

Michigan Molecular Interactions

Module 1

Finding Literature Based on Relevant Interactions and Pathways

National Center for Integrative Biomedical Informatics (NCIBI)

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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)

All: 11 Review: 1

Items 1 - 11 of 11 One page.

- 1: [Alzheimer's disease genetics current status and future perspectives.](#)
Bertram L.
Int Rev Neurobiol. 2009;84:167-84.
PMID: 19501718 [PubMed - in process]
[Related Articles](#)
- 2: [Genetic aspects of Alzheimer disease.](#)
Williamson J, Goldman J, Marder KS.
Neurologist. 2009 Mar;15(2):80-6. Review.
PMID: 19276785 [PubMed - indexed for MEDLINE]
[Related Articles](#)
- 3: [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.
J Alzheimers Dis. 2009 Mar;16(3):513-5.
PMID: 19276544 [PubMed - indexed for MEDLINE]
[Related Articles](#)
- 4: [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.
J Nutr Health Aging. 2009 Mar;13(3):214-9.
PMID: 19262956 [PubMed - in process]
[Related Articles](#)
- 5: [Editorial: CTAD International Research Conference: Clinical Trials in Alzheimer's Disease.](#)
Touchon J, Vellas B, Katchaturian Z.
J Nutr Health Aging. 2009 Mar;13(3):204.
PMID: 19262952 [PubMed - in process]

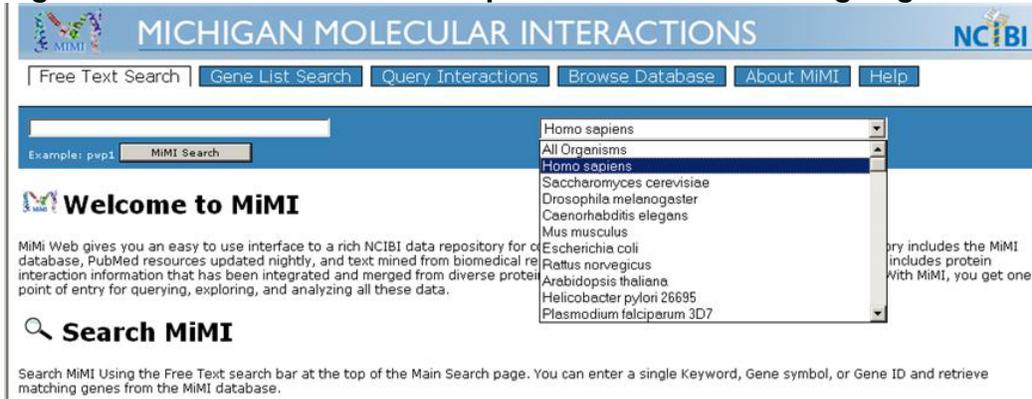
Ordinarily, following through on this and other PubMed queries would be the approach you would take for a question like the one you are exploring in this tutorial.

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

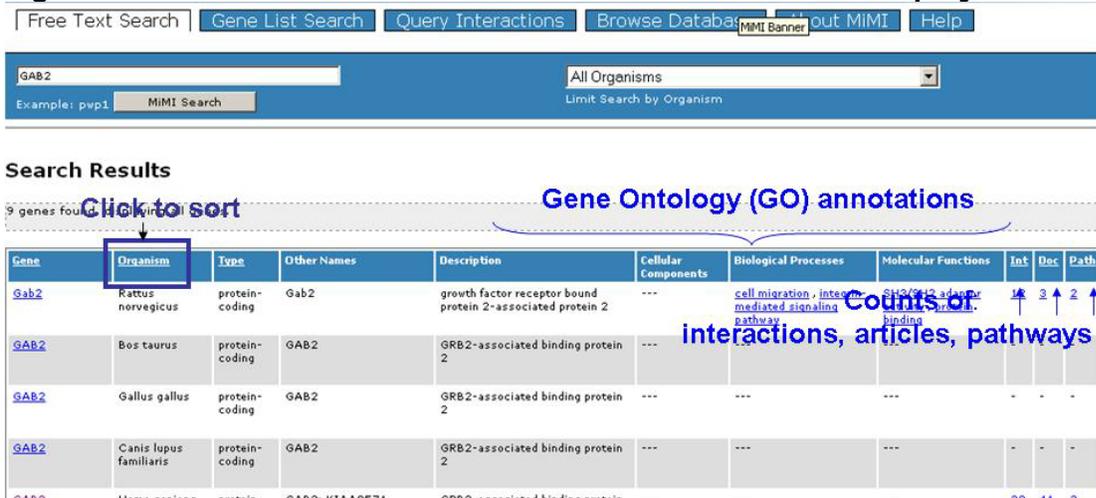
1. Go to MiMI Web: mimi.ncibi.org
2. Type GAB2 in the Search box. Change the filter to All Organisms (from Homo Sapiens) as shown in Figure 2.

