



National Center for Integrative Biomedical Informatics

PubAnatomy Tutorial



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TUTORIAL OBJECTIVES

In this tutorial you will:

- Query PubAnatomy by keyword and genes to retrieve results
- Export results for bibliographic management
- Filter results to find literature of interest
- Use PubPath to explore gene relationships

QUERYING PUBANATOMY

Background

PubAnatomy website:

<http://brainarray.mbni.med.umich.edu/Brainarray/prototype/PubAnatomy/>

PubAnatomy is an integrative [PubMed](#) and [Allen Brain Atlas](#) exploration tool developed by the [Molecular and Behavioral Neuroscience Institute \(MBNI\)](#) and the [National Center for Integrative Biomedical Informatics \(NCIBI\)](#) at the University of Michigan.

Research Questions

- A. For a specific P2X-related disease and associated genes, find relevant articles and other useful information that suggests and explains interrelated behaviors that may implicate a P2X receptor in influencing disease-related processes.
- B. Speculate about what you have been reading by relating insights, methods, findings, and/or conclusions from 2 or more articles. These hunches need to be different from reported explanations in the first task, which are basically conclusions that articles present.

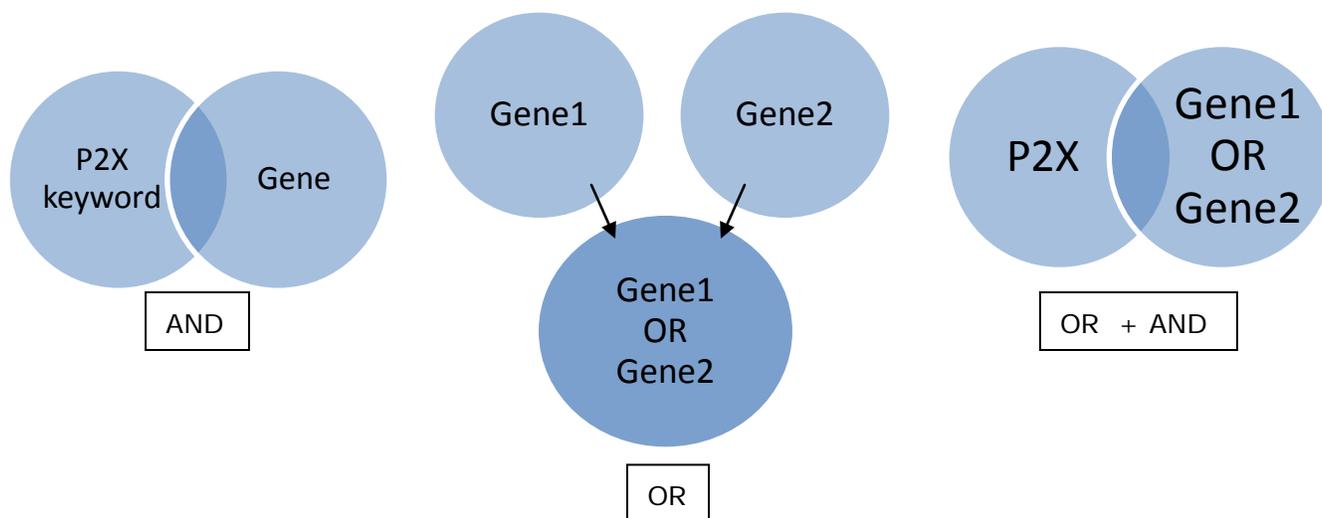
PubAnatomy searches PubMed for your query terms and retrieves a set of relevant articles. From these articles, PubAnatomy then relates other concepts to the articles. For example, literature relevant to your query is associated with mouse brain regions, gene expression data in mouse brain, Medical Subject Headings (MeSH), and diseases associated with query terms and resulting retrieved articles.

You have multiple options for querying in PubAnatomy. How the search terms are combined by PubAnatomy is dependent on the search combination that you use.

Search Options	Searching Logic Combination by PubAnatomy	Example of How PubAnatomy will search
Keyword	Searches keyword as a phrase and is not case sensitive	p2x (in any record)
Gene	Searches tagged gene information for each record	bdnf (any record that is tagged with this gene)
Multiple genes (gene1, gene2, gene3)	Boolean OR: searches for any of the genes in each record	IL1B or CREB1 or ESR2 or TRPV1 in any record
Keyword + gene	Boolean AND: looks for the keyword and gene in the same record	p2x and IL1B together in any record
Keyword + multiple genes (gene1, gene2, gene3)	Boolean OR for genes, Boolean AND with keyword: searches for any of the genes plus the keyword in the same record	(BDNF or IL1B or CREB1 or ESR2 or TRPV1 in any record) and p2x together

Boolean Logic for Searching

The darker color indicates retrieved search set using that particular Boolean logic.



When you AND two concepts together such as P2X in the keyword searching box and a gene in the Gene ID or Symbol box, you are taking the intersection of those articles that were retrieved using P2X as a keyword and those articles that were retrieved with that gene tagged.

1. In the Search Panel, enter your keyword (not case-sensitive) into the Keywords text box. Multiple words like “bipolar disorder” will be handled as a phrase. For example, enter in P2X into the search box.
2. Click on the Search button.

PubAnatomy will retrieve any articles that contain your keyword.

Querying by Gene

To search by a gene rather than by a keyword, you can query on a gene directly.

1. In the Search Panel, enter a gene symbol (for example, BDNF) into the Gene ID or Symbol box.
2. Click on the Search button.

PubAnatomy will retrieve those records that have been tagged with that gene.

Tip: The Gene IDs are the unique identifiers available from the National Center for Biotechnology's (NCBI) Entrez Gene database which provides human curated information about the gene including gene information, protein information, genomic regions, bibliography, reference sequences and more.

Querying by Gene List

1. To search on multiple genes, enter the gene symbols or gene IDs separated by commas (for example, IL1B,CREB1,ESR2,TRPV1). Multiple genes will be searched using a Boolean OR methodology. PubAnatomy will retrieve any records that are tagged for any one of these genes.
2. Click on the Search button.

In this example, you will retrieve 497 citations, all of records that have been tagged for IL1B or CREB1 or ESR2 or TRPV1.

Querying by Keyword and Gene

If you are interested in combining a keyword with a gene, then you may use a combination of both search boxes for combined search querying.

1. In the Search Panel, enter your single keyword into the Keywords text box. For example, enter in P2X.
2. In the Search Panel, enter your gene symbol or gene ID into the Gene ID or Symbol box. For example, enter in IL1B.
3. Click on the Search button.

