

## Workshop Reactome

Please upload the solution of the workshop with their correspondent evidence

### Grupo 1:

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### Part 1. Explore your favorite pathway

1. Use keywords to search for protein/reaction/pathway for your research interest or expertise.

Ass keywords we used the name of our genes of interest, BBS6/MKKS, BBS10 y BBS12

BBS6

Go!

Search results for **BBS6**

Showing 2 results out of 2

Species

☒ Homo sapiens (2)

Types

☐ Protein (1)  
☐ Reaction (1)

Compartments

☐ cytosol (2)

Search properties

☒ Group by type

Protein

(1 results from a total of 1)

● MKKS

Identifier: R-HSA-5624086  
Compartment: cytosol

Species: Homo sapiens  
Primary external reference: UniProt: [MKKS: Q9NPJ1](#)

Reaction

(1 results from a total of 1)

➤ Formation of the BBSome

Identifier: R-HSA-5624125  
Compartment: cytosol

Species: Homo sapiens  
The BBSome is a complex of 8 conserved proteins with roles in ciliary trafficking (Nachury et al, 2007; Loktev et al, 2008; reviewed in Nachury et al, 2010; Hsiao et al, 2012). Mutations in the BBS genes... [Read more](#)

Reset filters

BBS10

Go!

Search results for **BBS10**

Showing 2 results out of 2

Species

☒ Homo sapiens (2)

Types

☐ Protein (1)  
☐ Reaction (1)

Compartments

☐ cytosol (2)

Search properties

☒ Group by type

Protein

(1 results from a total of 1)

● BBS10

Identifier: R-HSA-5624080  
Compartment: cytosol

Species: Homo sapiens  
Primary external reference: UniProt: [BBS10: Q8TAM1](#)

Reaction

(1 results from a total of 1)

➤ Formation of the BBSome

Identifier: R-HSA-5624125  
Compartment: cytosol

Species: Homo sapiens  
The BBSome is a complex of 8 conserved proteins with roles in ciliary trafficking (Nachury et al, 2007; Loktev et al, 2008; reviewed in Nachury et al, 2010; Hsiao et al, 2012). Mutations in the BBS genes... [Read more](#)

Reset filters



Participates

as a component of

BBS/CCT complex [cytosol] (Homo sapiens)

Interactors (1)

Accession	#Entities	Entities	Confidence Score	Evidence (IntAct)
UniProt:Q9BWZ6-BBS7_F1	1	BBS7 [cytosol] (R-HSA-5617632)	0.748	5

BBS12 [Protein]

BBS12 [cytosol]

Stable Identifier

Type

Species

Compartment

R-HSA-5624082

Protein [EntityWithAccessionedSequence]

Homo sapiens

cytosol

Locations in the PathwayBrowser

Organelle biogenesis and maintenance (Homo sapiens)

Interactors (3)

Accession	#Entities	Entities	Confidence Score	Evidence (IntAct)
UniProt:Q9BWZ6-BBS7_F1	1	BBS7 [cytosol] (R-HSA-5617632)	0.784	8
UniProt:Q9BAC1-FERMT2_F1	1	FERMT2 [cytosol] (R-HSA-430275)	0.534	2
UniProt:Q9BIC9-BBS2_F1	1	BBS2 [cytosol] (R-HSA-5617637)	0.499	2

Formation of the BBSome [Reaction]

Formation of the BBSome

Stable Identifier

Type

Species

Compartment

ReviewStatus

R-HSA-5624125

Reaction [binding]

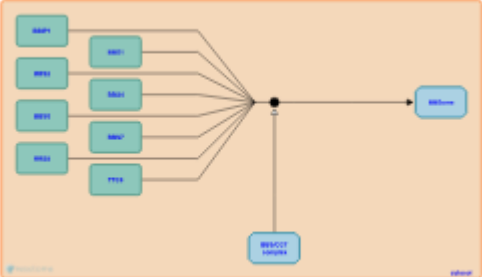
Homo sapiens

cytosol

5/5

Locations in the PathwayBrowser

Organelle biogenesis and maintenance (Homo sapiens)



Participants

Input

BBS1P1 [cytosol] (Homo sapiens)

BBS1 [cytosol] (Homo sapiens)

BBS2 [cytosol] (Homo sapiens)

BBS4 [cytosol] (Homo sapiens)

BBS5 [cytosol] (Homo sapiens)

BBS7 [cytosol] (Homo sapiens)

BBS9 [cytosol] (Homo sapiens)

Output

BBSome [cytosol] (Homo sapiens)

Participants

as an event of

BBsome-mediated cargo-targeting to cilium (Homo sapiens)

This event is regulated

Positively by

Regulator

BBS/CCT complex [cytosol] (Homo sapiens)

It has 1 reported interactor with MI confidence score of 0.748

For general information, our BBS12 protein has a stable identifier: R-HSA-5624082, it is from *Homo sapiens*, and it is in the cytosol compartment. In the Pathway Browser it can be found in Organelle biogenesis and maintenance, specifically in the Formation of the BBSome and it participates as a component of the BBS/CCT complex.

It has 3 reported interactors with MI confidence score ranging from 0.499 to 0.784.

