Semantic integration of Biological Data with Allonto

Application to the analysis of gene duplication

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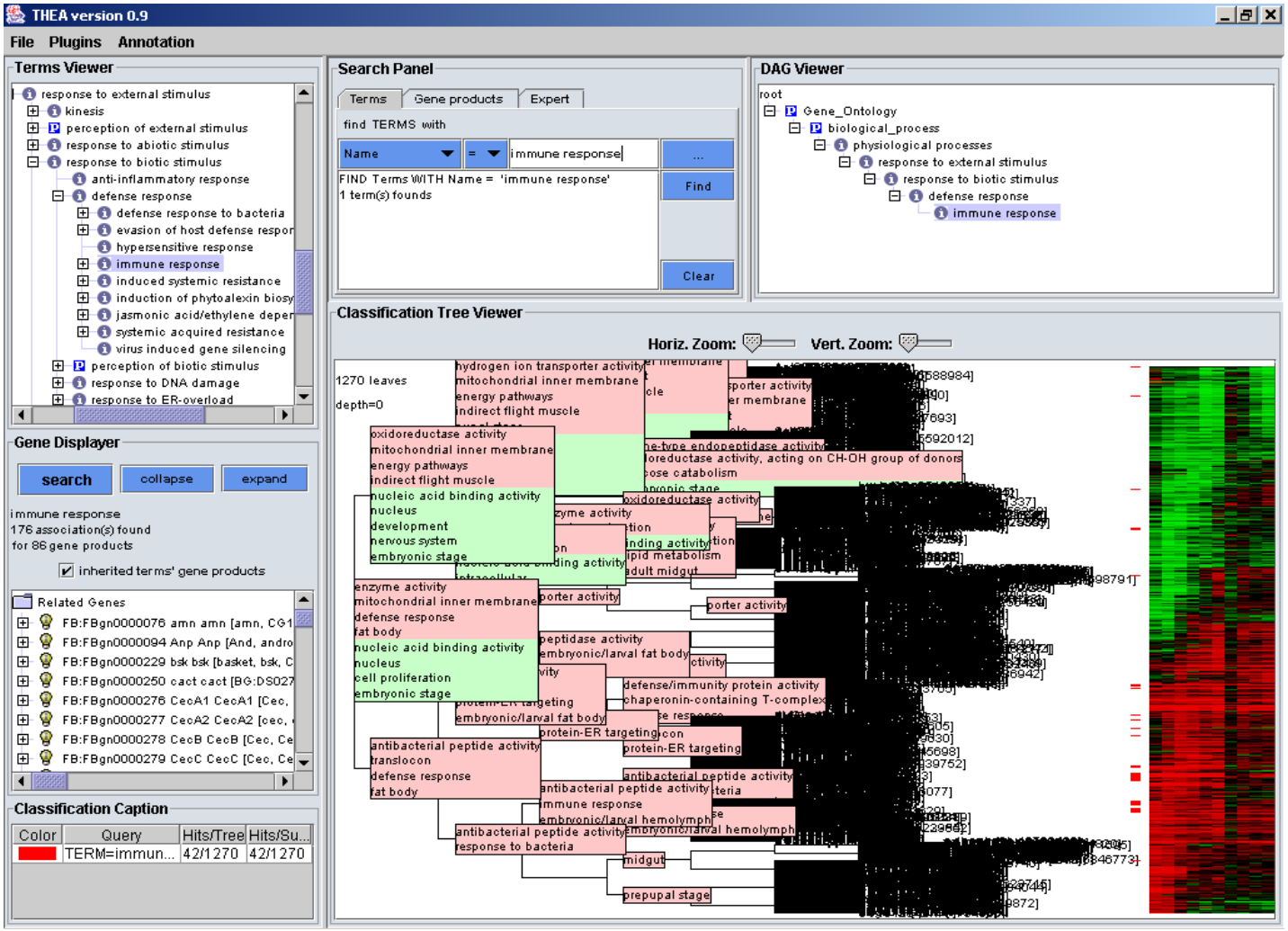
Thea (reminder)



Analysis of a dataset consisting of 1270 regulated genes (De Gregorio, E., Spellman, P.T., Rubin, G.M. and Lemaitre, B. (2001) Genome-wide analysis of the Drosophila immune response by using oligonucleotide microarrays. Proc Natl Acad Sci U S A, 98, 12590-12595).