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



Focus on Data Related to GAB2 in Humans

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

 **Gene Details**

 Molecule Details for Gene Entry GAB2 (GeneId: 9846) - [show/hide](#)

| | | | |
|--|------------------------|-------------------------|------------------------|
| GRB2-associated binding protein 2 | Gene Attributes | | |
| GAB2(Homo sapiens) | Cellular Components... | Biological Processes... | Molecular Functions... |

- Gene Type: protein-coding
- Chromosome: [11](#)
- Map Locus: [11q24.1](#)
- Locus Tag: null

Other Names...

- GAB2
- KIAA0571

Descriptions...

- **Authorized Gene Description:** GRB2-associated binding protein 2
- **Other descriptions...**
 - Grb2-associated binder 2

 **Protein Interactions (39 gene interactions found)** - [show/hide](#)

 **Literature on gene GAB2 (41 publications found)** - [show/hide](#)

 **Pathways (2 pathways found)** - [show/hide](#)

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 ε4 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. | Slegers K, Bettens K, Brouwers N, Engelborghs S, van Mieghroet 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 genome-wide association results. | Schjerve 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, Rönstrand 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, Guilhaum M, James DE, Daly RJ |
| 18314909 | view | 2008 | Genes | Amplification of 11q13 in ovarian | Brown LA, Kallanar SF, Miller MA, Shih TaM, McKinnau SF, Santos H, Swanerton K, Spallman DT, Grau |

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

- 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.
- 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.

- 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.

Find Potentially Relevant Articles About GAB2 Interactions

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.

Protein Interactions (39 gene interactions found) - [show/hide](#)

View [documents](#) Click “documents” to see all the articles on GAB2 and an interactor

3 interactions found, displaying all 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 | GRB2 |
| 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

The screenshot displays a section of a web page for the GRB2 gene. It features four horizontal bars, each with an icon and text: a DNA helix icon for "Protein Interactions (239 gene interactions found/6 NLP interactions found) - [show/hide](#)", a book icon for "Literature on gene GRB2 (375 publications found) - [show/hide](#)", a pathway diagram icon for "Pathways (34 pathways found) - [show/hide](#)", and a chemical structure icon for "Compounds associated with Gene [show/hide](#)". Below these bars is a row of navigation buttons: "View GRB2 With Other NCIBI Tools" followed by "Gene2MeSH", "Cytoscape", "Netbrowser", "GIN", and "MiSearch", each with a small question mark icon.

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.