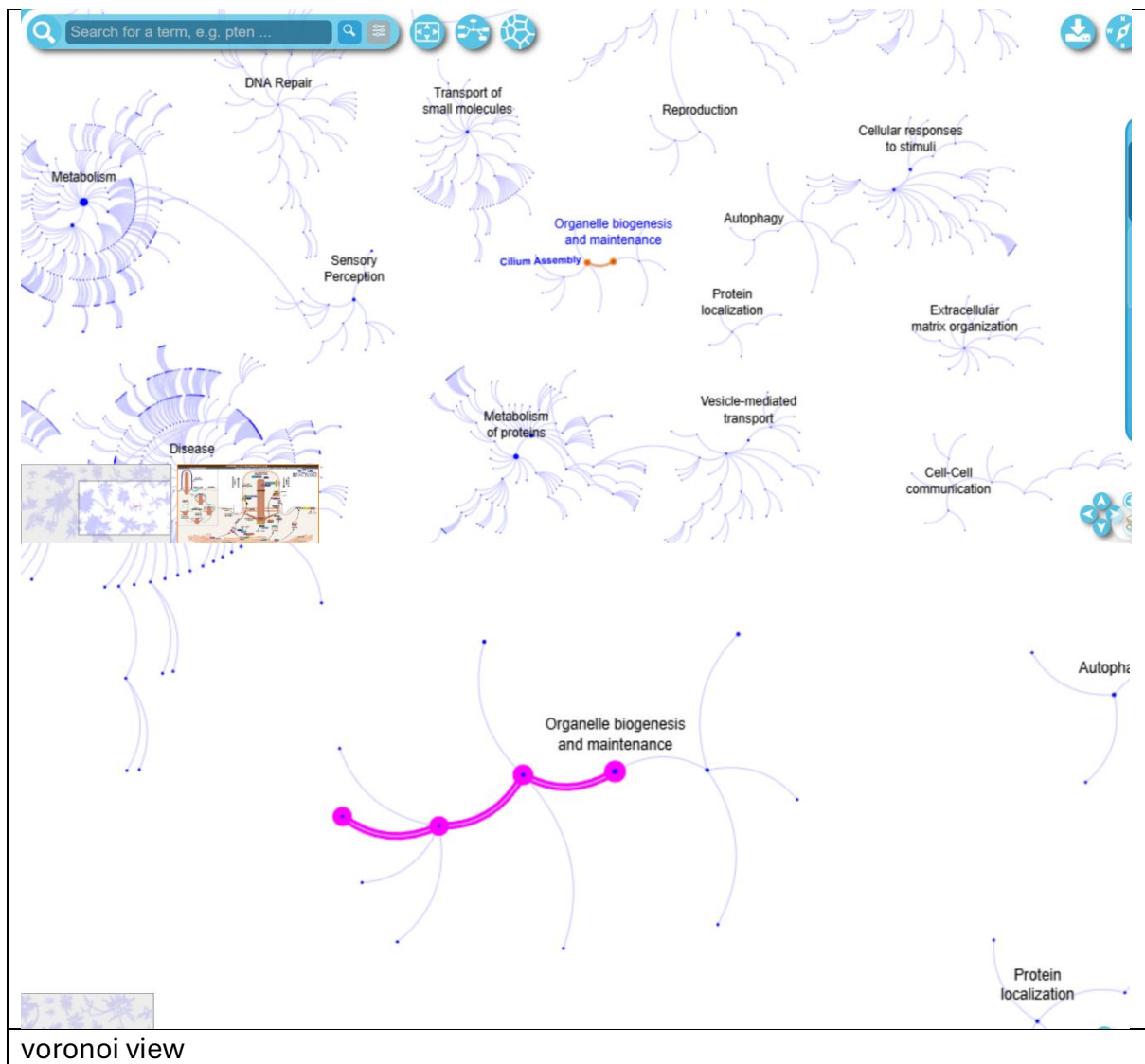
The next entry to explore is the Reaction entry of the Formation of the BBSome that is also from *Homo sapiens*, and it is also located in the cytosol compartment. Something important is that this reaction has a 5/5 review status. This reaction has the following input and output participants:

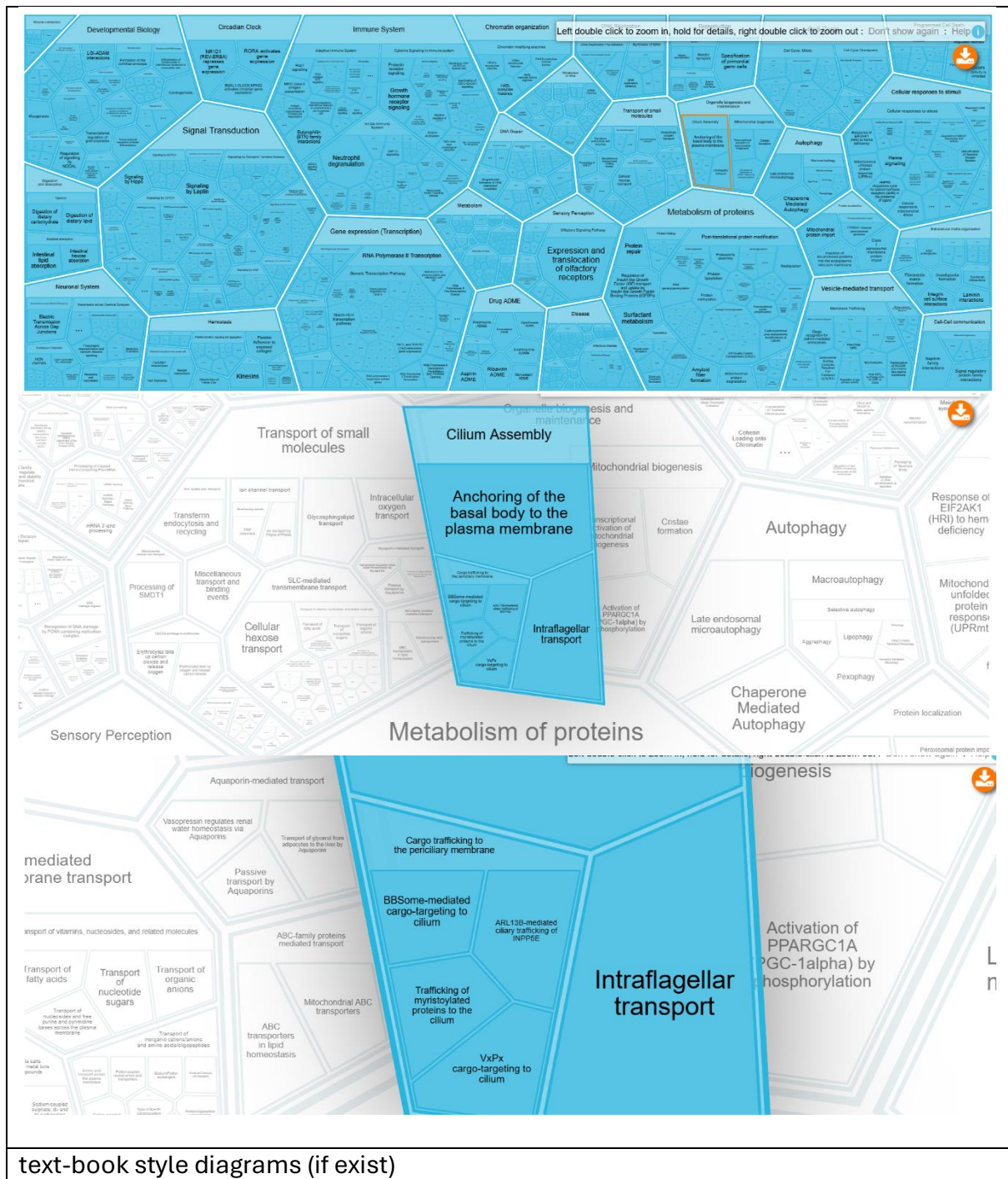
Our proteins of interest act according to this as regulatos as they are part of the BBS/CCTcomplex