Limitations

- Information integration is difficult
  - Many databases (several hundred) with heterogeneous schemas
  - Traceability problems
    - Identifiers may change (ex.: Unigene IDs)
  - Semantic problems
    - One name ➔ different concepts
    - One concept ➔ different names
- Goal directed search

One possible solution

- Representation of information with a semantic network using ontologies
- Use of OWL (Ontology Web Language) as the exchange format
  - Several databases export information in this format (UniProt, Reactome, …)
- Information integration consists in the merging of several graphs

Partial view of a graph

Partial view of information extracted from SwissProt, Gene Ontology, IntAct and Reactome

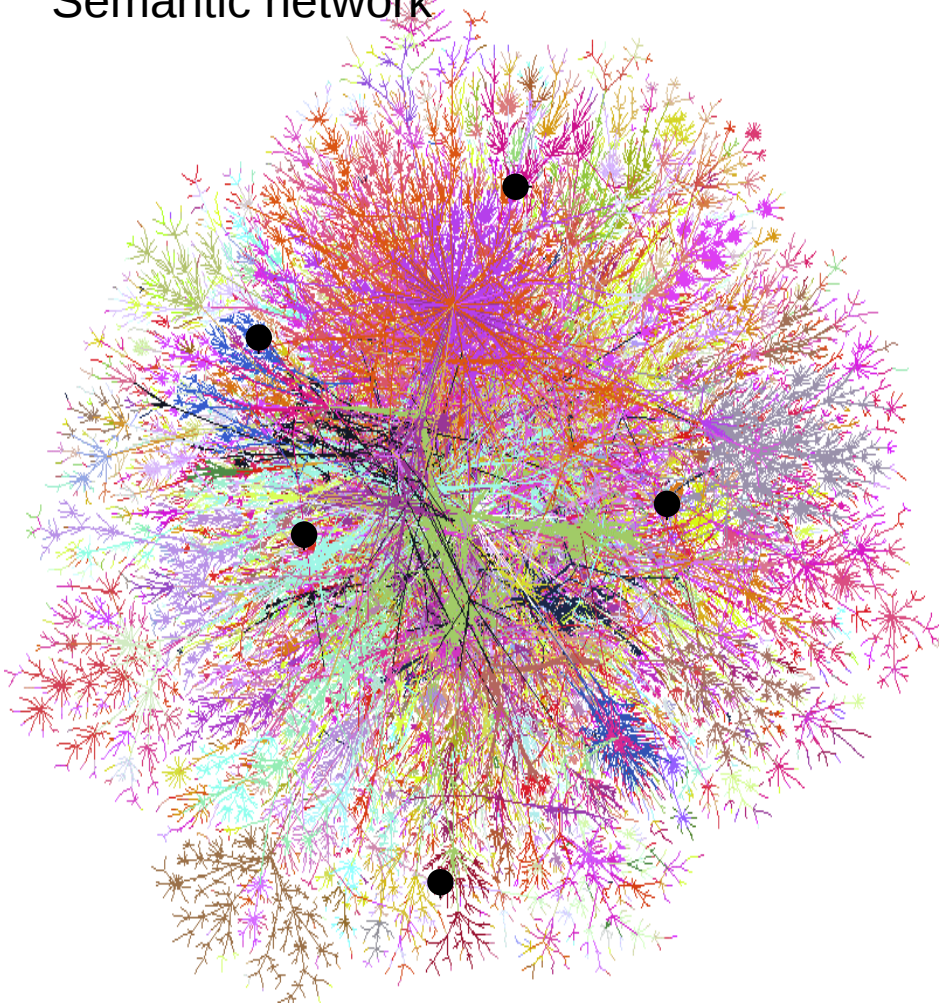
Example of searches

- Goal directed searches
  - Graph queries
    - Ex: what are the proteins annotated « cell proliferation » which interact with CDC6
- Non directed searches
  - Search of a shortest path
    - Ex: what are the paths connecting CDC6 to K17
  - Search of a subgraph
    - Ex: what is the minimal graph connecting CDC6, ERBB2, BRCA1 and K17 (allows to retrieve the shared properties)

Partial view of information extracted from SwissProt, Gene Ontology, IntAct and Reactome

