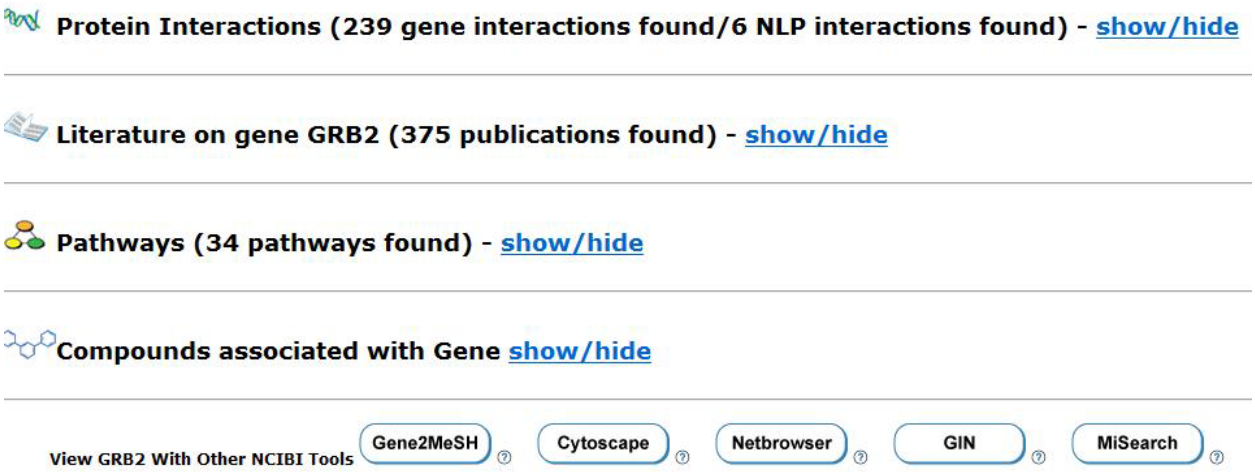
Steps

1. Press the Back button to go back to the "Documents for Gene Interactions GAB2 and GRB2" page, and from there press again to go to the Interactions portion of the GAB2 gene page.

2. In the Interactions table, in the row that shows GAB2 and GRB2 interacting, click the hotlinked GRB2. You will go to the GRB2 Gene page

3. On the GRB2 gene page, scroll to the bottom of the page and click the GIN button (See Figure 7). Excerpts from articles related to GRB2 interactions with other gene products appear.

Figure 7. GIN Button for an Integrated Query on GRB2



GIN uses Natural Language Processing (NLP) to mine PubMed articles. GIN's NLP approach infers interactions between the query gene and other genes based on a number of semantic rules. Outcomes are presented as prose summaries of interactions discussed in the article.

4. Skim the GIN results. Decide if any of this information about GRB2 may be interesting in a non-direct way for connections with GAB2 and Alzheimer's disease.

You now speculate that you may uncover source literature about interactions related to AD by exploring interactions and pathways in a visual form.

You'll return to GAB 2 to do that.