Examine a Network of GAB2 Interactions for More Insights

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

Menu items

| Gene ID | Gene Name | Description | Function | Pathway |
|---------|-----------|-----------------------------------|---|--|
| 1869 | E2F1 | E2F transcription factor 1 | protein binding [GO:0005515], transcription activat... | Cell cycle [path:hsa04110], Pancreatic cancer [path... |
| 5294 | PIK3CG | phosphoinositide-3-kinase, ca... | 1-phosphatidylinositol-3-kinase activity [GO:00163... | Inositol phosphate metabolism [path:hsa00562], E... |
| 8792 | TNFRSF11A | tumor necrosis factor receptor | protein binding [GO:0005515], receptor activity [GO... | Cytokine-cytokine receptor interaction [path:hsa040... |
| 2885 | IGFB2 | growth factor receptor-bound p... | epidermal growth factor receptor binding [GO:0005... | Neurodegenerative Diseases [path:hsa01510], MA... |
| 2057 | EPOR | erythropoietin receptor | erythropoietin receptor activity [GO:0004800], quany... | Cytokine-cytokine receptor interaction [path:hsa040... |
| 5295 | PIK3R1 | phosphoinositide-3-kinase, re... | ErbB-3 class receptor binding [GO:0043125], insuli... | ErbB signaling pathway [path:hsa04012], Phosphat... |
| 5336 | PLCO2 | othosholioase C. gamma 2 (to... | calcium ion binding [GO:0005509], hydrolase activ... | Inositol phosphate metabolism [path:hsa00562], E... |

Selected fields

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

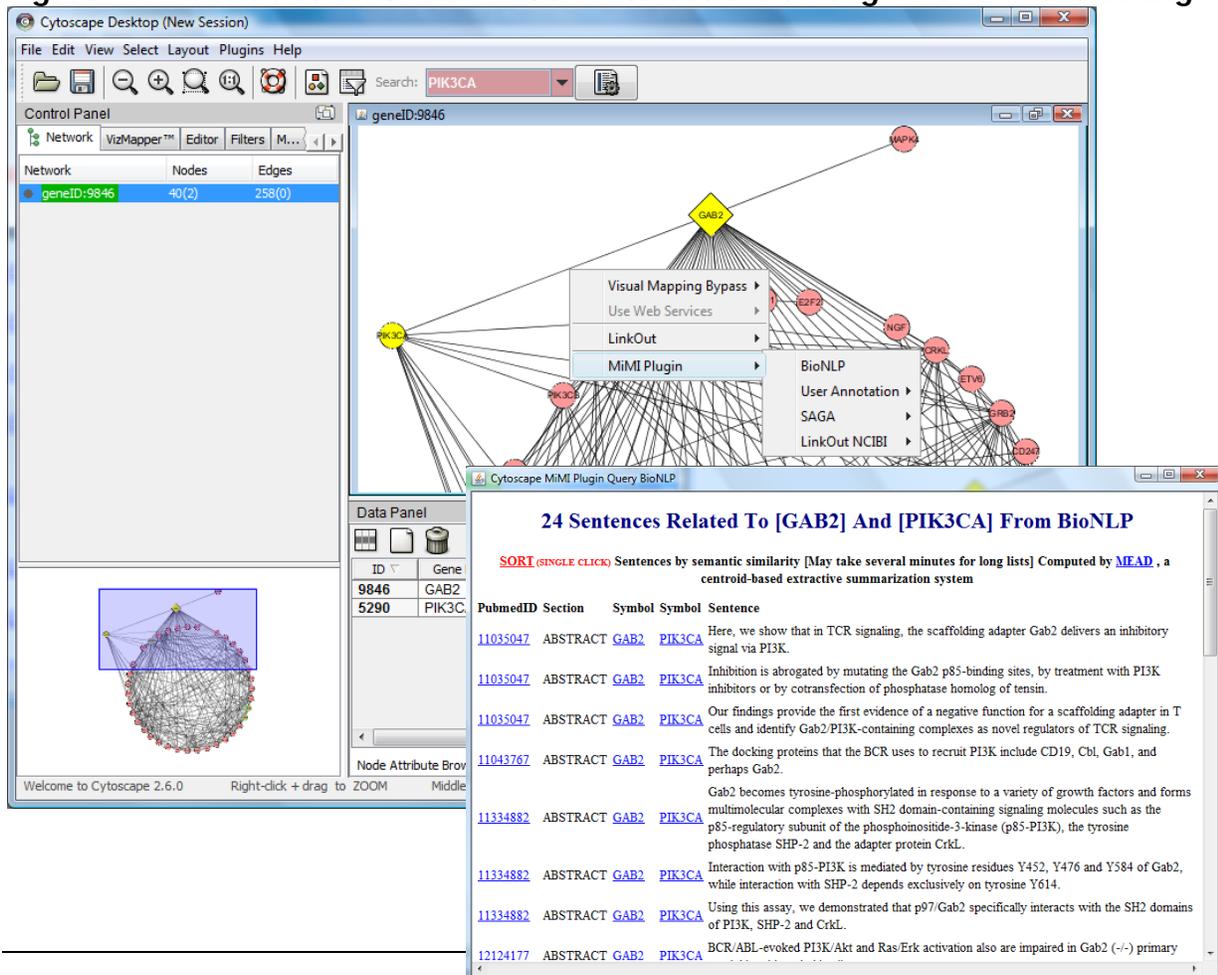
Notice PIK3CA, and Look for Articles on Interactions with GAB2