Search for pertinent information characterizing a set of nodes

Semantic network



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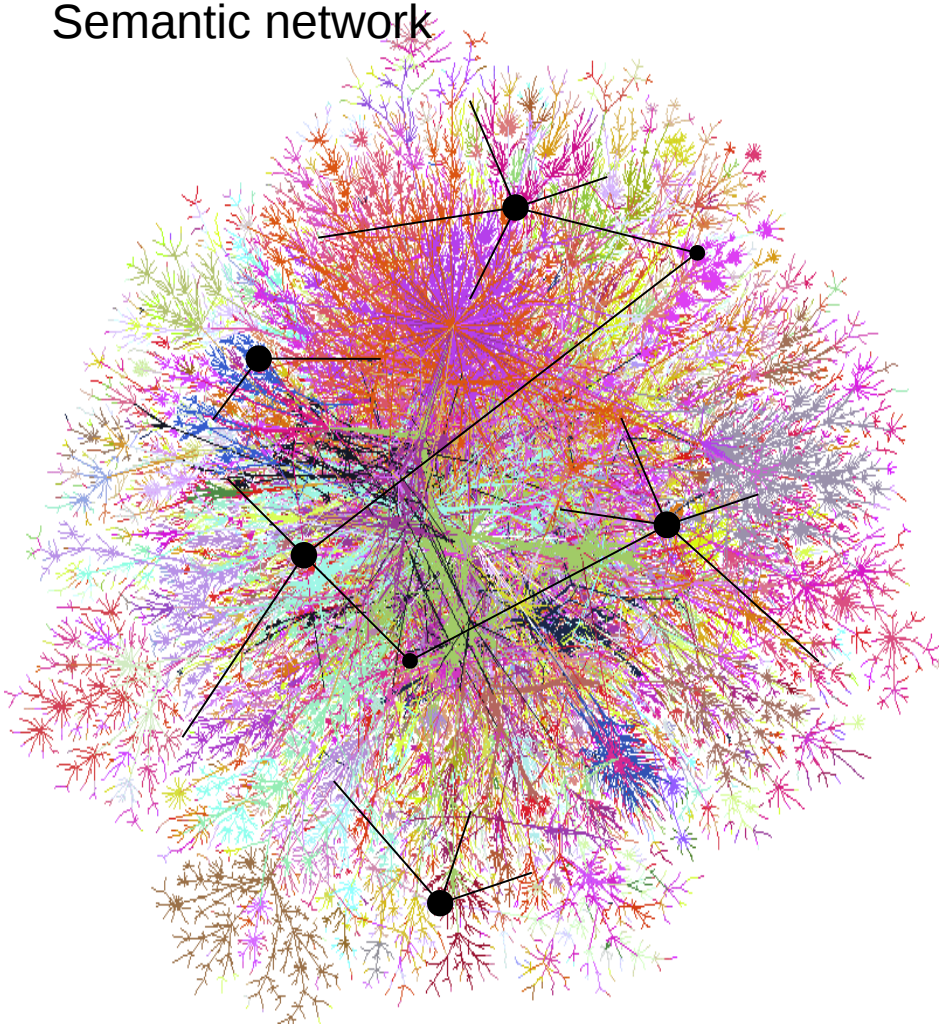
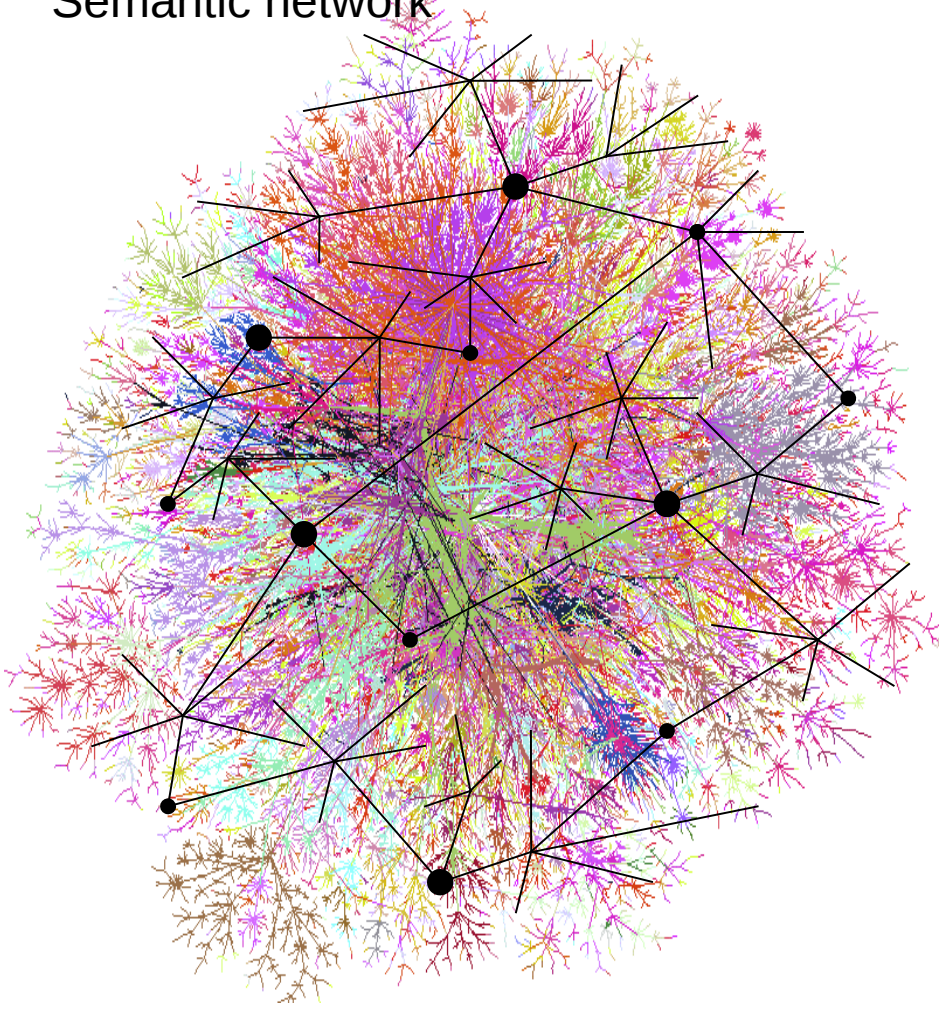


