

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)

The screenshot shows the PubMed search results interface. At the top, there are tabs for 'All: 11' and 'Review: 1'. Below the tabs, it says 'Items 1 - 11 of 11' and 'One page.' The results are listed as follows:

- 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

MICHIGAN MOLECULAR INTERACTIONS NCIBI

Free Text Search | Gene List Search | Query Interactions | Browse Database | About MiMI | Help

Example: pwp1

Welcome to MiMI

MiMI Web gives you an easy to use interface to a rich NCIBI data repository for a database, PubMed resources updated nightly, and text mined from biomedical research interaction information that has been integrated and merged from diverse protein point of entry for querying, exploring, and analyzing all these data.

Search MiMI

Search MiMI Using the Free Text search bar at the top of the Main Search page. You can enter a single Keyword, Gene symbol, or Gene ID and retrieve matching genes from the MiMI database.

Organism dropdown list:

- Homo sapiens
- All Organisms
- Homo sapiens
- Saccharomyces cerevisiae
- Drosophila melanogaster
- Caenorhabditis elegans
- Mus musculus
- Escherichia coli
- Rattus norvegicus
- Arabidopsis thaliana
- Helicobacter pylori 26695
- Plasmodium falciparum 3D7

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

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

Search Results

9 genes found

[Click to sort](#)

Gene Ontology (GO) annotations

Counts of interactions, articles, pathways

Gene	Organism	Type	Other Names	Description	Cellular Components	Biological Processes	Molecular Functions	Int	Dec	Path
GAB2	Rattus norvegicus	protein-coding	Gab2	growth factor receptor bound protein 2-associated protein 2	---	cell migration, integrin-mediated signaling pathway	SH2/SH3 adaptor binding	4	3	2
GAB2	Bos taurus	protein-coding	GAB2	GRB2-associated binding protein 2	---	---	---	-	-	-
GAB2	Gallus gallus	protein-coding	GAB2	GRB2-associated binding protein 2	---	---	---	-	-	-
GAB2	Canis lupus familiaris	protein-coding	GAB2	GRB2-associated binding protein 2	---	---	---	-	-	-

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) <ul style="list-style-type: none">• Gene Type: protein-coding• Chromosome: 11• Map Locus: 11p14.1• Locus Tag: null	Cellular Components...	Biological Processes...	Molecular Functions...
Other Names... <ul style="list-style-type: none">• GAB2• KIAA0571			
Descriptions... <ul style="list-style-type: none">• Authorized Gene Description: GRB2-associated binding protein 2• Other descriptions...<ul style="list-style-type: none">○ 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 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 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, Guilhaus M, James DE, Daly RJ
18314909	view	2008	Genes	Amplification of 11p13 in ovarian	Brown I A, Kallander SF, Millar MA, Skik TaM, McKinnon SF, Santos B, Suenarten 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

 **Protein Interactions (239 gene interactions found/6 NLP interactions found) - [show/hide](#)**

 **Literature on gene GRB2 (375 publications found) - [show/hide](#)**

 **Pathways (34 pathways found) - [show/hide](#)**

 **Compounds associated with Gene [show/hide](#)**

View GRB2 With Other NCIBI Tools [Gene2MeSH](#) [Cytoscape](#) [Netbrowser](#) [GIN](#) [MiSearch](#)

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

Zoom icons

Select all – yellow nodes, red edges

Network tab

Zoomed in

Blue pan box

Table icon

Click headings to sort. Move headings to arrange

Dock icon

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	PIK3CQ	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	OR62	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:0004890], guar...	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	phospholipase 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

The screenshot shows the Cytoscape Desktop interface. The main window displays a network of nodes and edges. A context menu is open over the network, showing options like 'Visual Mapping Bypass', 'Use Web Services', 'LinkOut', 'MiMI Plugin', and 'BioNLP'. The 'MiMI Plugin' is selected, and a sub-menu shows 'BioNLP' as the chosen option. A pop-up window titled '24 Sentences Related To [GAB2] And [PIK3CA] From BioNLP' is displayed, showing a list of sentences extracted from articles. The sentences are sorted by semantic similarity and include PubMed IDs, sections, and symbols.

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.