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



24 Sentences Related To [GAB2] And [PIK3CA] From BioNLP

Sort (single click) Sentences by semantic similarity [May take several minutes for long lists] Computed by **MEAD**, a centroid-based extractive summarization system

| PubmedID | Section | Symbol | Symbol | Sentence |
|----------|----------|--------|--------|--|
| 11035047 | ABSTRACT | GAB2 | PIK3CA | Here, we show that in TCR signaling, the scaffolding adapter Gab2 delivers an inhibitory signal via PI3K. |
| 11035047 | ABSTRACT | GAB2 | PIK3CA | Inhibition is abrogated by mutating the Gab2 p85-binding sites, by treatment with PI3K inhibitors or by cotransfection of phosphatase homolog of tensin. |
| 11035047 | ABSTRACT | GAB2 | PIK3CA | Our findings provide the first evidence of a negative function for a scaffolding adapter in T cells and identify Gab2/PI3K-containing complexes as novel regulators of TCR signaling. |
| 11043767 | ABSTRACT | GAB2 | PIK3CA | The docking proteins that the BCR uses to recruit PI3K include CD19, Cbl, Gab1, and perhaps Gab2. |
| 11334882 | ABSTRACT | GAB2 | PIK3CA | Gab2 becomes tyrosine-phosphorylated in response to a variety of growth factors and forms multimolecular complexes with SH2 domain-containing signaling molecules such as the p85-regulatory subunit of the phosphoinositide-3-kinase (p85-PI3K), the tyrosine phosphatase SHP-2 and the adapter protein Crkl. |
| 11334882 | ABSTRACT | GAB2 | PIK3CA | Interaction with p85-PI3K is mediated by tyrosine residues Y452, Y476 and Y584 of Gab2, while interaction with SHP-2 depends exclusively on tyrosine Y614. |
| 11334882 | ABSTRACT | GAB2 | PIK3CA | Using this assay, we demonstrated that p97/Gab2 specifically interacts with the SH2 domains of PI3K, SHP-2 and Crkl. |
| 12124177 | ABSTRACT | GAB2 | PIK3CA | BCR/ABL-evoked PI3K/Akt and Ras/Erk activation also are impaired in Gab2 (-/-) primary |

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.