3. Play with the different visuals and take a snapshot of your observations:

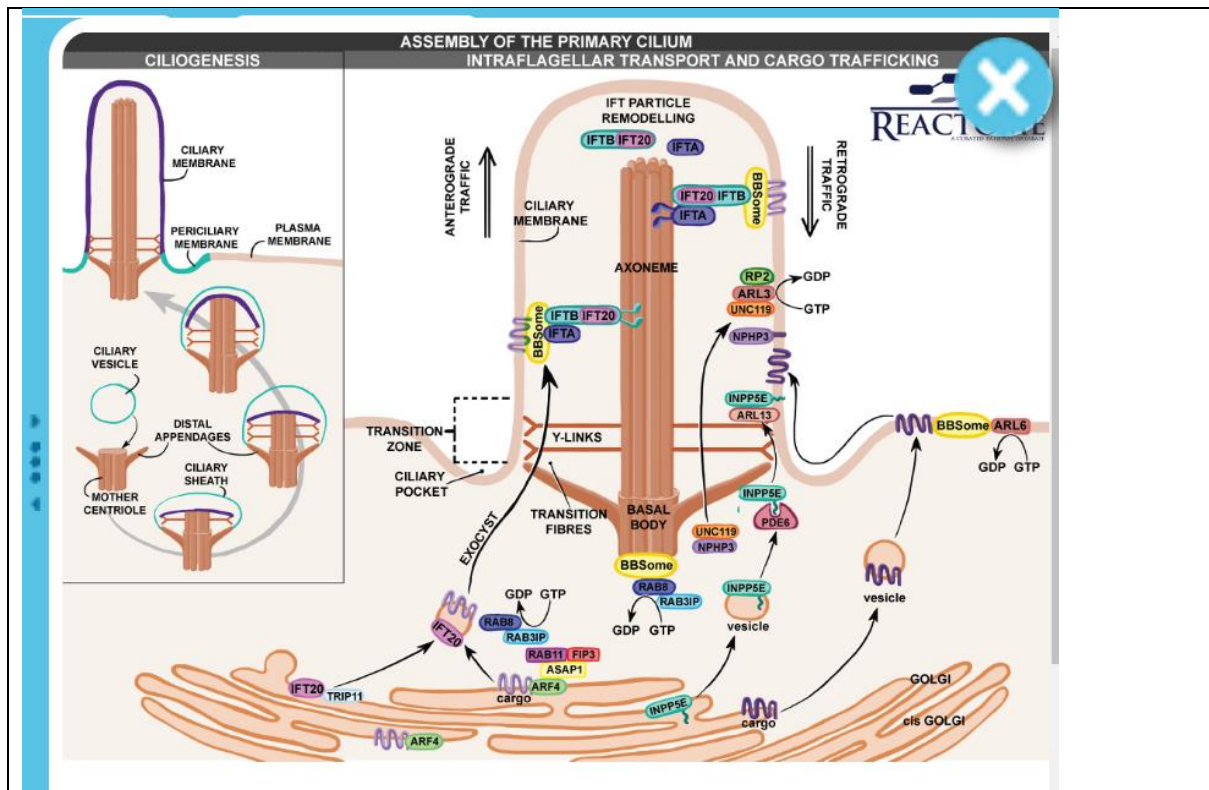
For this point we will use the entry of the Formation of the BBSome [Reaction]

Fireworks view



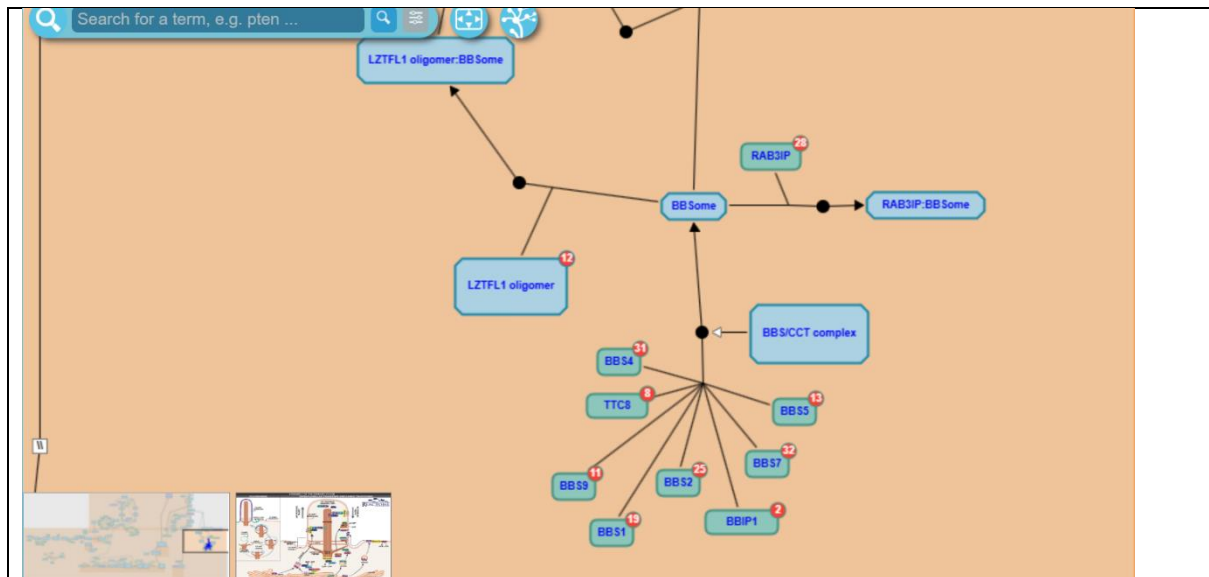






molecule-level view - (We assumed molecule view referred to SBGN)