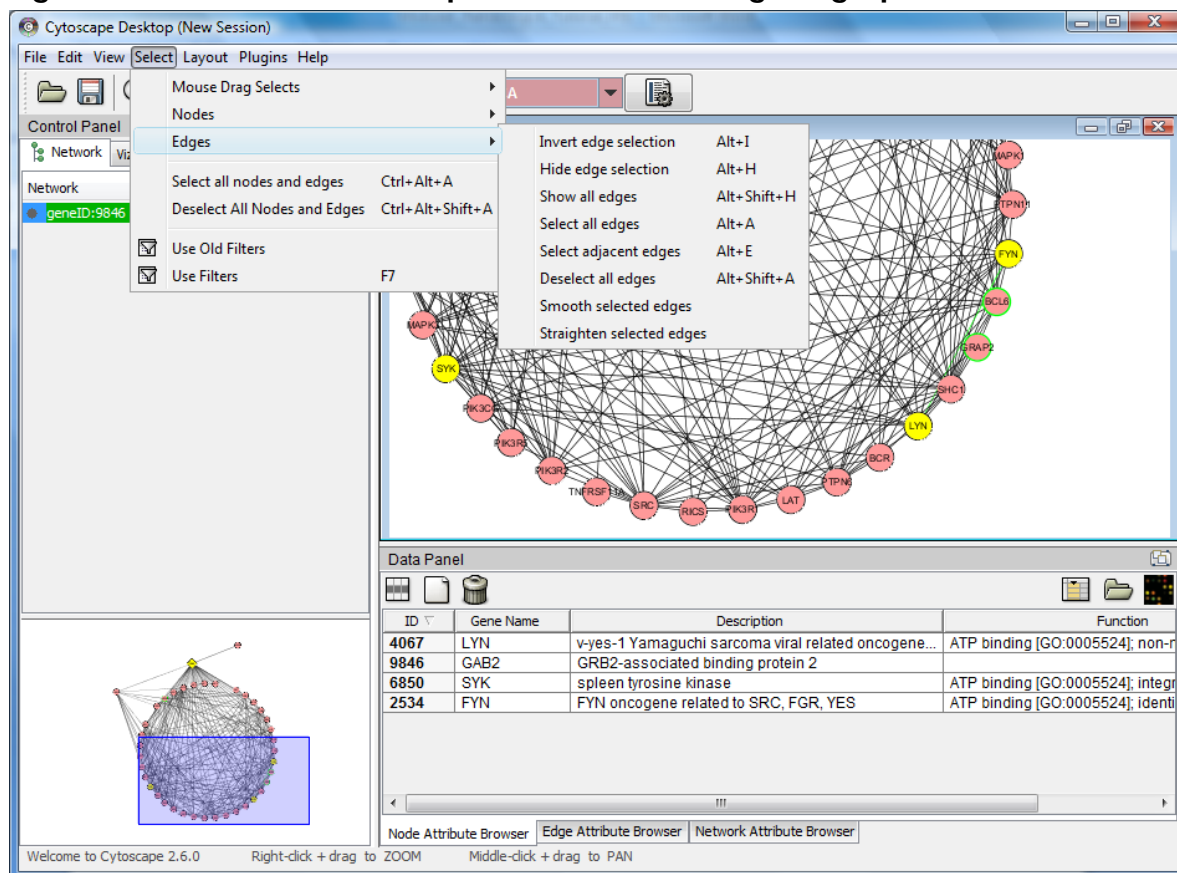
Look for Clues from Pathways

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

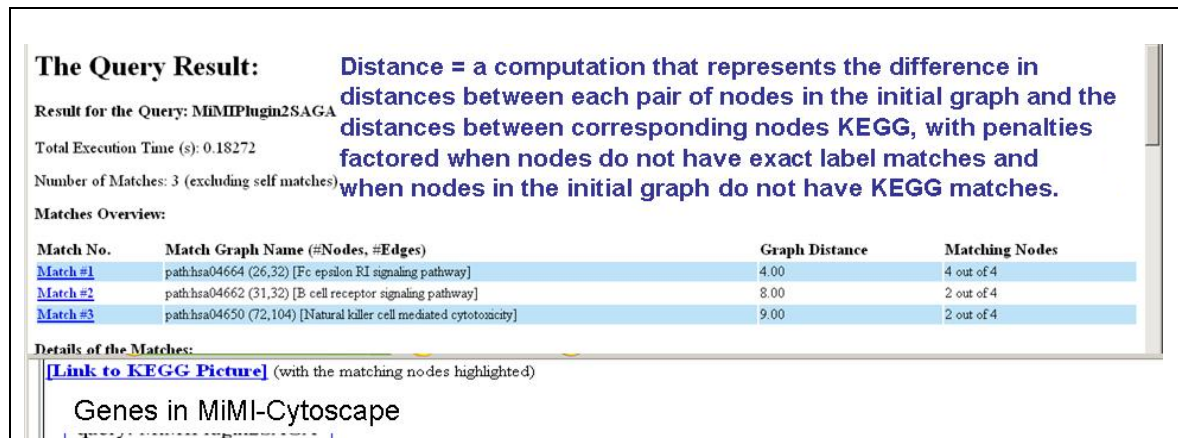


4. Right click on any one of the four selected nodes.
5. On the pop up box click, **MiMI Plugin- → SAGA → Do SAGA (Choose multiple nodes & edges)**. A query box appears.