- Extract associated information

Search for pertinent information characterizing a set of nodes

Semantic network



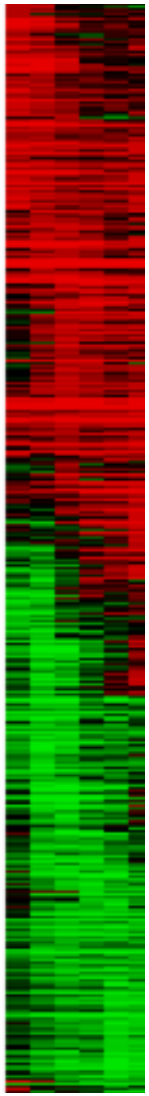
- Extract associated information
- Select pertinent information with an evaluation function
  - Common resources
  - Statistically significant
  - Other

Application of Allonto to Detect DNA copy-number changes

- As copy number and expression level are correlated, it should be possible to detect amplifications (and may be deletions) by using expression levels alone.
- The idea:
  - if an increase of expression level of a set of transcripts is due to an amplification, then, these transcripts should be co-localized.
- If such a method is effective, we will be able to extract very valuable information about cancer related genes by processing the large amount of expression level measurement stored in public databases.

The algorithm

Transcripts sorted by fold-change (cancer vs. normal)



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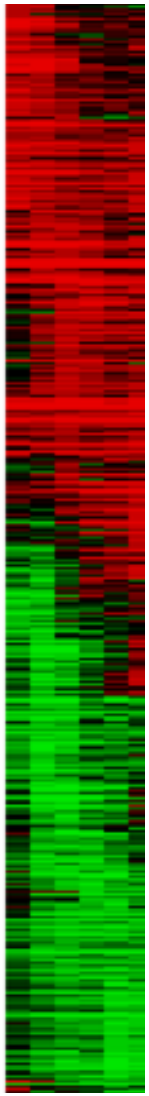

- Choose a set of transcripts that are over-expressed and co-expressed

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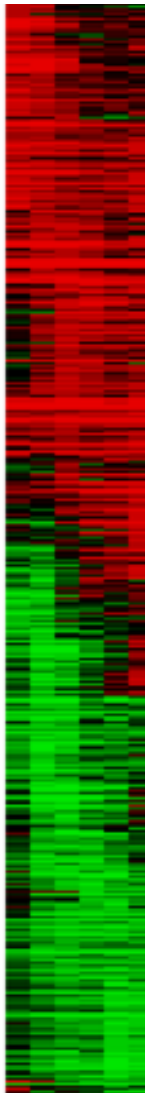

- Choose a set of transcripts that are over-expressed and co-expressed
- Select the corresponding resources on the semantic network

The algorithm

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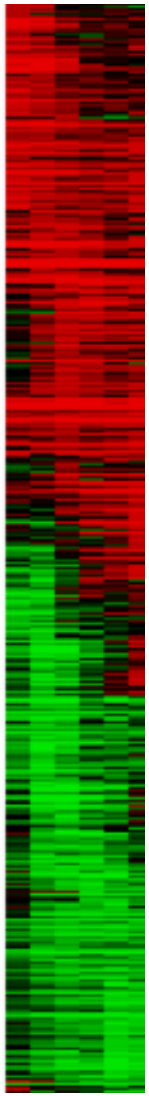

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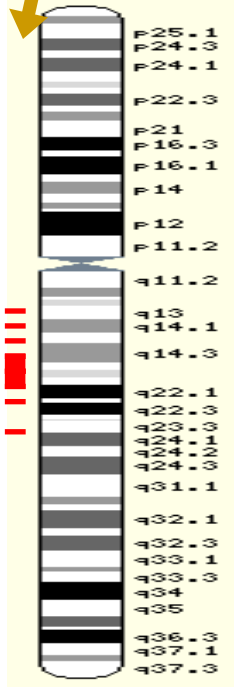
- Search in the network for the localization of the corresponding genes on chromosomes