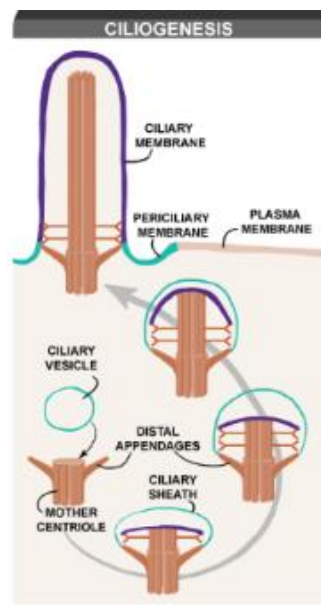




<https://www.ebi.ac.uk/training/online/courses/reactome-exploring-biological-pathways/understanding-the-pathway-browser/diagram-panel/pathway-overview/>

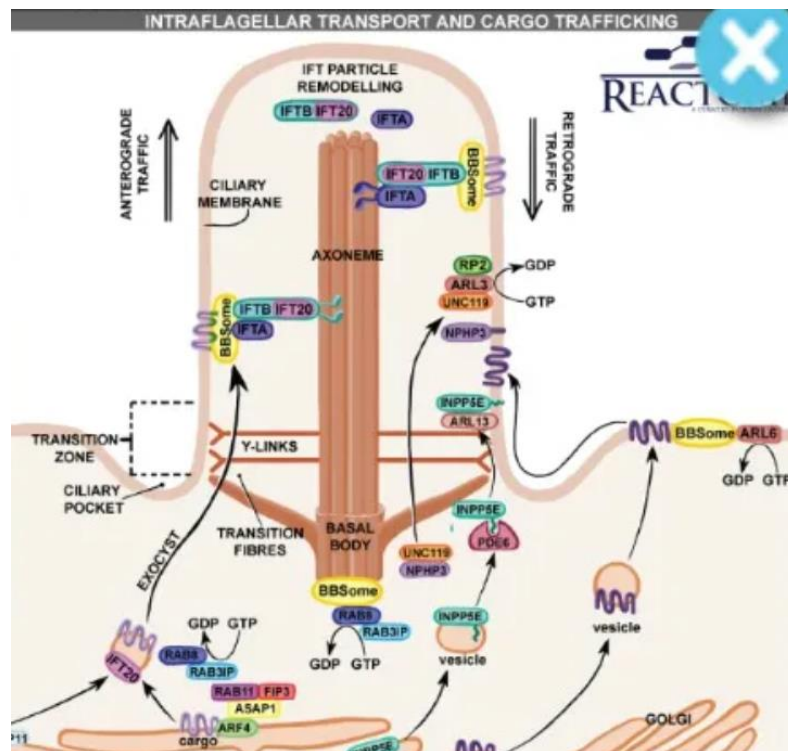
4. Can you understand the symbols and shapes in the diagram? Using snapshots, please explain your understanding of the same?

As no diagram was specified, we have decided to choose the text-book diagram type to explain it as it is the most detailed and important from the other options available:



This part shows the step-by-step formation of the primary cilium (Ciliogenesis). It starts with a ciliary membrane extending upward and shows how the structure develops from

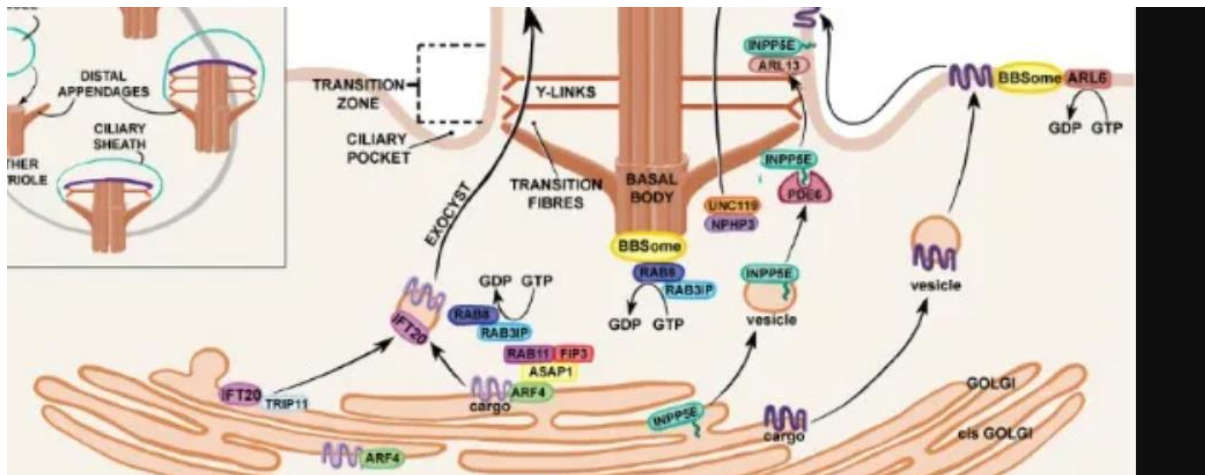
top to bottom, including the formation of different zones like the transition zone and ciliary pocket. Think of it as the construction manual for building the cellular antenna.



The diagram shows arrows indicating movement of proteins up and down the cilium. The BBSome (shown in yellow) acts like a cargo carrier, helping to transport proteins. The specific proteins of interest (the chaperonins) help in assembling these transport complexes - they're essentially the construction crew that helps build the transport machinery.

The diagram includes various molecules like GTP/GDP (energy molecules) and shows how they interact with the BBSome complex. These are like the fuel and switching mechanisms that control the transport system. The different colored shapes represent different proteins working together in this complex machinery.