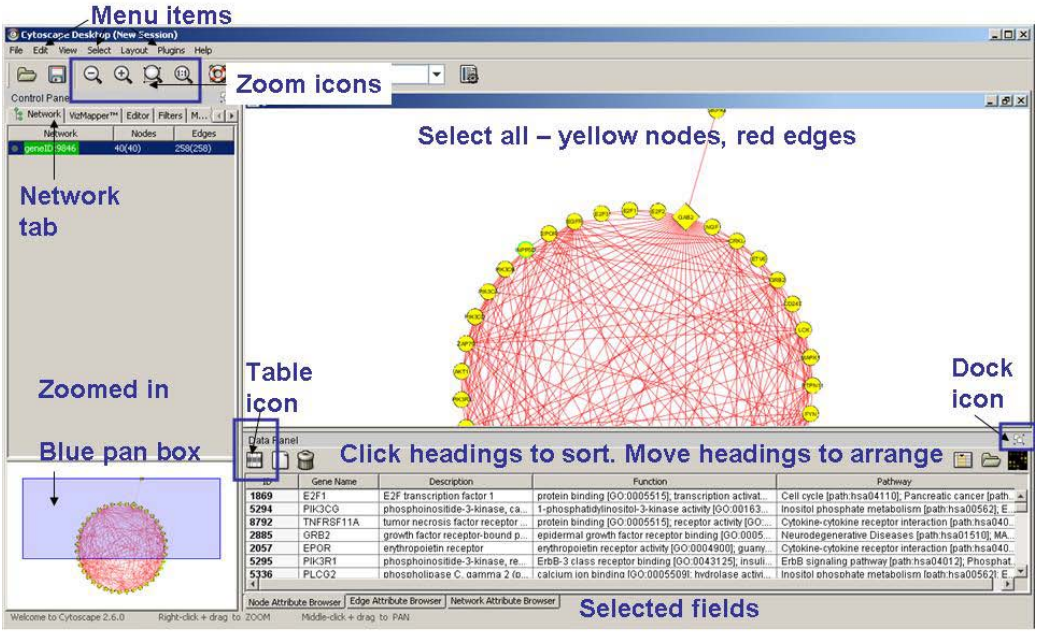
Steps

1. After using GIN, click the browser's Back Arrow multiple times to go back to the **GAB 2** Gene Details page.

2. Scroll to the bottom of the page and click the Cytoscape button. Java Web Start launches an interactive visualization of all gene products interacting with GAB2.

3. Press Run on the dialogue box that asks you to run the Java app.
    a. **In Cytoscape**, do the following:
        i. Size the Cytoscape window and the network window within it to enlarge them
        ii. In the lower panel, under Data Panel, click the Table icon (leftmost icon).
        iii. In the pop up check list, check: Description, Function, Gene Name, Pathway.