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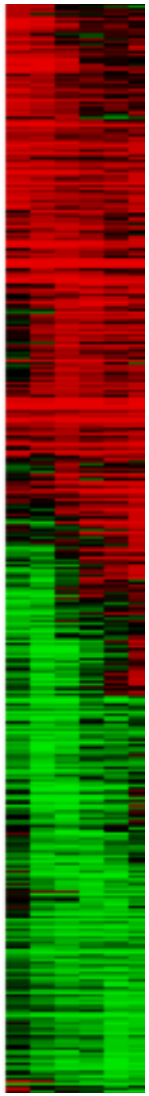
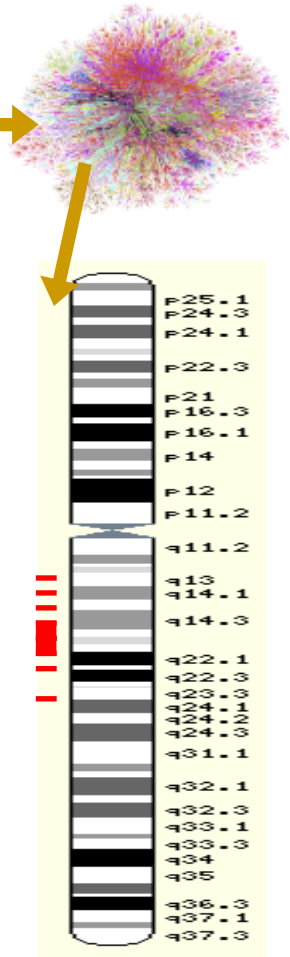


- Choose a set of transcripts that are over-expressed and co-expressed
- Select the corresponding resources on the semantic network
- Search in the network for the localization of the corresponding genes on chromosomes
- Evaluate the proximity of these genes by computing:
  - **p-value** = probability for these genes to be grouped in a portion of a chromosome by chance
  - **IF p-value** < given **cutoff**

    THEN select this group of genes (over-expression might be due to an amplification)



Dataset and parameters

- Use of a semantic network integrating data from Ensembl, SwissProt, IntAct, Pubmed and Reactome
- Analysis of the dataset from:
  - Pollack JR, Sorlie T, Perou CM, Rees CA, Jeffrey SS, Lonning PE, Tibshirani R, Botstein D, Borresen-Dale AL, Brown PO. Microarray analysis reveals a major direct role of DNA copy number alteration in the transcriptional program of human breast tumors. Proc Natl Acad Sci U.S.A. 2002 Oct 1;99(20):12963-8
  - Experiments done for the 4 cell lines and 37 tumors
  - 6096 Unigenes IDs ➔ 2898 ENSEMBL IDs
- parameters
  - P-value < 10^{-5}
  - At least 3 co-localized genes
  - Fold-change (cancer vs. normal) > 1.5

Amplifications and deletions in BT474 cell line

High-level alterations detected by array CGH					
Cell line	Locus	Size (kb)		Locus	Size (kb)
BT474	**Amplifications**			**Amplifications**	
	1q21.2-q25.1			15q11.2 -q12	5030
Peaks:	*1q21.2-q21.3*	*366*	*Peaks:*	*15q11.2*	*949*
	1q22-q23.1	*510*		*15q11.2*	*624*
	1q24.2	*540*		17q12-21.2	4090
	1q31.3	***1661***		17q21.32-23.2	13800
	1q32.1	**936**	*Peaks:*	*17q21.32-q21.33*	*2500*
	1q42.12-q42.13	*500*		*17q22-23.2*	*2180*
	1q43	449		*17q23.2*	*1170*
	1q44-q43	865		17q24.1-24.3	5300
	1q44	1720	*Peak:*	*17q24.1*	*482*
	4p16.1-15.33	1210		19p13.2-13.12	6310
	4q21.1	**2700**		20p12.1	*800*
	9p13.3	**2060**		20q11.22	1300
	9q33.1-34.13	**12600**		20q13.11-13.32	14800
	11q13.1-13.5	19800		20q13.33	305
Peaks:	*11q13.1*	*704*		20q13.33-tel	1380
	11q13.4	*1030*		**Deletions**	
	11q22.1-22.2	**3560**		5q14.1-14.3	5390
	14q11.2-q21.1	**21230**		**6q24.1**	**3200**
	14q31.3-32.12	**3080**		**20q11.22**	**670**
				20p11.23-13.11	**7140**

Shadeo A, Lam WL. Comprehensive copy number profiles of breast cancer cell model genomes. Breast Cancer Res. 2006 Jan 3;8(1):R9

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	14q11.2-q21.1	**21230**	**6q2**		
	14q31.3-32.12	**3080**	**20q11.22**		**670**
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3q25.2-3q26.2 (16030 kb)

17q12-17q21.2 (6.650 kb)

17q23.2 (1311 kb)

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20q11.22-20q13.13 (13980 kb)

20q13.2-20q13.31 (9002 kb)