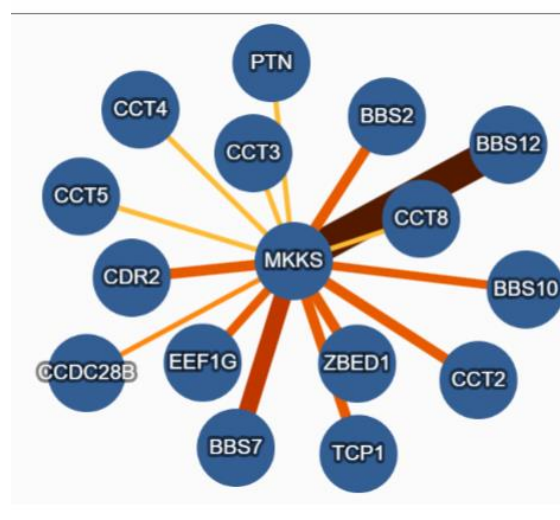
Finally, the GOLGI visualization shows how the BBSome complex assists in moving cargo along the microtubules (the orange finger-like structures at the bottom). This is essentially showing the "highway" system that proteins use to move cargo within the cilium.

This entire process is crucial for proper cilium function, and defects in any of these components (especially in the BBS proteins) can lead to ciliopathies - diseases affecting the primary cilium.

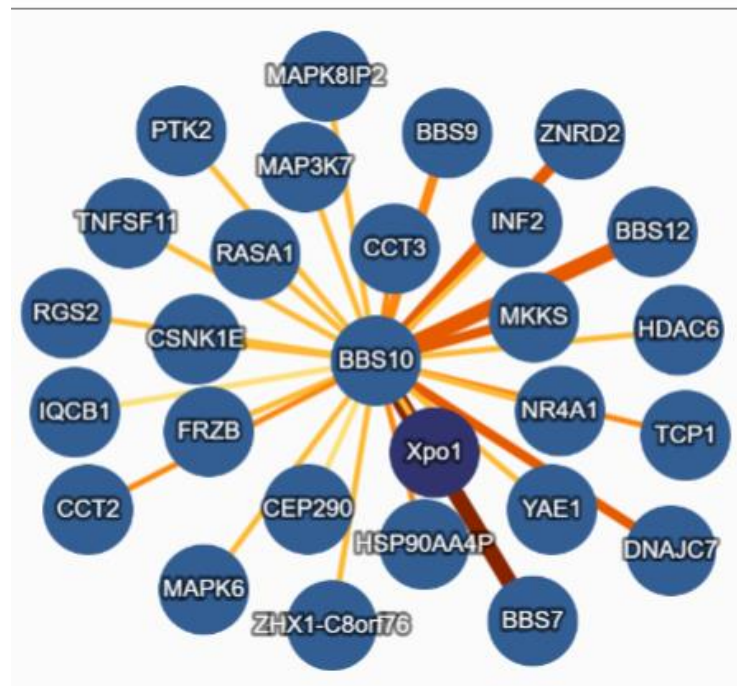
- Are there interactors in this pathway from IntAct? if yes, write the protocol to visualize the same and take a screenshot of your finding.

As we are focusing the searches for BBS6 (Uniprot: Q9NPJ1), BBS10 (Q8TAM1) & BBS12 (Q6ZW61) we have made the searches using their respective UniProt ids on and obtained the following results:

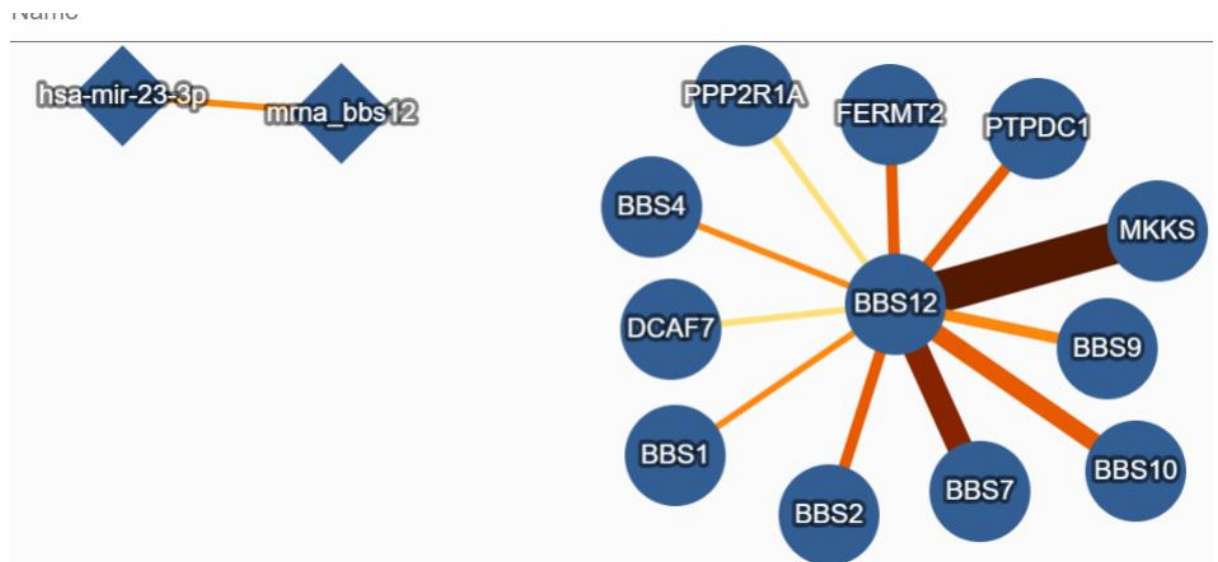
BBS6/MKKS: 15 interactors



BBS10: 29 interactors



BBS12: 11 interactors. Something interesting about the findings for BBS12 is that IntAct also identified mRNA interactions (triangle shaped figures), this indicates a regulatory relationship where the microRNA likely targets and regulates the BBS12 mRNA



- How can you find information on protein expressions in different tissues? Write the steps and take screenshot of each step taken?