Tip: PubAnatomy will retrieve records that contain both your keyword and are tagged by the gene. In this example, you will retrieve 3 citations.

Querying by Keyword and Gene List

1. In the Search Panel, enter your single keyword into the Keywords text box. For example, enter in P2X.
2. In the Search Panel, enter your gene symbols or gene IDs separated by commas into the Gene ID or Symbol box. For example, enter BDNF,IL1B,CREB1,ESR2,TRPV1.
3. Click on the Search button.

Tip: PubAnatomy will take your gene list search (combining the genes using an OR) and add it to your Keyword search (combining the results from the gene list search and adding the keyword search using an AND) with the gene list search. In this example, you will retrieve 7 citations.

VIEWING RESULTS

After you have clicked on the search button with any of the possible search combinations, the results screen with relevant citations appears (Figure 2). Run the P2X keyword search used in the Searching by Keyword section.

The darker color the brain sections are, the greater the number of citations that are associated with that brain region. Hovering your mouse over any region highlights the region (maroon color).

Tip: The number of citations that your keyword search has retrieved will be displayed in the upper right hand corner of the Results frame. In the P2X keyword search example, you will see 417 citations. Two numbers appear because in subsequent steps in which you filter your results set, the citation tab will only display a subset of citations that match your filter criteria. The denominator will always indicate the total number of citations originally retrieved to match your search criteria in the Search Panel.

Your initial search results will be displayed in the Citation tab. Related concepts to your initial search query results which have been consolidated from multiple data sources will be displayed in the individual tabs. For this lab, the summary information about your search results that will be reviewed include information in the Gene, MeSH, Author and Disease tabs.

Figure 2: Results Screen

Color legend: the darker the color the greater the number of articles.

Brain region name abbreviations

Brain map is now color coded according to the number of articles retrieved by the search that correspond to that brain region.

Number of articles displayed/retrieved

Citation tab: Literature search results are displayed; click on a row to display the full citation information.

PMID	Year	Journal	Title	Abstract
11380521	2001	M. Clin Exp Pharmacol	An electrophysiological study of the effects of propofol on na	1. Pharmacological evidence suggests that some of the clinical actions of propofol may be r
11007994	2000	Al. Pharmacol Ther	Diadenosine polyphosphate receptors. from rat and guinea-p	Diadenosine polyphosphates are a family of naturally occurring nucleotidic compounds pres
11153527	2001	Ja. Clin Exp Pharmacol	Differential patterns of sympathetic responses to selective sti	1. Studies are described that indicate that stimulation of different purinergic receptor subtyp

Tip: You can sort within the results frame by column headings in any tab. Click on the column heading label by which you would like to sort. The column by which the results are sorted are indicated by a small black arrow in the direction that the results are sorted (ascending or descending).

Related Concepts Provided in Tabs

Tab Header	Related Concept	Links to Additional Information	Filter Search Set
Citation	<ul style="list-style-type: none"> Citations specific to search criteria in Search Panel View detailed citation information 	<ul style="list-style-type: none"> View citation in PubMed Mark and view multiple citations in PubMed Execute a related articles search in PubMed for a specific citation 	
Gene	<ul style="list-style-type: none"> View all genes extracted and tagged from your search set in the Citation tab Export genes to PubPath – a gene list pathway tool for gene interaction comparison (View gene correlation and expression data) 	<ul style="list-style-type: none"> View Entrez Gene records 	By Gene
MeSH	<ul style="list-style-type: none"> View significantly associated MeSH terms from your search set in the Citation tab 	<ul style="list-style-type: none"> View significantly associated genes with a MeSH term View the MeSH database for a term directly Run a prepopulated PubMed search with a MeSH term and your keyword search criteria 	By a MeSH term
Author	<ul style="list-style-type: none"> View all of the authors who have contributed articles to your search set in the Citation tab 	<ul style="list-style-type: none"> Run a prepopulated PubMed search with an author and your keyword search criteria Run a prepopulated PubMed search with an author 	By an author
Disease	<ul style="list-style-type: none"> View all diseases extracted from your search set in the Citation tab View the number of citations that were associated with a particular disease 	<ul style="list-style-type: none"> View the OMIM entry for a disease Summary gene information about the disease extracted from the OMIM record 	By a disease

Citation Tab

The Citation Tab provides information about the citations that you have retrieved from your initial search set which for our example is for the keyword search on P2X.

1. To view a particular citation, click on the citation row to view detailed abstract information with links to PubMed.
2. To explore the citations more fully in PubMed, right mouse click on any row (Figure 3) to:
 - a. View the citation in PubMed
 - b. View all marked citations in PubMed
 - c. View related articles of the citation you have selected in PubMed

Figure 3: Citation Tab View

Citation	Gene	MeSH	Author	Disease	In Situ Image	Interaction	Expression Correlation	Gene Expression	Significant Gene	Import			
Filter 													
<input type="checkbox"/>	PMID	Year	Journal	Title	Abstract						Reset	Export	483/483 citation
<input type="checkbox"/>	17990047	2008	Eur Arch Psychiatry C	View this citation on PubMed	Single photon emission computed tomography (SPECT) with 99mTc-HMPAO was used to con								
<input type="checkbox"/>	19022630	2008	Psychiatry Res	View selected citations on PubMed	Structural and functional pathology of limbic structures including the hippocampus are frequ								
<input checked="" type="checkbox"/>	18989376	2008	PLoS One	View related articles of this citation on PubMed	BACKGROUND: Mitochondrial dysfunction was reported in schizophrenia, bipolar disorderand								
<input checked="" type="checkbox"/>	18980734	2008	Curr Psychiatry Rep	Settings...	The hippocampus and amygdala are key limbic regions for memory formation and emotion								
<input checked="" type="checkbox"/>	18951431	2008	Am J Med Genet B M	About Adobe Flash Player10...	An emerging literature has demonstrated an association between the dopamine D4 recepto								
<input type="checkbox"/>	18833430	2008	Rev Bras Psiquiatr		OBJECTIVE: The objective of this update article is to report structural and functional neuroim								
<input type="checkbox"/>	18827723	2008	J Am Acad Child Adc		OBJECTIVE: The current study combined baseline voxel-based morphometry and 1-year clin								

SAVING CITATIONS FROM PUBANATOMY

Marking Citations

1. In the Citation tab in the Results frame, click the box next to the individual citation that you would like to export. A check mark should appear in the box next to the PMID of successfully marked citations.
2. Repeat step 1 for all citations that you would like to export and save.