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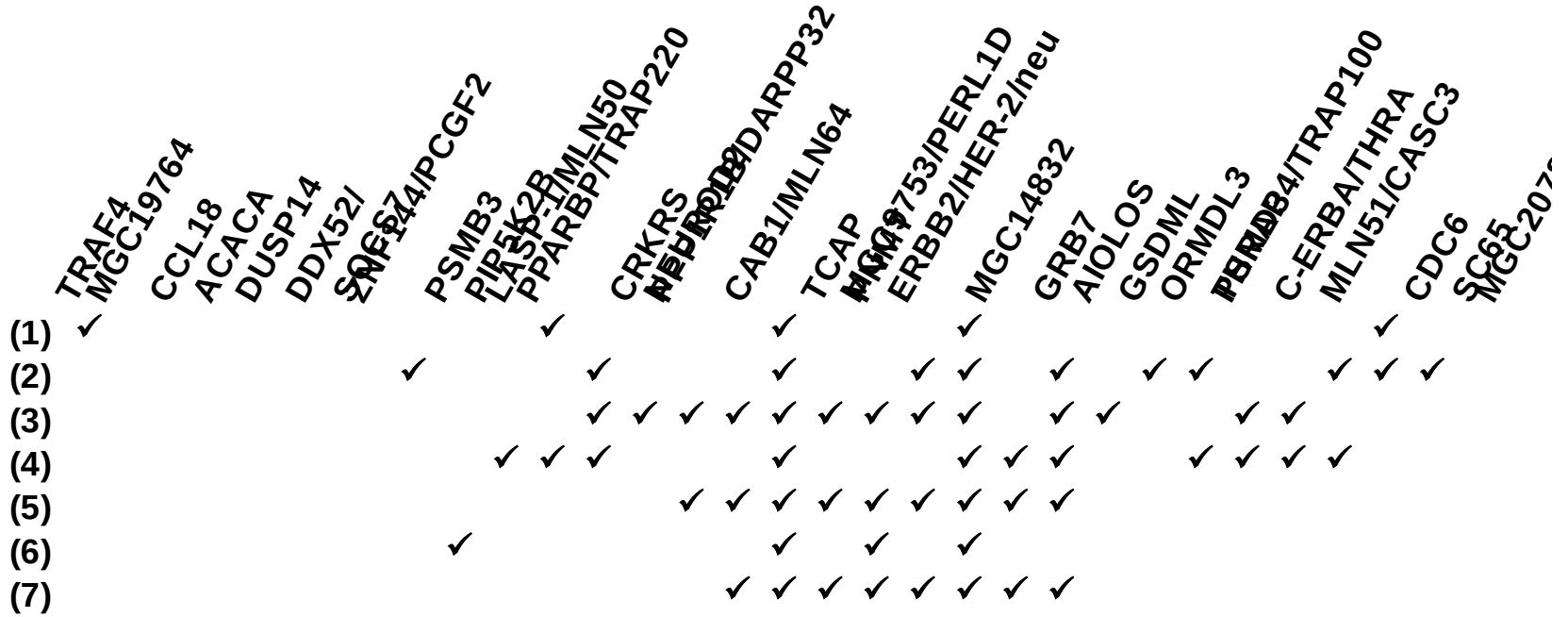
Detail of the amplicon 17q11.2-21.2