Steps taken:

- a. Reactome search with common names (MKKS, BBS10, BBS12)

Find Reactions, Proteins and Pathways

[Go!](#)

- b. Select corresponding protein and click on its name

**Protein** (1 results from a total of 1)

● **MKKS**

Identifier: R-HSA-5624086

Compartment: cytosol

Species: Homo sapiens

Primary external reference: UniProt: [MKKS: Q9NPJ1](#)

- c. Open cross reference Human Protein Atlas [HPA] link by clicking on the blue text next to it

Cross References	
RefSeq	<a href="#">NP_061336.1, NP_740754.1</a>
OpenTargets	<a href="#">ENSG00000125863</a>
HPA	<a href="#">ENSG00000125863-MKKS</a>
GeneCards	<a href="#">Q9NPJ1</a>
Ensembl	<a href="#">ENST00000651692, ENSP00000382008, ENST00000399054, ENSG00000125863, ENST00000347364, ENSP00000246062, ENSP00000498849</a>
PRO	<a href="#">Q9NPJ1</a>
Pharos - Targets	<a href="#">Q9NPJ1</a>
Orphanet	<a href="#">16403</a>

- d. Open “Tissue” tab for protein in HPA page

THE HUMAN PROTEIN ATLAS

MKKS

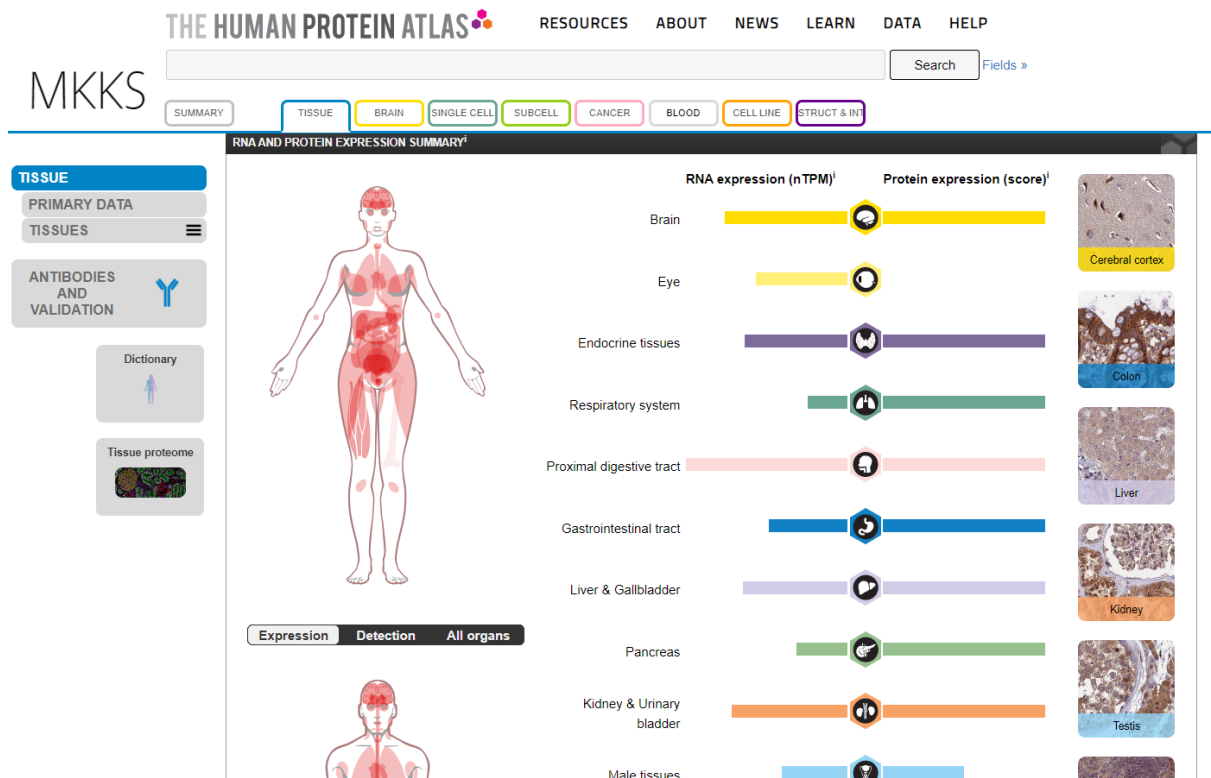
SUMMARY

TISSUE

BRAIN

SINGLE CELL

And finally, all the information about the protein expression on the tissues can be found here.



7. Are there mathematical models that describe your favourite model and how can you get details? Write the steps to find the model details and id?

At a first glance this question might be considered as controversial, as it does not defines or characterizes the meaning of the “math model” this question refers to. Nevertheless, we will consider a “math model” as a mathematical model that includes any of the following:

- Differential equations
- Rate constants
- Concentration values
- Kinetic parameters
- Numerical simulations
- Mathematical formulas describing the dynamics

Given this new definition, we find out that Reactome provides pathway diagrams and interaction networks, but does not provide mathematical models, because they provide a qualitative description of a biological pathway/reaction - it shows WHAT happens and WHERE it happens, but not HOW MUCH or HOW FAST (which would require mathematical equations).

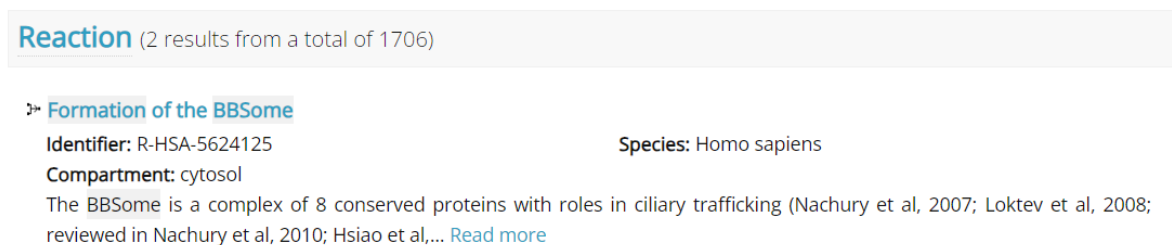
Now, once all these considerations of a math model are taking into account, if one considers models like the ones Reactome provides as diagrams one could say these are the steps to obtain them:

- a. Search for the term, in this case “Formation of the BBSome”



The screenshot shows the Reactome website. The search bar at the top right contains the text "Formation of the BBSome". Below the search bar, the text "Search results for Formation of the BBSome" is displayed. Underneath, it says "Showing 18 results out of 2333".