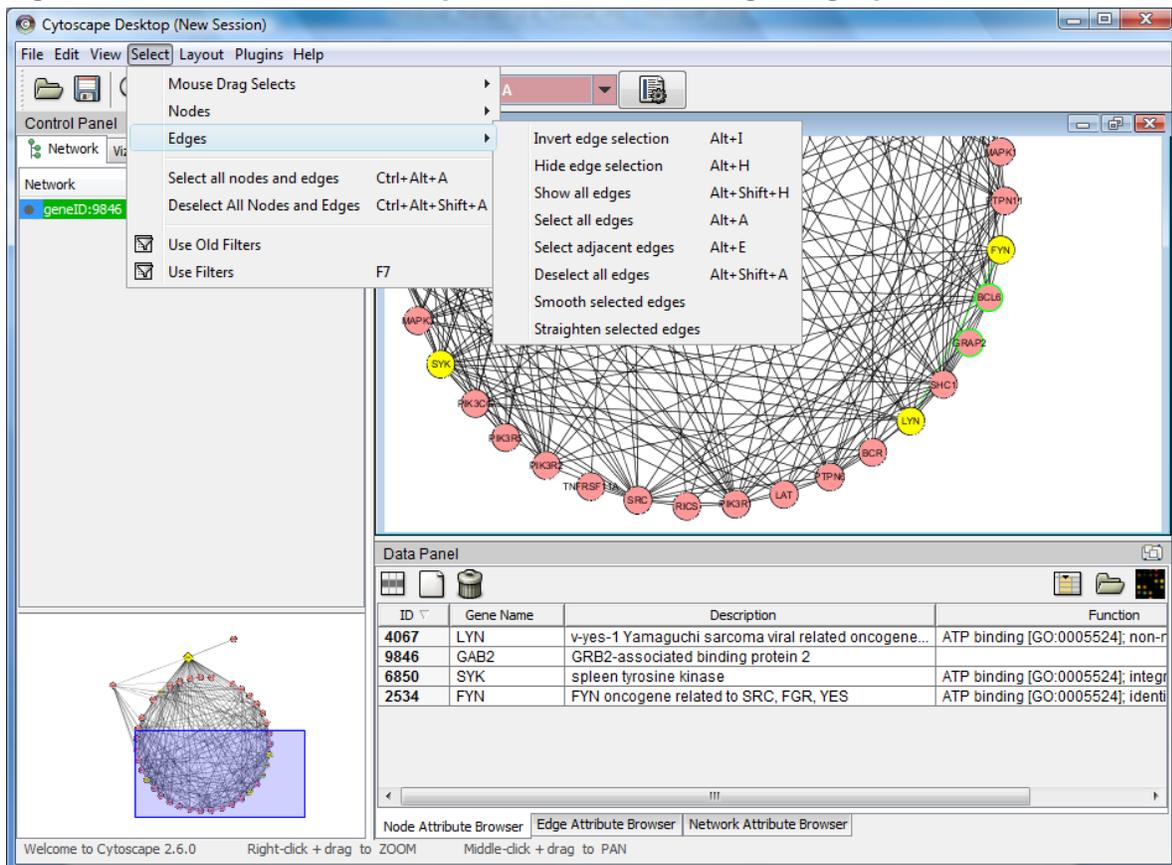
Look for Clues from Pathways

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

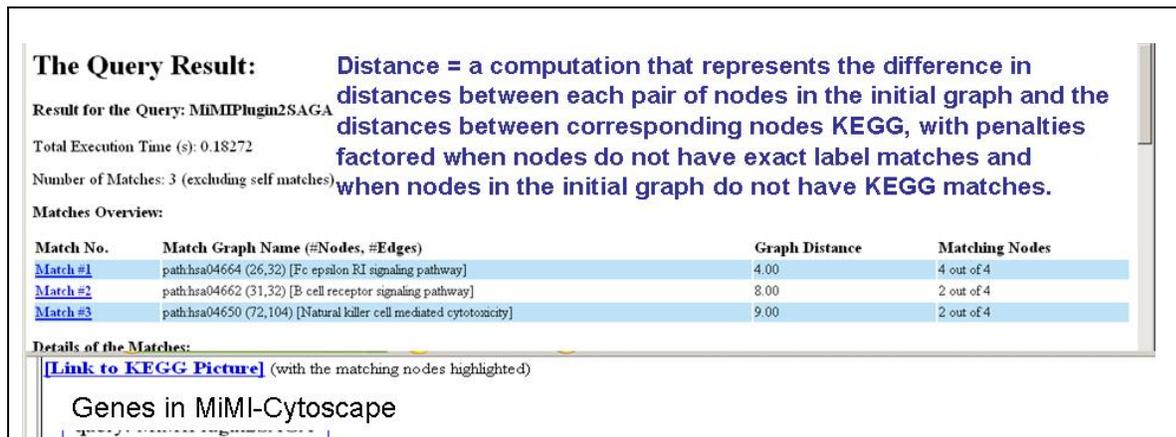


- Right click on any one of the four selected nodes.
- On the pop up box click, **MiMI Plugin- → SAGA → Do SAGA (Choose multiple nodes & edges)**. A query box appears.