Exporting Citations to a Tab Delimited File

1. After marking all the citations that you would like to export, go to the PubAnatomy File menu (not the browser File menu) and click on Export to Tab Delimited Text File.
2. In the ensuing File Download window, click on the Save button.
3. In the Save As window, browse to the location that you would like to save the file to file path box.
4. Optionally, enter a name for the Excel file that will be created in the File Name box.
5. Click on the Save button.

Your file will be saved to the specified location with the file name you specified. If

you did not specify a file name, then the default file name of the Excel spreadsheet will be called, "Citation_ExportByPubAnatomy".

FILTERING RESULTS

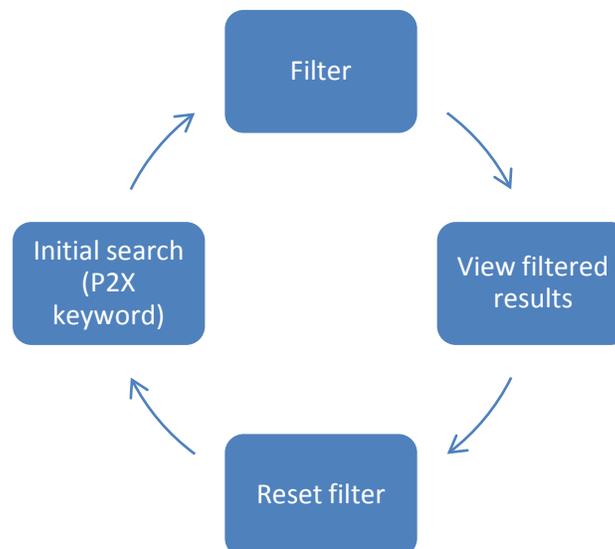
PubAnatomy provides filtering functionality so that you can filter your search results by specific concepts to help focus your area of exploration. You can filter your initial citation search set by the following criteria:

- Gene
- MeSH term
- Author
- Disease

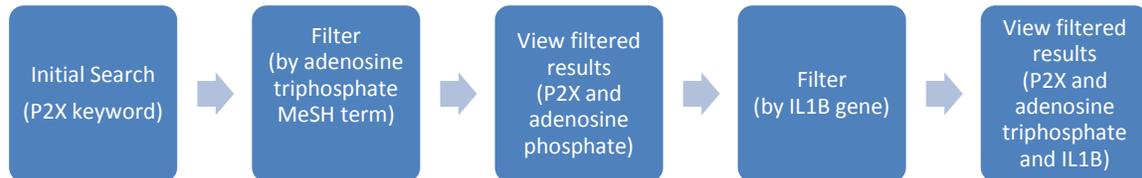
The Process: When you filter by a specific criterion, PubAnatomy narrows your initial search set by your filter criterion and then updates all of the subsequent information in the tabs to reflect the newly narrowed search set.



Iterative Filtering: After you filter by a specific criterion and have viewed your filtered results, you can reset the filter and repeat the process. Resetting a filter will undo the filtering process and return you to the original search criteria set in the Search Panel. You can then go to the Gene, MeSH, Author or Disease tabs to select another filter criterion. Once you have applied the new filter criterion, your initial search set will again be narrowed by the new filter criterion.



Cascading Filtering: PubAnatomy also provides cascading filtering. After you filter by a specific criterion and have viewed your filtered results, you can go to the Gene, MeSH, Author or Disease tabs to select another filter criteria. Once you have applied the second filter criterion, your initial search set will be narrowed even further by this additional filter criterion.



Filtering by Gene

In the Gene Tab View (Figure 4), genes that have been extracted or tagged from the abstracts that you retrieved from your initial search will be listed. The unique gene identifiers for both the mouse and human species will be listed along with the corresponding gene symbol and summary information describing that gene.

Figure 4: Gene Tab View

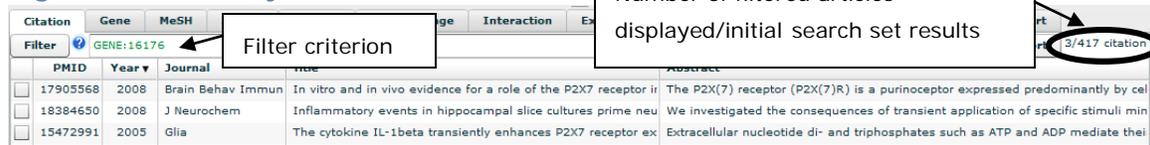
Citation	Gene	MeSH	Author	Disease	In Situ Image	Interaction	Expression Correlation	Gene Expression
Related genes in retrieved citations Right click on a gene to show more choices Export								
	Mouse Gene	Human Gene	Symbol	Chromosome	Cytoband	Gene Description		
<input type="checkbox"/>	11441	1139	CHRNA7	15	15q14	cholinergic receptor, nicotinic	Draw Expression Correlation on Current Region	
<input type="checkbox"/>	11540	135	ADORA2A	22	22q11.23	adenosine A2a receptor	Draw Expression Correlation on Whole Brain	
<input type="checkbox"/>	11785	322	APBB1	11	11p15	amyloid beta (A4) precursor protein	Show Gene Expression Average Value on Map	
<input type="checkbox"/>	12064	627	BDNF	11	11p13	brain-derived neurotrophic factor	Show Gene Expression Median Value on Map	
<input type="checkbox"/>	12307	793	CALB1	8	8q21.3-q22.1	calbindin 1, 28kDa	Show Gene Expression Max Value on Map	
<input type="checkbox"/>	12367	836	CASP3	4	4q34	caspase 3, apoptosis-related cysteine peptidase	Show Gene Expression Min Value on Map	
<input type="checkbox"/>	12496	954	ENTPD2	9	9q34	ectonucleoside triphosphate diphosphate phosphodiesterase 2	Filter Citations by This Gene	
<input type="checkbox"/>	12912	1385	CREB1	2	2q34	cAMP responsive element binding protein 1	View Details of This Gene	
<input type="checkbox"/>	13983	2100	ESR2	14	14q23.2	estrogen receptor 2 (ERBB2)	Find Path for All Genes	
<input type="checkbox"/>	16176	3553	IL1B	2	2q14	interleukin 1, beta	Find Path for this Gene	
<input type="checkbox"/>	18436	5023	P2RX1	17	17p13.3	purinergic receptor P2X1, low affinity	Settings...	
<input type="checkbox"/>	18438	5025	P2RX4	12	12q24.32	purinergic receptor P2X4, low affinity	About Adobe Flash Player10...	
<input type="checkbox"/>	18439	5027	P2RX7	12	12q24	purinergic receptor P2X7, low affinity		

- To filter your retrieved citations by a specific gene, right mouse click on the gene ID to open a context sensitive menu which will allow you to:
 - filter the retrieved citations by that gene
 - export your gene or gene list to explore additional gene pathways
- To continue to filter your citations by a specific gene, select the Filter Citations by This Gene option. For this example, select the gene IL1B.
- You will be brought back to the Citation tab. In the Filter box, you will see the filter criteria populated. Click on the Filter button to continue the filtering process.