- b. Once here select the respective reaction and the id is easily seen as “identifier”

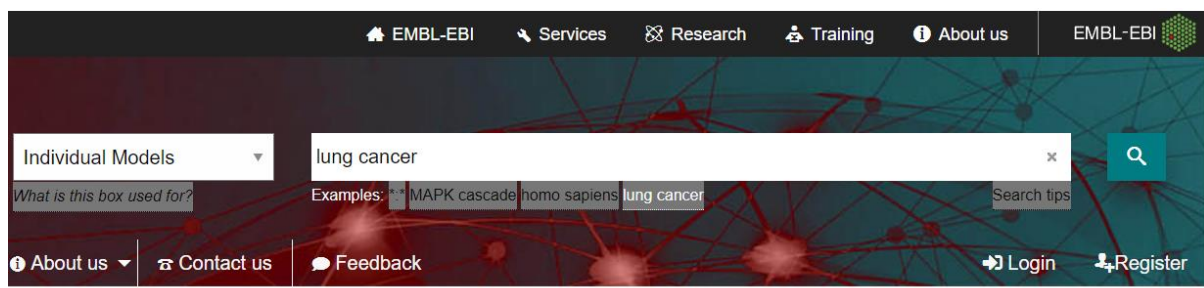


The screenshot shows the details of a reaction in Reactome. The title is "Formation of the BBSome". Below the title, the identifier "R-HSA-5624125" is shown. To the right, the species "Homo sapiens" is listed. Below the identifier, the compartment "cytosol" is shown. A description follows: "The BBSome is a complex of 8 conserved proteins with roles in ciliary trafficking (Nachury et al, 2007; Loktev et al, 2008; reviewed in Nachury et al, 2010; Hsiao et al,... [Read more](#)".

On the other hand, if one takes into the consideration of math model as something with the attributes described earlier and therefore not considering Reactome models as mathematical models, then one must consider a different approach to find these mathematical models.

In fact, EBI provides a tool called [BioModels](#) on which one can search for scientific mathematical models provided. Nevertheless, for our pathway of “Formation of BBSome” or other information and models about BBS disease and its genes were not found, so as example we will be showing the steps to access a lung cancer model:

- a. Open [BioModels](#) website and search for “lung cancer”



The screenshot shows the BioModels website. The top navigation bar includes links for "EMBL-EBI", "Services", "Research", "Training", and "About us". Below the navigation bar, there is a search bar with the text "lung cancer". To the left of the search bar, there is a dropdown menu labeled "Individual Models". Below the search bar, there are examples of search queries: "MAPK cascade", "homo sapiens", and "lung cancer". To the right of the search bar, there is a "Search tips" link. At the bottom of the page, there are links for "About us", "Contact us", "Feedback", "Login", and "Register".

- b. Once here a list of different models will be shown, use respective filters to find the one we need to narrow down the list to a smaller one.



Home Browse Submit Curation Help About us Contact us Feedback

**Filter results**

Sort by: Relevance

Page size: [10] [20] [50] [75] [100]

Curation status

☐ Non-curated (19)

☐ Manually curated (13)

Model format

☐ SBML (31)

☐ Open Neural Network Exchange (1)

Modelling Approach

Find your Modelling Approach

☐ Ordinary differential equation model (4)

☐ Constraint-based model (4)

☐ Logical model (2)

☐ Petri net (2)

Search terms: lung cancer Reset

Found: 32 models

Select all | Download

[Bianconi2012 - EGFR and IGF1R pathway in lung cancer](#)

ID: BIOMD0000000427 | Submitter: Fortunato Bianconi | Format: SBML | Uploaded date: 23/09/2012 | Last modified date: 21/08/2024 | Published in: 2012

[Liu2023 - Predicting the efficacy of immune checkpoint inhibitors monotherapy in advanced non-small cell lung cancer: a machine learning method based on multidimensional data](#)

ID: BIOMD0000001074 | Submitter: Haoxue Wang | Format: Open Neural Network Exchange | Uploaded date: 12/07/2023 | Last modified date: 12/07/2023 | Published in: 2023

[Nikolaev2019 - Immunobiochemical reconstruction of influenza lung infection-melanoma skin cancer interactions](#)

ID: BIOMD0000000865 | Submitter: Johannes Meyer | Format: SBML | Uploaded date: 18/11/2019 | Last modified date: 22/08/2024 | Published in: 2019

[Tham2008 - PDmodel, Tumour shrinkage by gemcitabine and carboplatin](#)

ID: BIOMD0000000234 | Submitter: Nick Holford | Format: SBML | Uploaded date: 15/11/2009 | Last modified date: 21/08/2024 | Published in: 2008

[Ito2019 - gefitinib resistance of lung adenocarcinoma caused by MET amplification](#)

ID: BIOMD0000000827 | Submitter: Szeyi Ng | Format: SBML | Uploaded date: 30/09/2019 | Last modified date: 22/08/2024 | Published in: 2019

c. For our example of usage, we will open the first one about EGFR

### Bianconi2012 - EGFR and IGF1R pathway in lung cancer

Choose Reactome Pathway

Overview Files History Components Curation

**Model Identifier**

**Short description**

BIOMD0000000427

Bianconi2012 - EGFR and IGF1R pathway in lung cancer

EGFR and IGF1R pathways play a key role in various human cancers and are crucial for tumour transformation and survival of malignant cells. High EGFR and IGF1R expression and activity has been associated with multiple aspects of cancer progression including tumourigenesis, metastasis, resistance to chemotherapeutics and other molecularly targeted drugs. Here, the biological relationship between the proteins involved in EGFR and IGF1R pathways and the downstream MAPK and PIK3 networks has been modelled to study the time behaviour of the overall system, and the functional interdependencies among the receptors, the proteins and kinases involved.