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

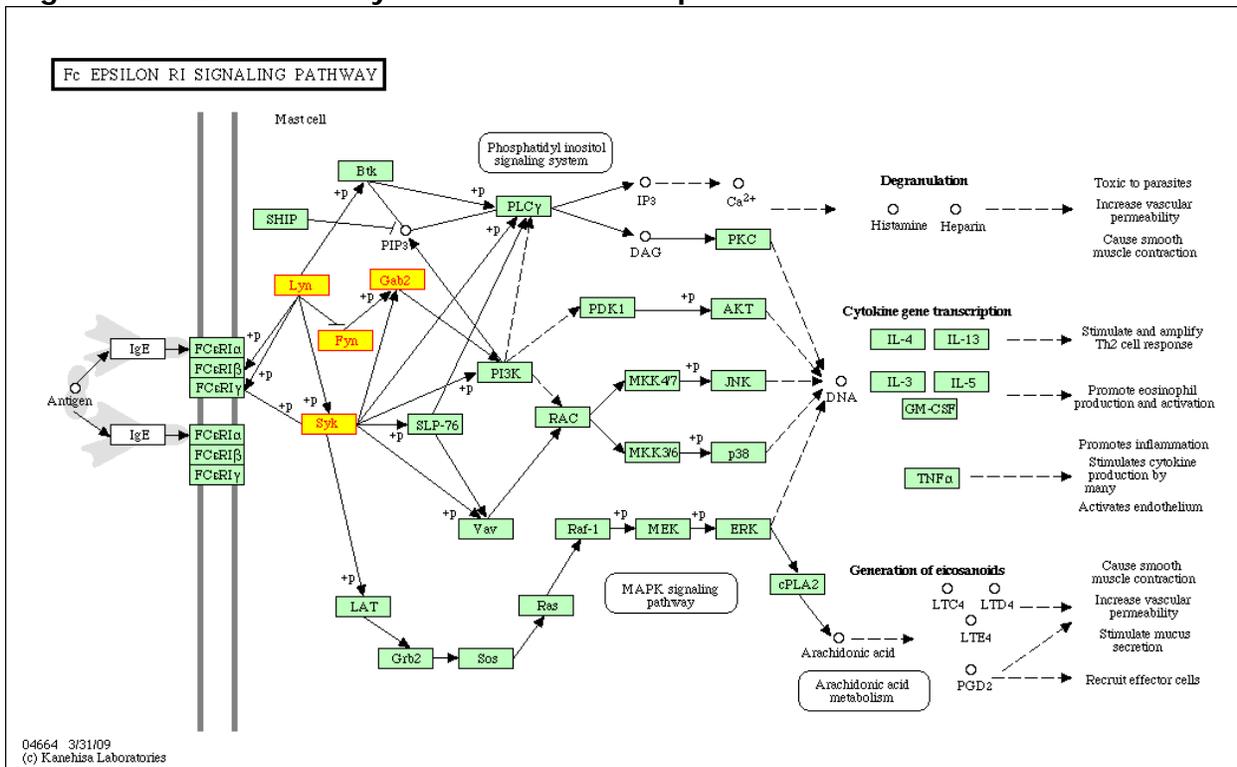
- In the SAGA dialogue box, click Query. The query box will send a query to KEGG (a database of metabolic pathways) and see if any pathways in KEGG match the subnetwork you have chosen involving GAB2, FYN, LYN, and SYK.
- Results show that in the first result 4 out of 4 nodes match (Figure 11).