        iv. With your mouse, draw a box around all the nodes/edges in the network or alternately select all by pressing Control+Alt+A. The nodes and edges are highlighted to show they are selected. Their details appear in the table.

Figure 8. Set up Cytoscape



4. Click on the Gene Name column. Scroll through the interactors.

Notice PIK3CA, and Look for Articles on Interactions with GAB2

In the data panel and network you notice a number of PIK3 family interactors. You had overlooked them earlier and wonder what the literature says about their interactions with GAB2.

Steps

1. Select PIK3CA by clicking on the node (hovering your mouse over the nodes displays gene names).

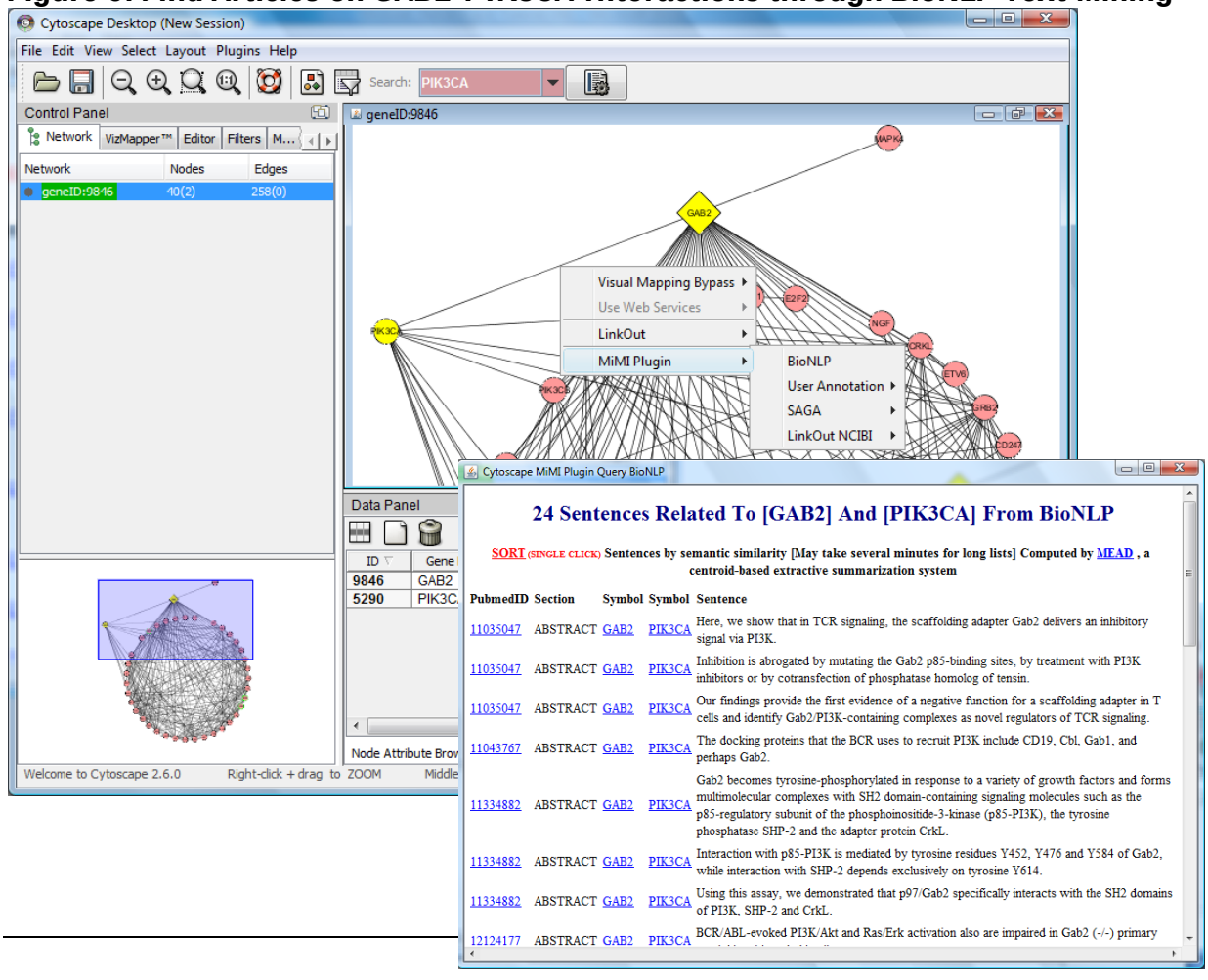
2. Shift+Click on GAB2 to select it too.