Your search results numbers will be updated in the upper right corner of the results panel (Figure 5) to indicate your filtered results count (the numerator).

Figure 5 shows your initial search results (P2X searched as a keyword) narrowed down by the IL1B gene.

Figure 5: Filtered by Gene



Citation	Gene	MeSH	Abstract
Filter	GENE:16176		
PMID	Year	Journal	Abstract
<input type="checkbox"/> 17905568	2008	Brain Behav Immun	In vitro and in vivo evidence for a role of the P2X7 receptor in
<input type="checkbox"/> 18384650	2008	J Neurochem	Inflammatory events in hippocampal slice cultures prime neu
<input type="checkbox"/> 15472991	2005	Glia	The cytokine IL-1beta transiently enhances P2X7 receptor ex

Iterative Filtering: Resetting and Setting New Filter Criteria

1. In order to filter by a different gene, you will need to reset the filter criteria. Click on the Reset button next to the filter box in the Citation tab.

Your original search results will be restored as indicated by the citation count display.

2. Click on the Gene tab.
3. Select another gene (for example, BDNF) by which you would like to filter your search results and repeat the steps listed in the Filtering by Gene section.

Your search results numbers will be updated in the upper right corner of the results panel to indicate your filtered results count (the numerator). Now the Citation tab displays your initial search results (P2X searched as a keyword) narrowed down by the BDNF gene.

Filtering by MeSH

In the MeSH Tab View (Figure 6), MeSH terms that are statistically significantly associated by frequency with your search set will be listed. MeSH refers to Medical Subject Headings and is the controlled vocabulary used to index most articles in PubMed to associate the most relevant MeSH terms with each article. These vocabulary terms are assigned by a human curator to the articles.

To filter solely by MeSH term, ensure that all previous filter criteria have been reset by clicking on the Reset button in the Citation tab. Then, proceed with the steps below.

- To filter your search results by a specific MeSH term, click on the MeSH tab to view the MeSH terms that are statistically significant to your search set. The information presented in this tab are summary statistics meant to convey the significance of the term in your search set and include frequency of the term in the citations of your search set, a significance score, and the ratio of the term appearing in your search set versus the entire Medline corpus.
- Right mouse click on the MeSH term you are interested in (for this example, select the MeSH term “Adenosine Triphosphate”) to open a context sensitive menu which will allow you to:
 - filter the retrieved citations by that MeSH term
 - view that MeSH term in the MeSH database (term definition and tree hierarchy)
 - view that MeSH term in the Gene2MeSH tool which shows genes that are significantly associated with MeSH terms in PubMed.
 - run a search in PubMed with that MeSH term and your PubAnatomy entered keyword

Figure 6: MeSH Tab View

Citation	Gene	MeSH	Author	Disease	In Situ Image	Interaction	Expression Correlation	Gene Expression	Significant Gene	Import
MeSH Profiling (significant concepts for given literature set): Right click a MeSH to show more choices Export										
MeSH Concepts		Frequency	Score (significance measure)	Ratio (vs. Medline)						
Receptors, Purinergic P2		336	1659.97	387.9						
Adenosine Triphosphate			551.8	23.7						
Pyridoxal Phosphate			174.8	68.5						
Suramin			141.38	112						
Patch-Clamp Techniques			121.17	21.8						
Rats, Wistar			118.91	6.8						
Receptors, Purinergic			112.86	67.6						
Neurons			79.21	4.2						
Presynaptic Terminals			70.57	27.6						

- To continue to filter your citations by the MeSH term, select the Filter Citations by this MeSH option.
- You will be brought back to the Citation tab. In the Filter box, you will see the filter criteria populated. Click on the Filter button to continue the filtering process.

Your search results numbers will be updated in the upper right corner of the results panel to indicate your filtered results count (the numerator). The Citation tab displays your initial search results (P2X searched as a keyword) narrowed down by the “Adenosine Triphosphate” MeSH term (Figure 7).

Figure 7: Filtered by MeSH

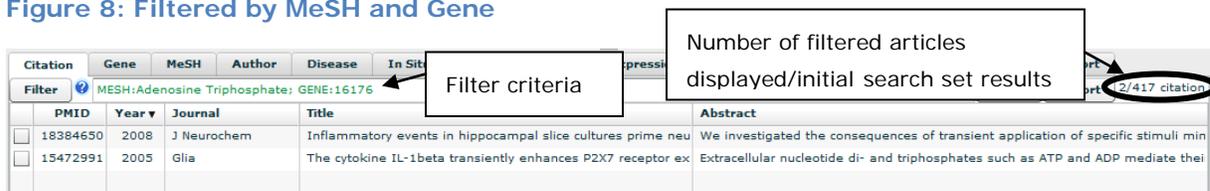
Citation	Gene	MeSH	Author	Disease	Interaction	Expression	Import
Filter MESH:Adenosine Triphosphate 250/417 citation							
PMID	Year	Journal	Title				
<input type="checkbox"/>	11914528	2002 Ja	Audiol Neurootol	Purinergic regulation of sound transduction and auditory neur...			
<input type="checkbox"/>	12566690	2003 Ja	Audiol Neurootol	Expression of the P2X7 receptor subunit of the adenosine 5'-...			
<input type="checkbox"/>	17624242	2007 Ar	Int J Immunopathol	Activation of P2X(7) receptors stimulates the expression of P...			
<input type="checkbox"/>	18590708	2008	Brain Res	Purinergic P2X receptors facilitate inhibitory GABAergic and gl...			
<input type="checkbox"/>	18583548	2008	J Pharmacol Exp Th	Purinergic type 2 receptors at GABAergic synapses on ventral...			