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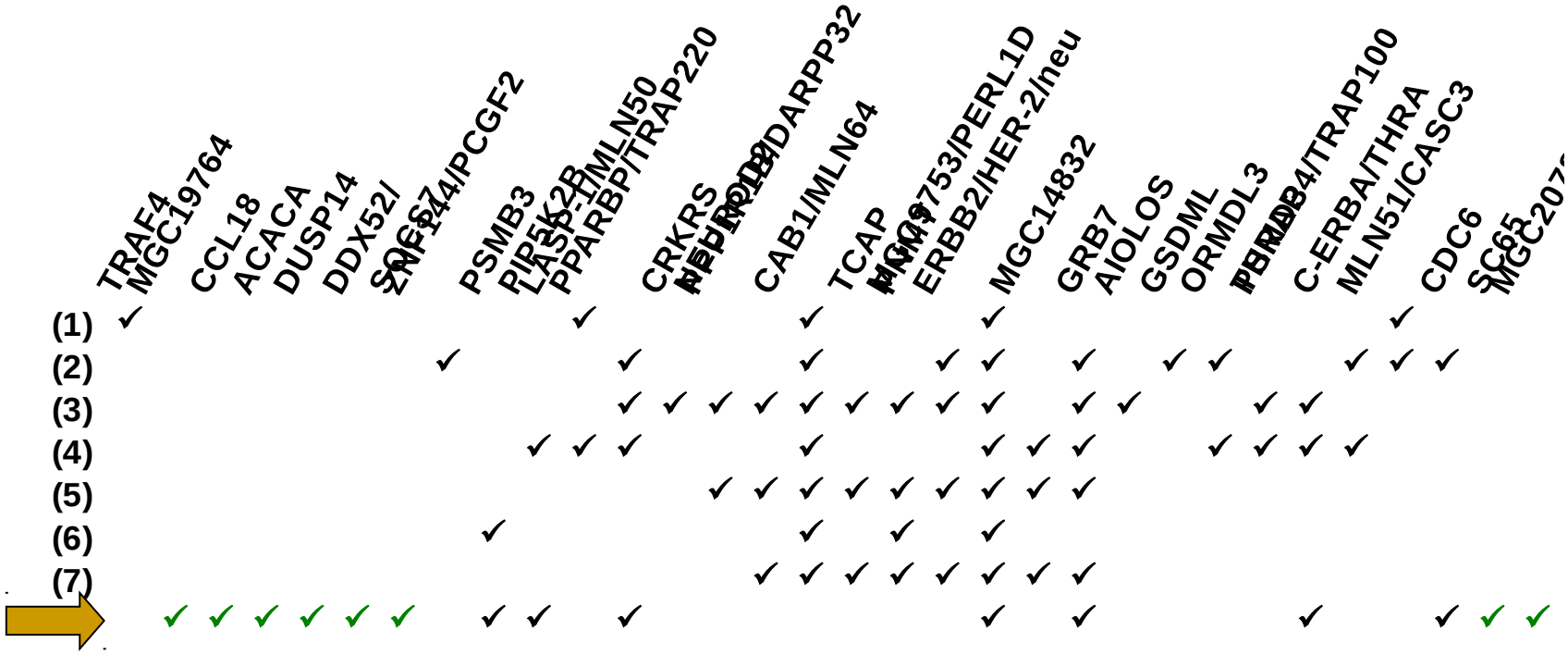

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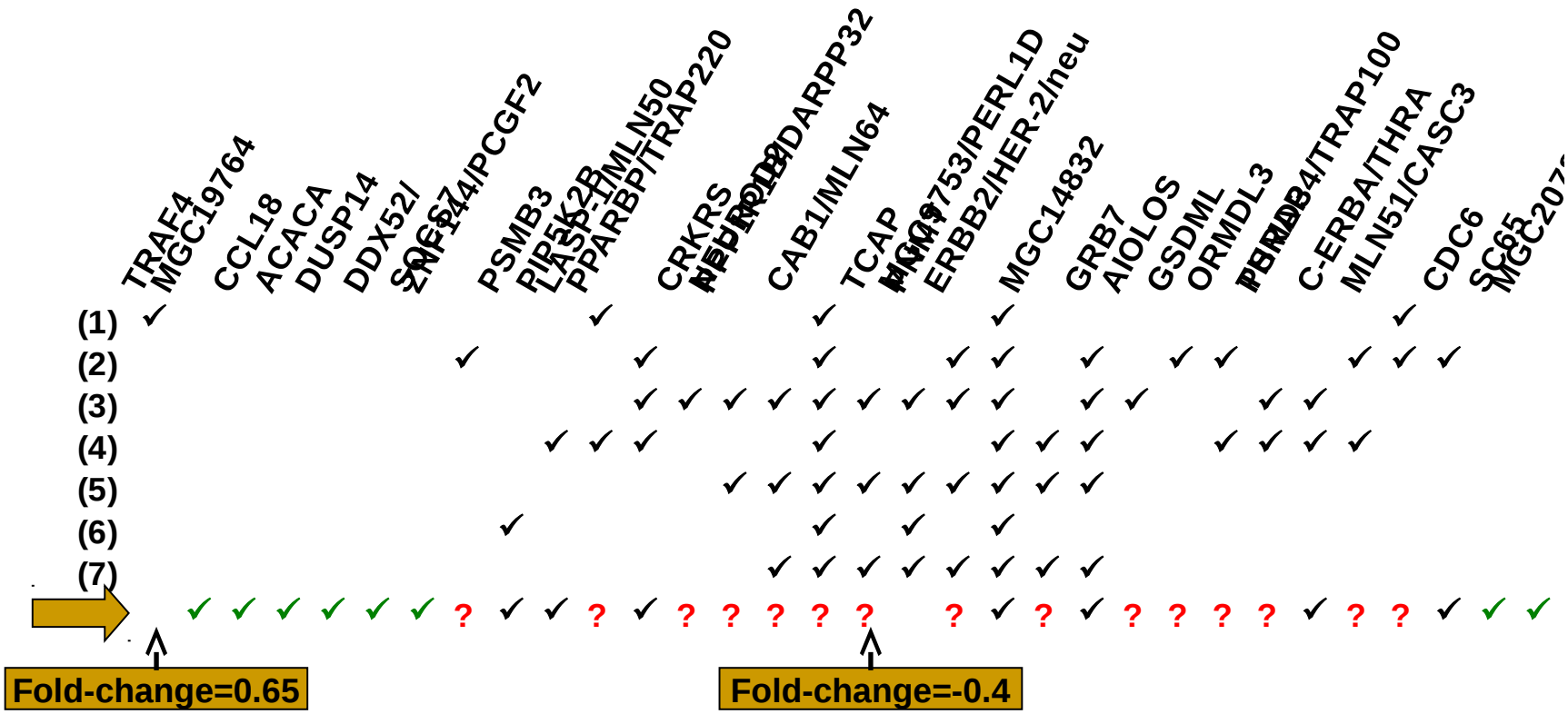