3. With your mouse, pull GAB2 out of the circle to see the link (edge) between PIK3CA.

4. Right click on the edge between the two gene products.

5. On the pop up menu select MiMI plugin → BioNLP. Extracts from articles on the Interactions between GAB2 and PIK3CA appear.

Figure 9. Find Articles on GAB2-PIK3CA Interactions through BioNLP Text Mining



BioNLP extracts 20 sentences from several articles (you see their PMIDs). Skim them. You increasingly understand how GAB2 works in signaling and phosphorylation. But there is no mention of tau phosphorylation, a key to tying GAB2 to AD. You move on.

Look for Clues from Pathways

You decide to look further into the GAB2-FYN interaction. You wonder: Could they be involved directly or indirectly in a pathway relevant to Alzheimer's disease?

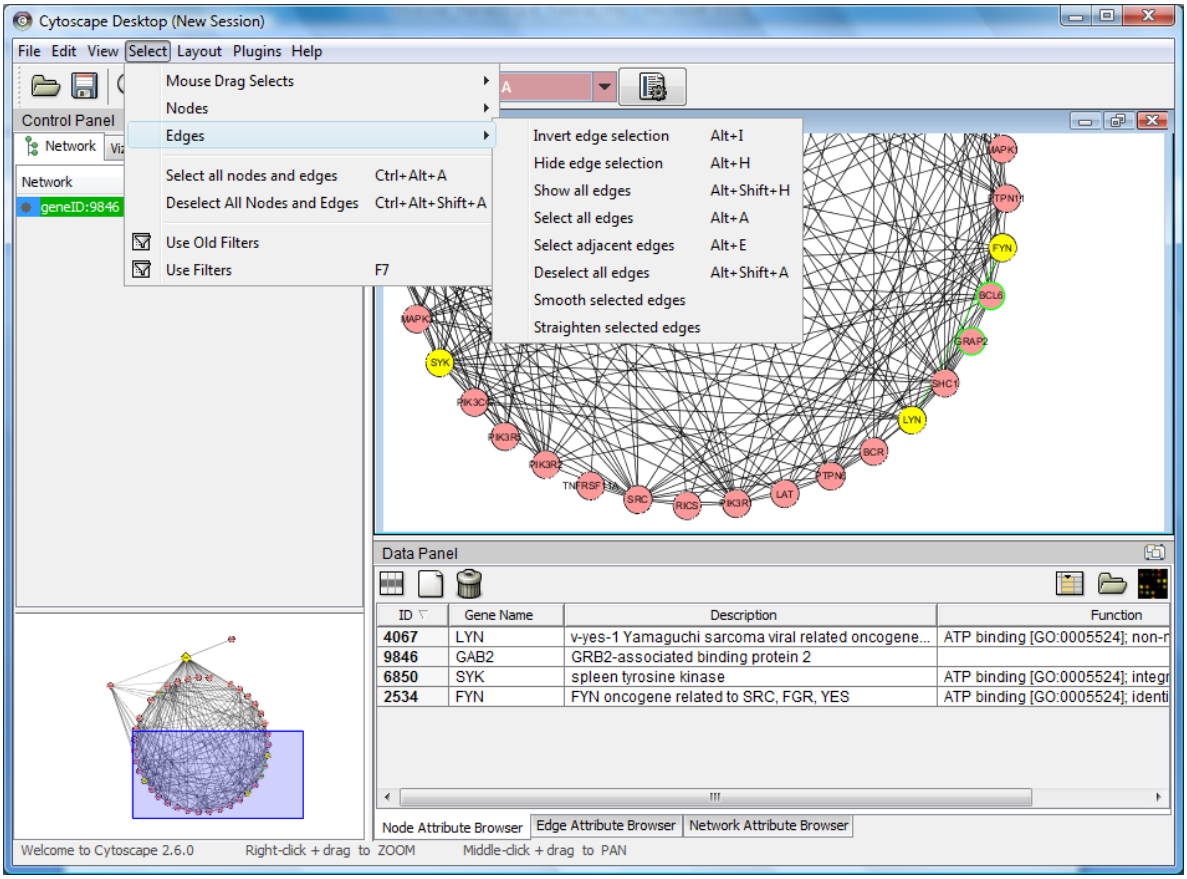
Steps

1. In **Cytoscape**, click on GAB2. It should turn yellow.

2. Shift+Click on: **FYN**, **LYN**, and **SYK**. Four nodes should be yellow.

3. On the menu bar, click **Select → Edges → Select adjacent edges**. The edges showing interactions that the 4 selected nodes have will be selected (red). (See Figure 10).

Figure 10. Select Nodes in Preparation for Matching Subgraphs to KEGG Pathways



4. Right click on any one of the four selected nodes.

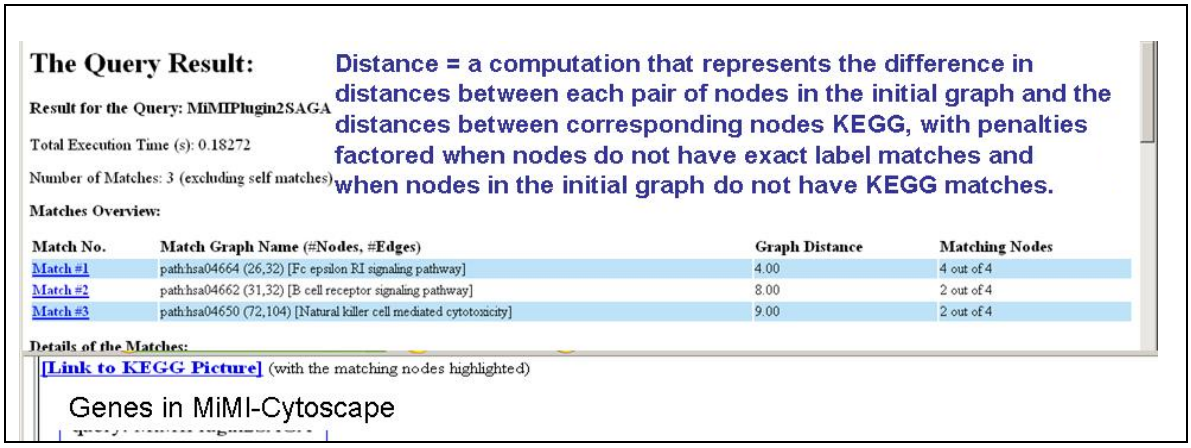
5. On the pop up box click, **MiMI Plugin- → SAGA → Do SAGA (Choose multiple nodes & edges)**. A query box appears.