Cascading Filtering: Adding More Filter Criteria

1. In order to filter by an additional concept, you will need to add filter criteria to your currently filtered search set.
2. In our P2X example, we have narrowed our original P2X keyword search by the MeSH term, Adenosine Triphosphate. We will further narrow our results by a gene. Click on the Gene tab.
3. Select a gene (for example, IL1B) by which you would like to filter your previously filtered search results and repeat the steps listed in the Filtering by Gene section.

Your search results numbers will be updated in the upper right corner of the results panel to indicate your filtered results count (the numerator). The Citation tab displays your initial search results (P2X searched as a keyword) narrowed down by the “Adenosine Triphosphate” MeSH term and then further narrowed by the IL1B gene.

Figure 8: Filtered by MeSH and Gene



Citation	Gene	MeSH	Author	Disease	In Sit	Filter criteria	Number of filtered articles displayed/initial search set results
Filter		MESH:Adenosine Triphosphate;				GENE:16176	2/417 citation
PMID	Year	Journal	Title	Abstract			
<input type="checkbox"/> 18384650	2008	J Neurochem	Inflammatory events in hippocampal slice cultures prime neu	We investigated the consequences of transient application of specific stimuli min			
<input type="checkbox"/> 15472991	2005	Glia	The cytokine IL-1beta transiently enhances P2X7 receptor ex	Extracellular nucleotide di- and triphosphates such as ATP and ADP mediate thei			

Filtering by Author

In the Author Tab View (Figure 5), authors who contributed to the retrieved search set are listed. To filter solely by an author on your original search set, ensure that all previous filter criteria have been reset by clicking on the Reset button in the Citation tab. Then, proceed with the steps below.

1. To filter your retrieved citations by a specific author, right mouse click on an author name (for this example, select Burnstock, G) to open a context sensitive menu which will allow you to:
 - a. filter the retrieved citations by that author
 - b. search PubMed using the Author and other search criteria
2. To continue to filter your citations by the author, select the Filter Citations by This Author option.
3. You will be brought back to the Citation tab. In the Filter box, you will see the filter criteria populated. Click on the Filter button to continue the filtering process.

- To set new filter criteria, follow the steps in the Iterative Filtering: Resetting and Setting New Filter Criteria section.

Figure 9: Author Tab View

Citation	Gene	MeSH	Author	Disease	In Situ Image	Interaction	Expression Correlation	Gene Expression	Significant Gene	Import
Aggregated author info of current literature set: Right click a row to show more choices Export										
Last Name	First Name		Citation Count							Search Link
Burnstock	G		27							More citations
Miras-Portugal	M T		15							More citations
Burnstock	Geoffrey		13							More citations
Illes	P		11							More citations
Illes	Peter		10							More citations
Surprenant	A		10							More citations
Housley	G D		10							More citations

Filtering by Disease

In the Disease Tab View (Figure 4), diseases that have been extracted from the abstracts in your Citation tab will be listed. To see all diseases extracted from your initial search set, ensure that all previous filter criteria have been reset by clicking on the Reset button in the Citation tab. The unique disease identifiers (from NCBI's Online Mendelian Inheritance in Man database which is a human curated compendium of human genes and genetic phenotypes on all known Mendelian disorders and associated genes for each disease) that have been obtained will be listed along with the corresponding genetic information related to that disease.

- To filter your search results by a specific disease, click on the Disease tab to view the diseases that are related to your retrieved citation set. The information presented in this tab will direct you to the diseases associated with the citation set you retrieved. The number of citations in your result set, presented in the #PMID column, is an indication of the number of articles that this disease is mentioned in the abstract, title, MeSH or keywords in your citation set.

Tip: Just because the frequency of citations is not high, however, should not preclude you from investigating the disease relationship further. Use your own discretion in exploring the disease relationships. We will explore the genes associated with the disease, epilepsy, and the genes associated with P2X even though there is only one citation for this disease association because the one article retrieved shows interesting evidence that shows P2 receptors affected microglia membrane currents in mice subjected to an epilepsy-type state. Further searching in PubMed provides additional articles that show increasing research being conducted on nucleotide function and Central Nervous System diseases including microglia and P2X receptors.

- To filter your retrieved citations by a specific disease, right mouse click on a disease name (for this example, select epilepsy) to open a context sensitive menu which will allow you to:
 - filter the retrieved citations by that disease

3. To continue to filter your citations by a disease, select the Filter Citations by This Disease option.
4. You will be brought back to the Citation tab. In the Filter box, you will see the filter criteria populated. Click on the Filter button to continue the filtering process.

Figure 10. Disease Tab View

Citation	Gene	MeSH Profiling	Author	Disease	In Situ Image	MIMI Interaction	Expression Correlation	Gene Expression	Significant Gene	Import
<input type="checkbox"/>	182390			seizures		2q23-q24.3		2	6325	SCN2A1, SCN2A
<input type="checkbox"/>	608072			epilepsy		6p22.3		6	378884	NHLRC1, EPM2A, EPM2B
<input type="checkbox"/>	607145			schizophrenia		6p22.3		6	84062	DTNBP1, HPS7
<input type="checkbox"/>	124030			parkinsonism		22q13.1		22	1565	CYP2D@, CYP2D, P450C2I
<input type="checkbox"/>	221820			gliosis		17q21-q22		17	8156	GPSC
<input type="checkbox"/>	300139			corpus callosum		Xq13.1-q13.3		X	3476	IGBP1
<input type="checkbox"/>	602569			dementia		5q35		5	6620	SNCB
<input type="checkbox"/>	606157			neurodegeneration		20p13-p12.3		20	80025	PANK2, NBIA1, PKAN, HAR1
<input type="checkbox"/>	602851			convulsions		5q14		5	84059	MASS1, VLGR1, KIAA0686,
<input type="checkbox"/>	602125			encephalopathy		17p12-p11.2		17	1352	COX10

EXPLORING GENE PATHWAYS

PubPath

PubAnatomy provides an integrated tool called PubPath which allows you to explore relationships across multiple genes. Using PubPath, you can compare two gene lists and find associations between genes in order to further explore potential genetic pathways. Comparing two gene lists can highlight gene relationships that you may not have considered. PubPath will compare the two gene lists and extract direct gene pair relationships. PubPath will also extract gene pair relationships that have one intermediary gene interaction between the two genes. These intermediary genes can then be imported back into PubAnatomy for further exploration. Gene lists that you compare in PubPath could be genes you have discovered through previous literature searches, experimentally derived data, or from searches conducted in PubAnatomy.