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

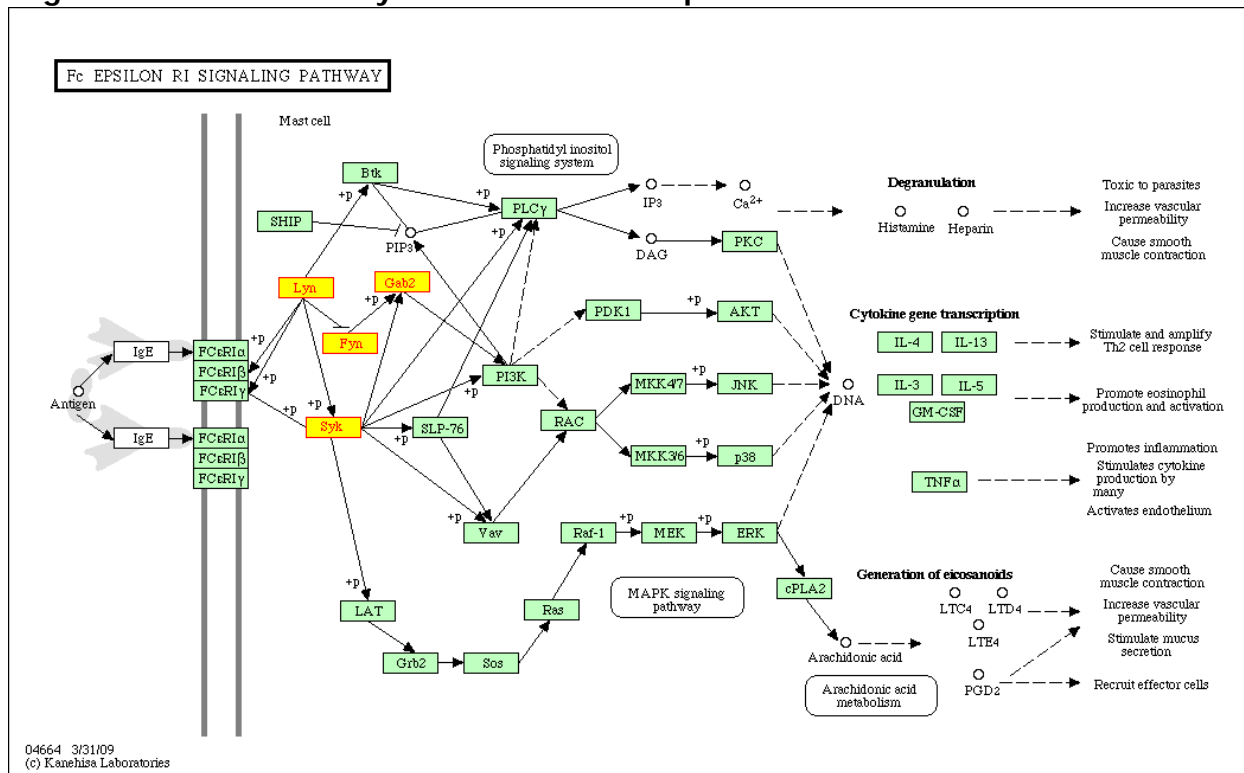
6. In the SAGA dialogue box, click Query. The query box will send a query to KEGG (a database of metabolic pathways) and see if any pathways in KEGG match the subnetwork you have chosen involving GAB2, FYN, LYN, and SYK.
7. Results show that in the first result 4 out of 4 nodes match (Figure 11).

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

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
	Adaptor Proteins, Signal Transducing	9606	2.1e-51	-	GRB2-associated binding protein 2	35
	Phosphoproteins	10090	2.5e-49	genetics	growth factor receptor bound protein 2-associated protein 2	32
	Phosphoproteins	9606	6.3e-36	metabolism	GRB2-associated binding protein 2	28
	Protein Tyrosine Phosphatase, Non-Receptor Type 11	9606	1.4e-23	-	GRB2-associated binding protein 2	12
	Signal Transduction	9606	1.9e-20	-	GRB2-associated binding protein 2	28
	Phosphorylation	9606	4.5e-16	-	GRB2-associated binding protein 2	23
	Protein Tyrosine Phosphatases	9606	7.1e-16	metabolism	GRB2-associated binding protein 2	12
	Protein Tyrosine Phosphatase, Non-Receptor Type 6	9606	3.4e-15	-	GRB2-associated binding protein 2	8
	Signal Transduction	10090	1.1e-14	-	growth factor receptor bound protein 2-associated protein 2	24
	1-Phosphatidylinositol 3-Kinase	10090	1.4e-14	metabolism	growth factor receptor bound protein 2-associated protein 2	12
	Adaptor Proteins, Signal Transducing	10090	2.3e-14	-	growth factor receptor bound protein 2-associated protein 2	13
	Protein Tyrosine Phosphatase, Non-Receptor Type 11	10090	1.7e-13	-	growth factor receptor bound protein 2-associated protein 2	7
	1-Phosphatidylinositol 3-Kinase	9606	1.3e-10	metabolism	GRB2-associated binding protein 2	10
	src-Family Kinases	10090	3.8e-10	metabolism	growth factor receptor bound protein 2-associated protein 2	7
	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)

bioRxiv preprint doi: <https://doi.org/10.1101/000000>; this version posted July 11, 2005. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

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
PMD: 15314156 [PubMed - indexed for MEDLINE] PMID: PMC506992

8: *J Cell Biol*. 2005 Jul 18;170(2):305-16. Epub 2005 Jul 11.

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.

PMD: 16009726 [PubMed - indexed for MEDLINE] PMID: PMC2171408

Related articles

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