   SAGA stands for **S**ubstructure Index-based **A**pproximate **G**raph **A**lignment. It is an NCIBI algorithm that matches graphes in Cytoscvape to metabolic pathways in KEGG.

6. In the SAGA dialogue box, click Query. The query box will send a query to KEGG (a database of metabolic pathways) and see if any pathways in KEGG match the subnetwork you have chosen involving GAB2, FYN, LYN, and SYK.

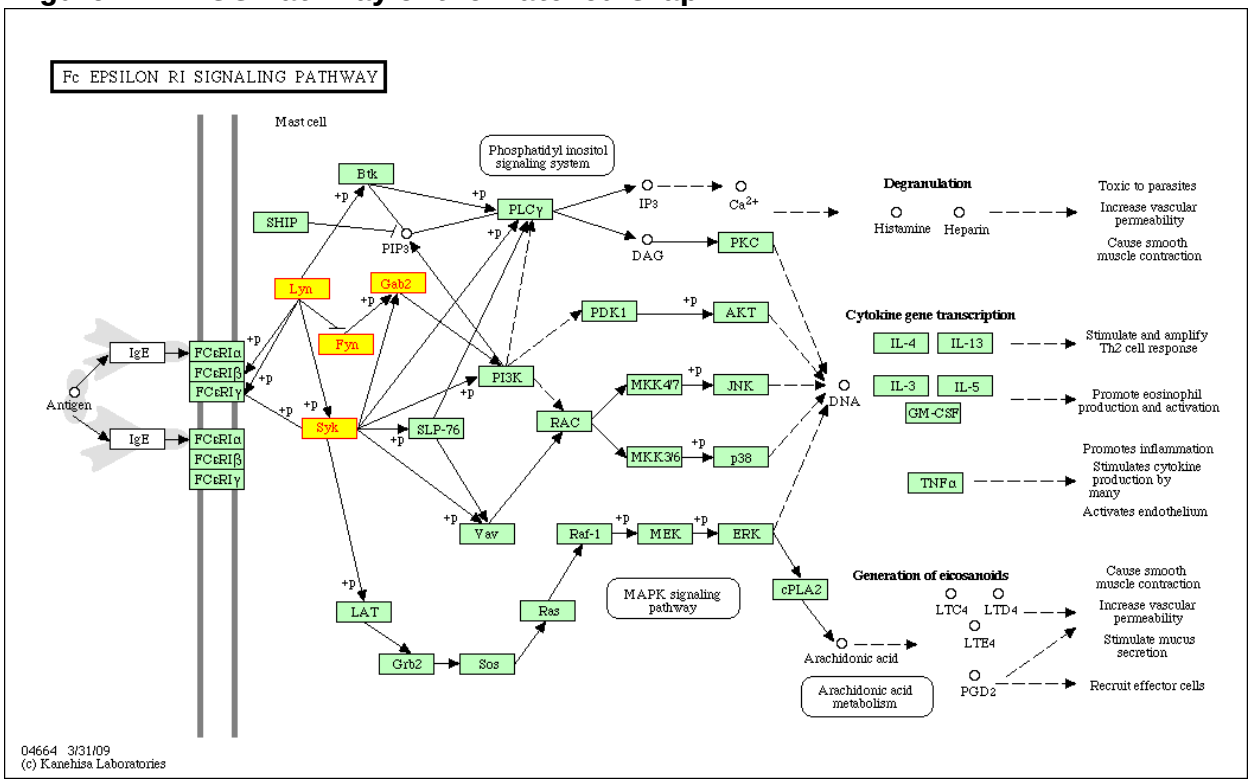
7. Results show that in the first result 4 out of 4 nodes match (Figure 11).

Figure 11. SAGA Query Results



8. For the 1st result, click Link to KEGG Picture. The KEGG network appears (See Figure 12).

Figure 12. KEGG Pathway of the Matched Graph



These matches are interesting and put much of what you've read into context. They may be worth pursuing later, but for now you still need evidence of GAB2 in Alzheimer's disease.

One More integrated Source for Literature

Steps

1. Close the KEGG and SAGA windows.

   You are coming to believe that, despite early encouragement, evidence does not support linking GAB2 to Alzheimer's Disease. You still are willing to try one more angle – looking into the mouse literature to see if you find any surprises.