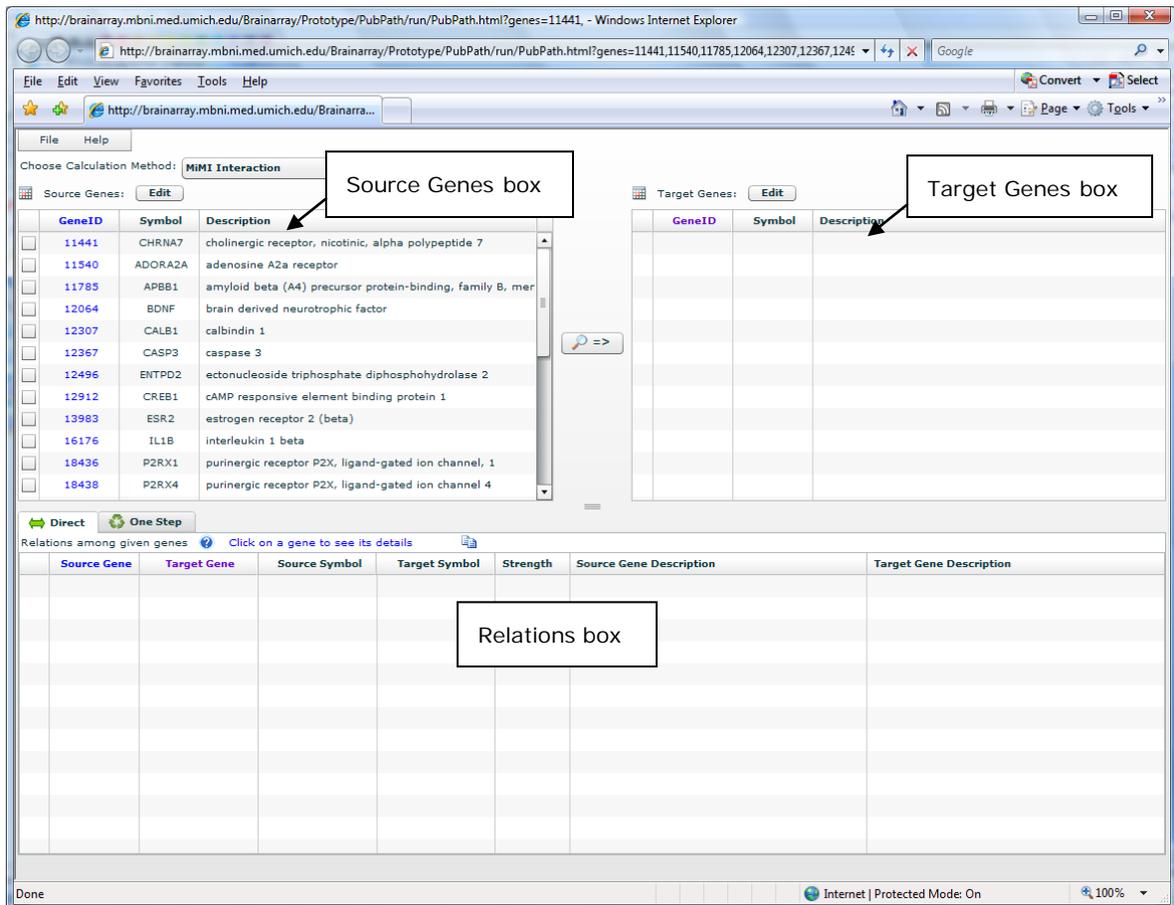
For this lab, we will compare the gene lists generated by a keyword search on P2X and a keyword search on epilepsy because we have some evidence of the physiological relationship between the receptors and the disease but would like to investigate possible genetic relationships.

Exporting Gene Lists from PubAnatomy

Recall from the Filtering by Gene section, in the Gene Tab View (Figure 4), genes that have been extracted or tagged from the abstracts that you retrieved from your initial search will be listed. You can export the gene list in the Gene Tab View into PubPath. Ensure that all previous filter criteria have been reset by clicking on the Reset button in the Citation tab. You should have the search result set related to the P2X keyword search in the Citation tab.

1. In the Gene Tab view, right mouse click on any gene symbol or gene ID to open a context sensitive menu which will allow you to export your gene list to PubPath.
2. Select the Find Path for All Genes option.
You will be brought to the PubPath tool (Figure 11) with your genes populated in the Source Genes box in upper left hand corner.

Figure 11: PubPath Screen



The screenshot shows the PubPath tool interface. At the top, there are navigation tabs: 'Direct' and 'One Step'. Below the tabs, there are two main tables: 'Source Genes' and 'Target Genes'. The 'Source Genes' table is populated with a list of genes, including their GeneID, Symbol, and Description. The 'Target Genes' table is currently empty. Below these tables is a 'Relations' table, which is also empty. The 'Relations' table has columns for Source Gene, Target Gene, Source Symbol, Target Symbol, Strength, Source Gene Description, and Target Gene Description. A 'Relations box' label points to the empty table. Arrows also point to the 'Source Genes box' and 'Target Genes box' labels.

GeneID	Symbol	Description
11441	CHRNA7	cholinergic receptor, nicotinic, alpha polypeptide 7
11540	ADORA2A	adenosine A2a receptor
11785	APBB1	amyloid beta (A4) precursor protein-binding, family B, member 1
12064	BDNF	brain derived neurotrophic factor
12307	CALB1	calbindin 1
12367	CASP3	caspace 3
12496	ENTPD2	ectonucleoside triphosphate diphosphohydrolase 2
12912	CREB1	cAMP responsive element binding protein 1
13983	ESR2	estrogen receptor 2 (beta)
16176	IL1B	interleukin 1 beta
18436	P2RX1	purinergic receptor P2X, ligand-gated ion channel, 1
18438	P2RX4	purinergic receptor P2X, ligand-gated ion channel 4

GeneID	Symbol	Description
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Source Gene	Target Gene	Source Symbol	Target Symbol	Strength	Source Gene Description	Target Gene Description
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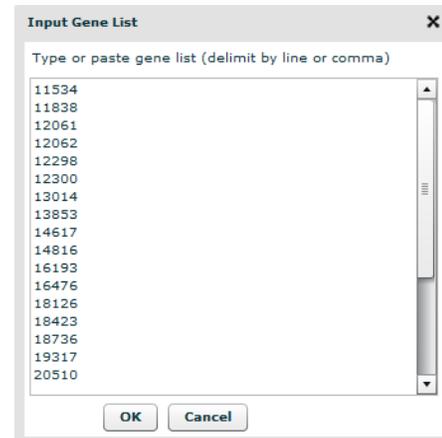
Importing Gene Lists into PubPath

To compare the genes in the Source Genes box with another list of genes, you will need to populate the Target Genes box.