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

Gene2MeSH – Gene Annotation with MeSH Terms

Search Gene2MeSH About Gene2MeSH

Search by: Gene Symbol MeSH Term Limit Search by Organism: All Organisms

Gene2MeSH Search examples: *brca2*, "Prostatic Neoplasms" Substances only

history: [Gab2](#)

49 MeSH headings found matching gene symbol "Gab2"
 = lookup gene or MeSH heading; = view interactions in MIMI Show All Columns | [download tab-delimited results](#)

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

- 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.
- 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.
- Read the abstract. Save this article.

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

cytoplasmic domain of MUC20 has the ability to oligomerize and that the oligomerization augments its affinity for Met. Taken together, these results suggest that MUC20 is a novel regulator of the Met signaling cascade which has a role in suppression of the Grb2-Ras pathway. Copyright 2004 American Society for Microbiology
 PMID: 15314156 [PubMed - indexed for MEDLINE] PMID: PMC506992

8: *J Cell Biol.* 2005 Jul 18; 170(2):305-16. Epub 2005 Jul 11. Final Version FREE *J Cell Biol.* Full text article In PubMed Central Links

A novel role for Gab2 in bFGF-mediated cell survival during retinoic acid-induced neuronal differentiation.

Mao Y, Lee AW.
 Department of Pharmacology, The University of Michigan Medical School, Ann Arbor, MI 48105, USA.

Gab proteins amplify and integrate signals stimulated by many growth factors. In culture and animals, retinoic acid (RA) induces neuronal differentiation. We show that Gab2 expression is detected in neurons in three models of neuronal differentiation: embryonic carcinoma (EC) stem cells, embryonic stem cells, and primary neural stem cells (NSCs). RA treatment induces apoptosis, countered by basic FGF (bFGF). In EC cells, Gab2 silencing results in hypersensitivity to RA-induced apoptosis and abrogates the protection by bFGF. Gab2 suppression reduces bFGF-dependent activation of AKT but not ERK, and constitutively active AKT, but not constitutively active MEK1, reverses the hypersensitization. Thus, Gab2-mediated AKT activation is required for bFGF's protection. Moreover, Gab2 silencing impairs the differentiation of EC cells to neurons. Similarly, in NSCs, Gab2 suppression reduces bFGF-dependent proliferation as well as neuronal survival and production upon differentiation. Our findings provide the first evidence that Gab2 is an important player in neural differentiation, partly by acting downstream of bFGF to mediate survival through phosphoinositide 3 kinase-AKT.

PMID: 16009726 [PubMed - indexed for MEDLINE] PMID: PMC2171403

Related articles

- ▶ G-CSF-induced tyrosine phosphorylation of Gab2 is Lyn kinase dependent and associated with enhanced Akt and differentiative, not prolifer [Blood. 2004]
- ▶ Basic fibroblast growth factor activates ERK and induces c-fos in human embryonic stem cell line MzhES1. [Stem Cells Dev. 2005]
- ▶ Activated STAT5 proteins induce activation of the PI 3-kinase/Akt and Ras/MAPK pathways via the Gab2 scaffolding adapter. [Biochem J. 2005]
- ▶ **Review** Embryonic stem cell-derived neurogenesis. Retinoic acid induction and lineage selection of neuronal cells. [Cell Tissue Res. 2001]
- ▶ **Review** Roles of phospholipase D in apoptosis and pro-survival. [Biochim Biophys Acta. 2002]

▶ See reviews... ▶ See all...

Patient Drug Information

- ▶ **Tretinoin (Vesanoïd®)** Tretinoin is used to treat acute promyelocytic leukemia (APL, a type of cancer in which there are too many immature blood cells in the blood and bone marrow) in people who have not been helped by other types of chemother...

Source: AHFS Consumer Medication Information

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.