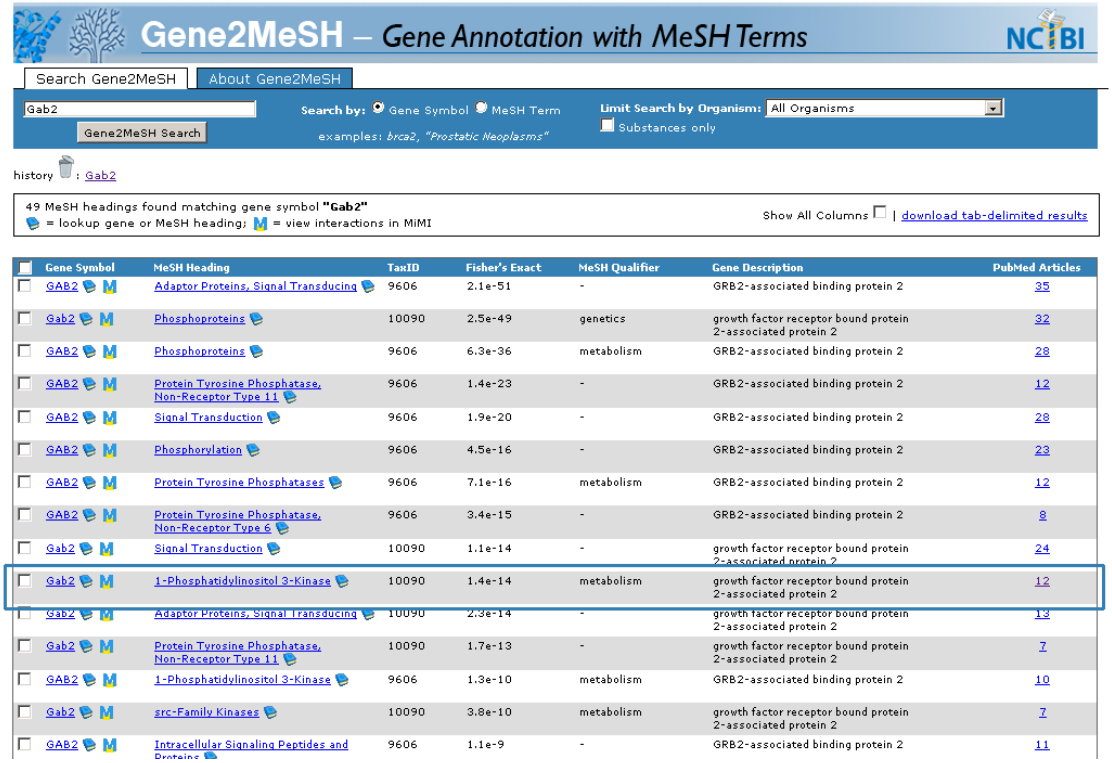
2. Return to MiMI and the Initial Search Results page listing all the GAB2s in all organisms.

3. Click Gab2 for Mus musculus. The Gene Details screen for mouse appears.

4. Scroll to the bottom of the screen and click the Gene2MeSH button. A query for Gab2 in Gene2MeSH is automatically run and results appear (See Figure 13). Results show Medical Subject Heading (MeSH) terms that are overrepresented for GAB2, ranked by strength of

significance. MeSH is the controlled vocabulary that curators at the National Library of Medicine use to assign topics to literature.