1. Click on the Edit button next to the Target Genes caption in the upper right hand corner of the main PubPath screen. An Input Gene List box will appear (Figure 12).
2. Enter or paste a set of genes into the box.

Multiple genes should be entered on separate lines or separated by commas. You may use gene symbols of gene IDs.

Figure 12: Input Gene List Box



Because we are interested in exploring the gene relationships between the genes associated with P2X and epilepsy, we will need to paste the gene list from our keyword search on epilepsy from PubAnatomy.

- a. Click back onto the PubAnatomy window.
- b. Clear P2X from the Keyword search box.
- c. Enter epilepsy in the Keyword search box.
- d. Click the Search button.
- e. In the Gene Tab view, click on the Export button. This will copy the gene tab information onto the computer's clipboard.
- f. Open a spreadsheet application like Excel, and paste the contents of the clipboard onto the spreadsheet (Ctrl+V or click the Paste icon).
- g. Copy the contents of the Mouse Gene column or the Symbol column. This is the gene list that you will be pasting into the Target genes box.

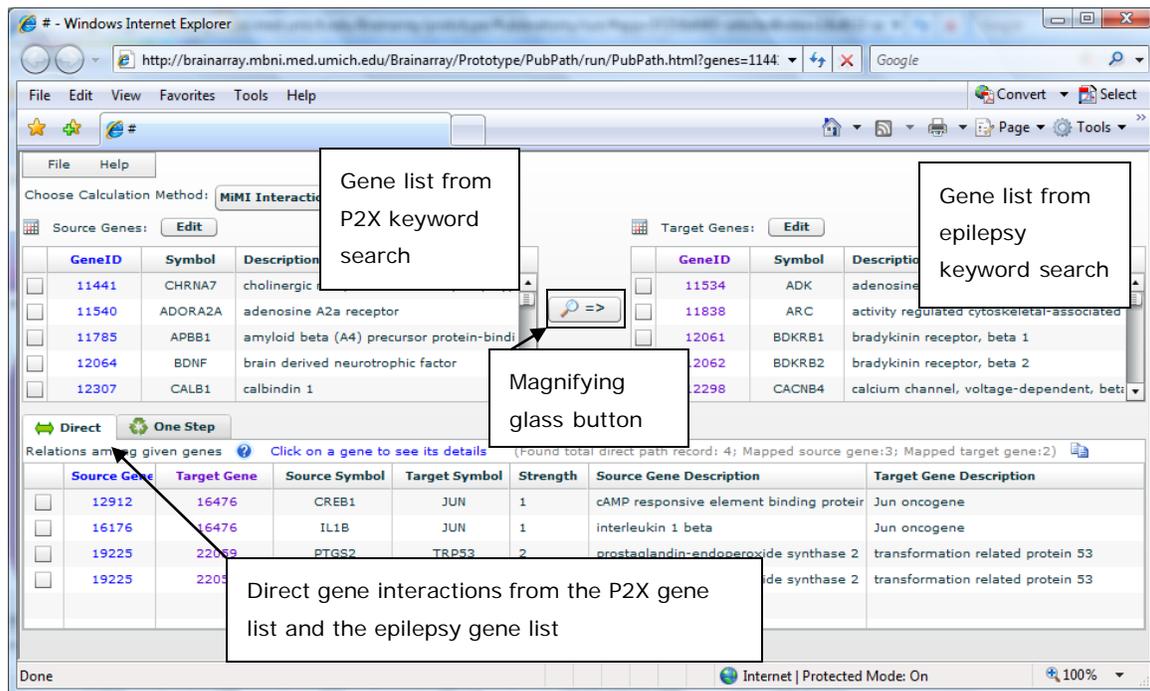
Genes symbols or IDs that cannot be matched to a unique gene identifier will be displayed at the bottom of your gene list in your Source or Target Genes box.

3. Click on the OK button.

Exploring Gene Relationships

1. Click on the Magnifying glass button between the Source Genes and Target Genes box to have PubPath search for direct and one step interactions between genes using the Michigan Molecular Interactions (MiMI) Database. MiMI is a database created by NCIBI which uses a deep merge process to combine gene interaction data from multiple databases and provides a single interface to access all of the combined interaction information.
2. After querying the database, the direct gene pair interactions will be displayed in the Relations box at the bottom of the screen (Figure 13).

Figure 13: Direct Interactions



The screenshot shows the PubAnatomy web interface in a Windows Internet Explorer browser. The URL is <http://brainarray.mbnl.med.umich.edu/Brainarray/Prototype/PubPath/run/PubPath.html?genes=1144>. The interface includes a 'Choose Calculation Method' dropdown set to 'MiMI Interactions', a 'Source Genes' table, a 'Target Genes' table, and a 'Direct' tab. The 'Direct' tab shows a table of direct interactions between source and target genes.

Source Genes (from P2X keyword search):

GeneID	Symbol	Description
11441	CHRNA7	cholinergic
11540	ADORA2A	adenosine A2a receptor
11785	APBB1	amyloid beta (A4) precursor protein-binding
12064	BDNF	brain derived neurotrophic factor
12307	CALB1	calbindin 1

Target Genes (from epilepsy keyword search):