This model is described in the article:

Computational model of EGFR and IGF1R pathways in lung cancer: a Systems Biology approach for Translational Oncology.

Bianconi F, Baldelli E, Ludovini V, Crinò L, Flacco A, Valigi P.

Biotechnol Adv. 2012 Jan-Feb;30(1):142-53.

**Metadata information**

is (2 statements)

BioModels Database BIOMD0000000427

BioModels Database MODEL1209230000

isDescribedBy (1 statement)

PubMed 21620944

hasTaxon (1 statement)

Taxonomy Homo sapiens

isPartOf (3 statements)

Gene Ontology epidermal growth factor receptor signaling pathway

[More about this page](#)

d. Here we can find information about the model metadata, components, curation, files and history. In this case the model ID would be: BIOMD0000000427.

e. Why would this model be considered as a math model considering the definition given for it initially? Well, if one checks the files tab and opens the first XML file as preview it will show the model itself and we can see the application of math equations, kinetic laws, usage of MATLAB and many other:

### Bianconi2012 - EGFR and IGF1R pathway in lung cancer

Choose Reactome Pathway

Overview Files History Components Curation

Name	Description	Size	Actions
<b>Model files</b>			
BIOMD0000000427_url.xml	SBML L2V4 representation of Bianconi2012 - EGFR and IGF1R pathway in lung cancer	54.98 KB	<a href="#">Preview</a>   <a href="#">Download</a>
<b>Additional files</b>			

```

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565     <power/>
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578 </reaction>
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581         <speciesReference metaid="_150264" species="EGFR_active"/>
582     </listOfReactants>
583     <listOfModifiers>
584         <modifierSpeciesReference metaid="_457704" species="EGFR_active"/>
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589                 <times/>
590                 <ci> gamma_EGFR </ci>
591                 <ci> EGFR_active </ci>
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594     </kineticLaw>
595 </reaction>
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597     <listOfReactants>

```

## Part 2. Analyze gene List

Use your favorite gene/protein list data

1. You can also use the example file (UniProt accession list) available in the Reactome website. Take a snapshot of your observation and your analysis of the same.

For this analysis we used the Uniprot accession related to BBS6, BBS10 y BBS12.

The screenshot shows the 'Your data' tab of the Reactome website. It has three sub-tabs: 'Your data' (selected), 'Options', and 'Analysis'. Below the tabs, there is a step instruction: 'Step 1: Select a file from your computer or paste your own data and click on the corresponding "Continue" button.' Below this, there is a text input field for 'Select data file for analysis:' with a placeholder 'Examinar...' and a 'Continue' button. To the right of the input field, it says 'No se ha seleccionado ningún archivo.' Below the input field, there is a section titled 'Paste your data to analyse or try example data sets:' with a text area containing the UniProt accession numbers 'Q9NPJ1', 'Q8TAM1', and 'Q5ZW61'. To the right of the text area, there is a list of 'Some examples:' with buttons for 'UniProt accession list', 'Gene name list', 'Gene NCBI / Entrez list', 'Small molecules (ChEBI)', 'Small molecules (KEGG)', 'Microarray data', 'Metabolomics data', 'Cancer Gene Census (COSMIC)', and 'Tissue Specific Expression (HPA)'.

These three proteins are related to organelle biogenesis and maintenance specially the cilium. BBS6, BBS10, and BBS12 are part of the BBsome complex, which is essential for cilia function, specifically in transporting proteins to and within the primary cilium. These proteins help in assembling and maintaining the BBsome, a complex needed for intraflagellar transport (IFT), which moves cargo along the ciliary axoneme. This transport system ensures that signaling

molecules reach the cilium's tip, where sensory functions are carried out, especially for pathways like Hedgehog and WNT.

Mutations in BBS genes, including BBS6, BBS10, and BBS12, disrupt BBSome formation and, consequently, the IFT process. This leads to ciliopathies such as Bardet-Biedl Syndrome, characterized by vision loss, kidney problems, and other symptoms due to defective ciliary signaling and transport. Thus, these BBS proteins are crucial for cilia structure, function, and cellular signaling integrity.



- Investigate if this list contains significantly more components of certain pathways in Reactome. List the pathway names.

These proteins are related to four pathways: BBSome-mediated cargo-targeting to cilium, Cargo trafficking to the periciliary membrane, cilium assembly and Organelle biogenesis and maintenance.

Overrepresentation analysis results for UNIPROT Data submitted with no name

Pathway name	Entities found	Entities Total	Entities ratio	Entities pValue	Entities FDR	Reactions found	Reactions total	Reactions ratio	Species name
BBSome-mediated cargo-targeting to cilium	3	23	0.002	7.33E-9	2.03E-8	1	5	0	Homo sapiens
Cargo trafficking to the periciliary membrane	3	51	0.004	7.99E-8	1.6E-7	1	27	0.002	Homo sapiens
Cilium Assembly	3	201	0.017	4.89E-6	4.89E-6	1	50	0.003	Homo sapiens
Organelle biogenesis and maintenance	3	299	0.025	1.61E-5	1.61E-5	1	86	0.006	Homo sapiens

- Can you interpret the biological meaning of the over-represented pathways? Write few sentences of your observation with biological relevance?

The BBSome complex is crucial for ciliary function and maintenance, as it regulates the transport of cargo proteins to and within the cilia. In the pathway diagrams, we see interactions involving ARL6 (ARL GTPase) and its association

with the BBSome complex in facilitating the movement of ciliary cargo. The involvement of BBS proteins in these processes aligns with the clinical manifestations of Bardet-Biedl Syndrome, which includes defects in ciliary structure and function, leading to symptoms such as retinal degeneration, kidney abnormalities, and polydactyly. This pathway over-representation suggests that disruptions or mutations in BBS6, BBS10, and BBS12 may significantly impact ciliary transport mechanisms, possibly explaining the phenotypic variability observed in Bardet-Biedl Syndrome patients.

The observed pathways are biologically relevant as they emphasize the dependency of ciliary assembly and function on the BBSome complex, underlining the importance of these BBS proteins in cellular processes associated with ciliopathies.