Figure 13. Gene2MeSH of GAB2's Enriched MeSH Terms



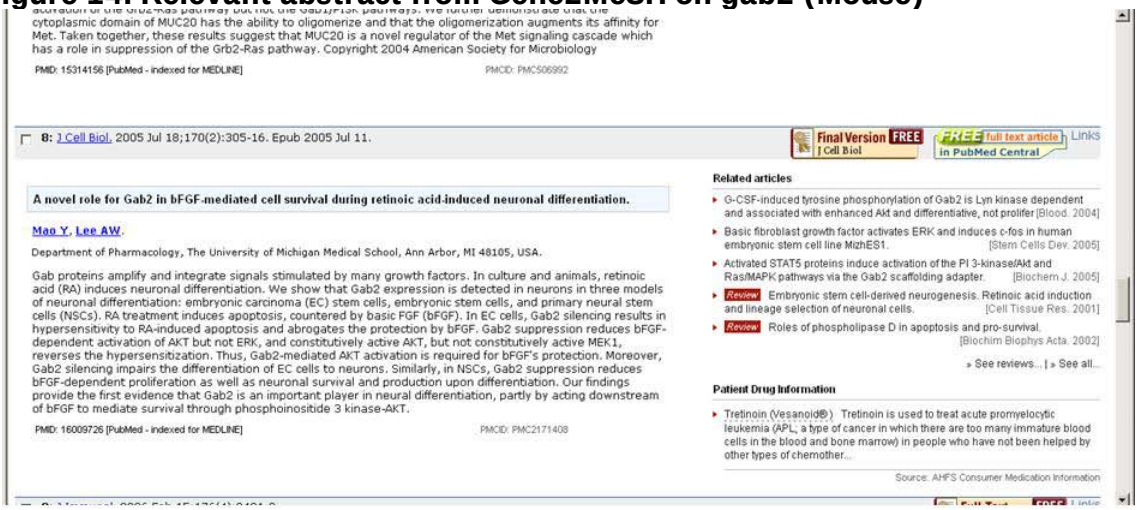
Gene Symbol	MeSH Heading	TaxID	Fisher's Exact	MeSH Qualifier	Gene Description	PubMed Articles
GAB2	Adaptor Proteins, Signal Transducing	9606	2.1e-51	-	GRB2-associated binding protein 2	35
Gab2	Phosphoproteins	10090	2.5e-49	genetics	growth factor receptor bound protein 2-associated protein 2	32
GAB2	Phosphoproteins	9606	6.3e-36	metabolism	GRB2-associated binding protein 2	28
GAB2	Protein Tyrosine Phosphatase, Non-Receptor Type 11	9606	1.4e-23	-	GRB2-associated binding protein 2	12
GAB2	Signal Transduction	9606	1.9e-20	-	GRB2-associated binding protein 2	28
GAB2	Phosphorylation	9606	4.5e-16	-	GRB2-associated binding protein 2	23
GAB2	Protein Tyrosine Phosphatases	9606	7.1e-16	metabolism	GRB2-associated binding protein 2	12
GAB2	Protein Tyrosine Phosphatase, Non-Receptor Type 6	9606	3.4e-15	-	GRB2-associated binding protein 2	8
Gab2	Signal Transduction	10090	1.1e-14	-	growth factor receptor bound protein 2-associated protein 2	24
Gab2	1-Phosphatidylinositol 3-Kinase	10090	1.4e-14	metabolism	growth factor receptor bound protein 2-associated protein 2	12
Gab2	Adaptor Proteins, Signal Transducing	10090	2.3e-14	-	growth factor receptor bound protein 2-associated protein 2	13
Gab2	Protein Tyrosine Phosphatase, Non-Receptor Type 11	10090	1.7e-13	-	growth factor receptor bound protein 2-associated protein 2	7
GAB2	1-Phosphatidylinositol 3-Kinase	9606	1.3e-10	metabolism	GRB2-associated binding protein 2	10
Gab2	src-Family Kinases	10090	3.8e-10	metabolism	growth factor receptor bound protein 2-associated protein 2	7
GAB2	Intracellular Signaling Peptides and Proteins	9606	1.1e-9	-	GRB2-associated binding protein 2	11

5. About 10 rows down with a highly significant Fisher's exact score is the term 1-Phosphatidylinositol 3-Kinase. In the PubMed Articles column, click the number "12." The 12 related abstracts appear.

6. Scan the abstracts. Scroll to the abstract with the PMID 16009726 (2005, Mao and Lee) that discusses GAB2 and GAB2 silencing functions in the brain.

7. Read the abstract. Save this article.

Figure 14. Relevant abstract from Gene2MeSH on gab2 (Mouse)



The Mao and Lee article was not in the original list that you got from PubMed. Information you uncovered throughout this MiMI-based exploration led you to try 1-Phosphatidylinositol 3-Kinase in Gene2MeSH and that turned out to be productive.

You are not as ready as you were before to dismiss an association between GAB2 and Alzheimer's disease. You now will look into SORL1 and GOML1, the two genes you found early on that have been associated with GAB2 and AD.