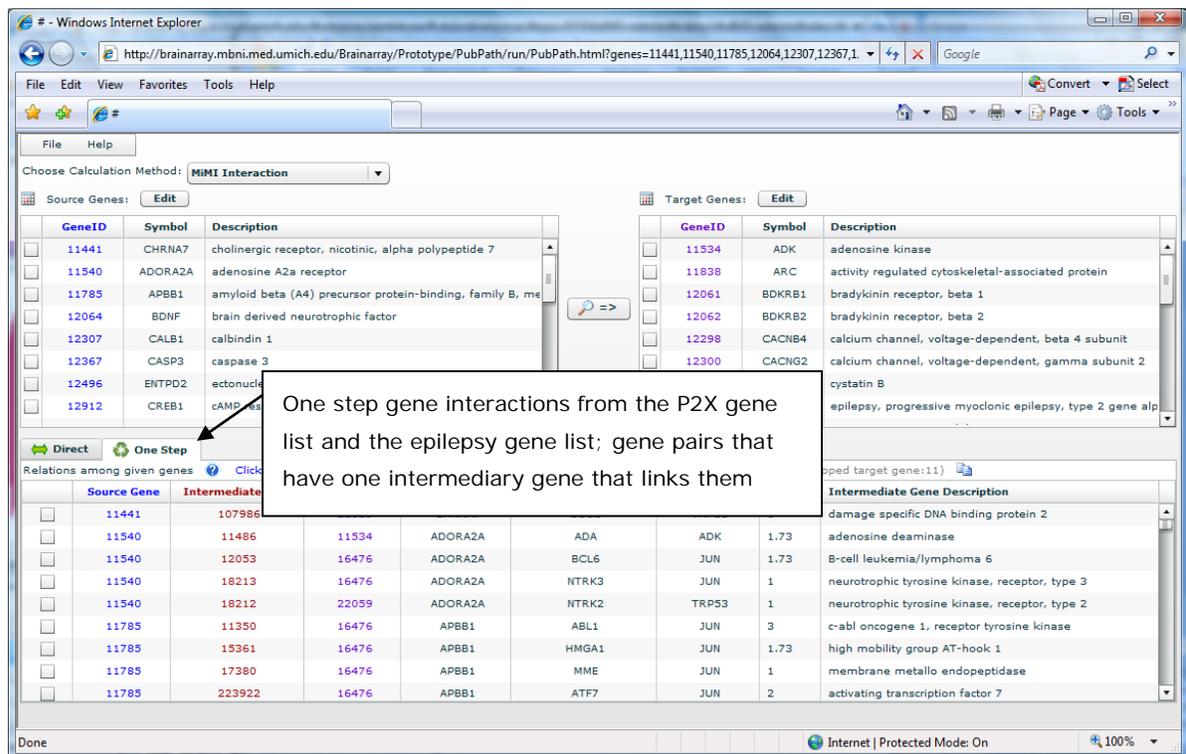
GeneID	Symbol	Description
11534	ADK	adenosine
11838	ARC	activity regulated cytoskeletal-associated
12061	BDKRB1	bradykinin receptor, beta 1
2062	BDKRB2	bradykinin receptor, beta 2
2298	CACNB4	calcium channel, voltage-dependent, bet

Direct Interactions Table:

Source Gene	Target Gene	Source Symbol	Target Symbol	Strength	Source Gene Description	Target Gene Description
12912	16476	CREB1	JUN	1	cAMP responsive element binding protein	Jun oncogene
16176	16476	IL1B	JUN	1	interleukin 1 beta	Jun oncogene
19225	22049	PTGS2	TRP53	2	prostaglandin-endoperoxide synthase 2	transformation related protein 53
19225	2205				de synthase 2	transformation related protein 53

3. Click on the One Step tab to view the gene pair interactions where there is one additional intermediary gene (Figure 14).
4. To export the gene interactions results so that you can copy gene symbols for further exploration in PubAnatomy, click on the File menu.
5. Select either the Copy Direct Path Result to Clipboard or Copy One Step Path Result to Clipboard depending on which gene list you would like to use.
6. Open a new Excel file and paste your results into the empty worksheet. You can then cut and paste the genes of interest into the PubAnatomy search box to continue refining your search results.

Figure 14: One Step Interactions



Choose Calculation Method: **MIMI Interaction**

Source Genes: **Edit**

GeneID	Symbol	Description
11441	CHRNA7	cholinergic receptor, nicotinic, alpha polypeptide 7
11540	ADORA2A	adenosine A2a receptor
11785	APBB1	amyloid beta (A4) precursor protein-binding, family B, member 1
12064	BDNF	brain derived neurotrophic factor
12307	CALB1	calbindin 1
12367	CASP3	caspase 3
12496	ENTPD2	ectonucleoside triphosphate diphosphatase 2
12912	CREB1	cAMP response element-binding protein 1

Target Genes: **Edit**

GeneID	Symbol	Description
11534	ADK	adenosine kinase
11838	ARC	activity regulated cytoskeletal-associated protein
12061	BDKRB1	bradykinin receptor, beta 1
12062	BDKRB2	bradykinin receptor, beta 2
12298	CACNB4	calcium channel, voltage-dependent, beta 4 subunit
12300	CACNG2	calcium channel, voltage-dependent, gamma subunit 2
		cystatin B
		epilepsy, progressive myoclonic epilepsy, type 2 gene allelic variant

Relations among given genes

	Source Gene	Intermediate						
<input type="checkbox"/>	11441	107986						
<input type="checkbox"/>	11540	11486	11534	ADORA2A	ADA	ADK	1.73	adenosine deaminase
<input type="checkbox"/>	11540	12053	16476	ADORA2A	BCL6	JUN	1.73	B-cell leukemia/lymphoma 6
<input type="checkbox"/>	11540	18213	16476	ADORA2A	NTRK3	JUN	1	neurotrophic tyrosine kinase, receptor, type 3
<input type="checkbox"/>	11540	18212	22059	ADORA2A	NTRK2	TRPS3	1	neurotrophic tyrosine kinase, receptor, type 2
<input type="checkbox"/>	11785	11350	16476	APBB1	ABL1	JUN	3	c-abl oncogene 1, receptor tyrosine kinase
<input type="checkbox"/>	11785	15361	16476	APBB1	HMGA1	JUN	1.73	high mobility group AT-hook 1
<input type="checkbox"/>	11785	17380	16476	APBB1	MME	JUN	1	membrane metallo endopeptidase
<input type="checkbox"/>	11785	223922	16476	APBB1	ATF7	JUN	2	activating transcription factor 7

Intermediate Gene Description

GeneID	Symbol	Description
107986	ADA	adenosine deaminase
11534	ADK	adenosine kinase
16476	BCL6	B-cell leukemia/lymphoma 6
16476	NTRK3	neurotrophic tyrosine kinase, receptor, type 3
22059	NTRK2	neurotrophic tyrosine kinase, receptor, type 2
16476	ABL1	c-abl oncogene 1, receptor tyrosine kinase
16476	HMGA1	high mobility group AT-hook 1
16476	MME	membrane metallo endopeptidase
16476	ATF7	activating transcription factor 7

One step gene interactions from the P2X gene list and the epilepsy gene list; gene pairs that have one intermediary gene that links them