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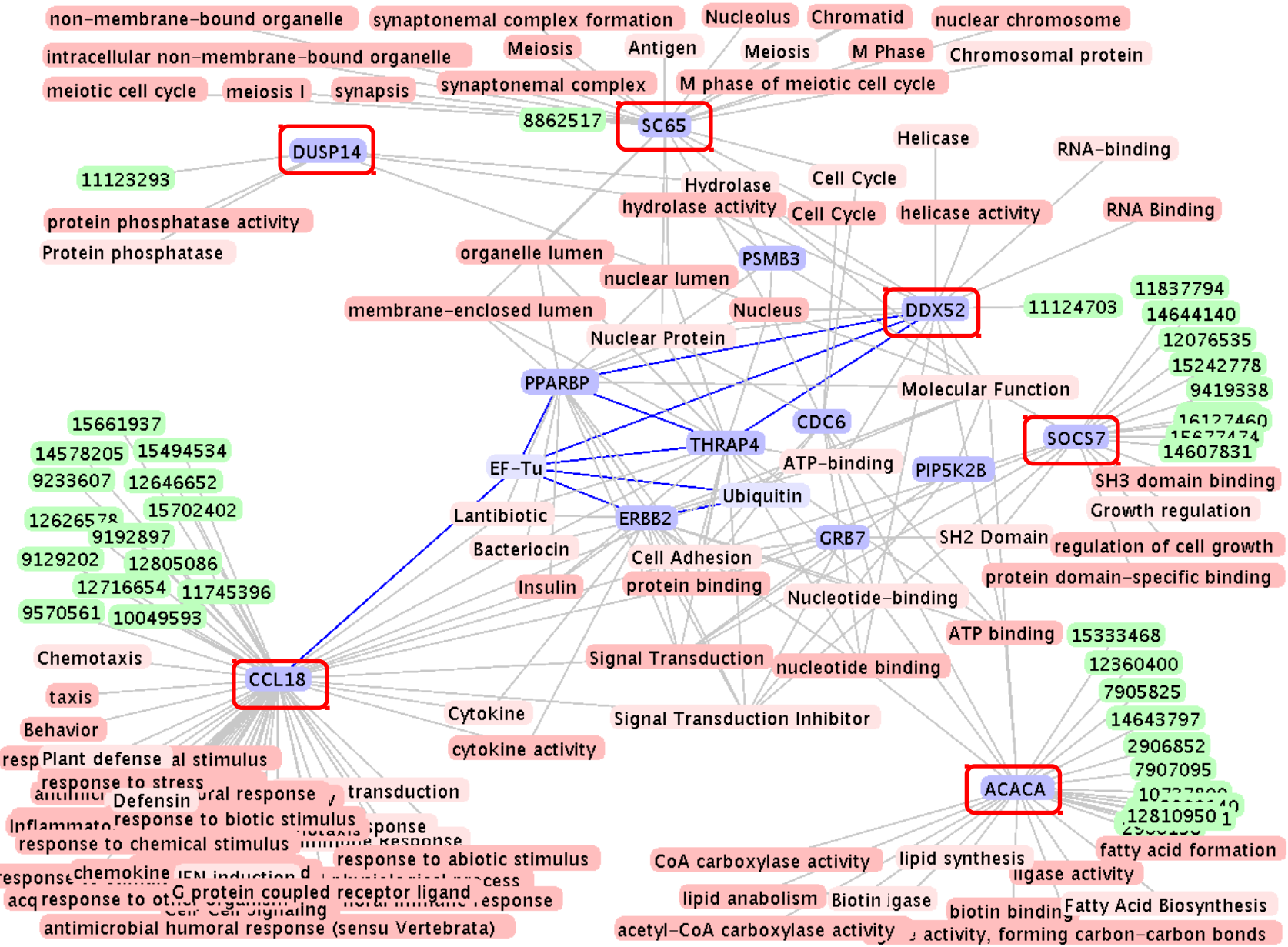
Annotations of new identified proteins



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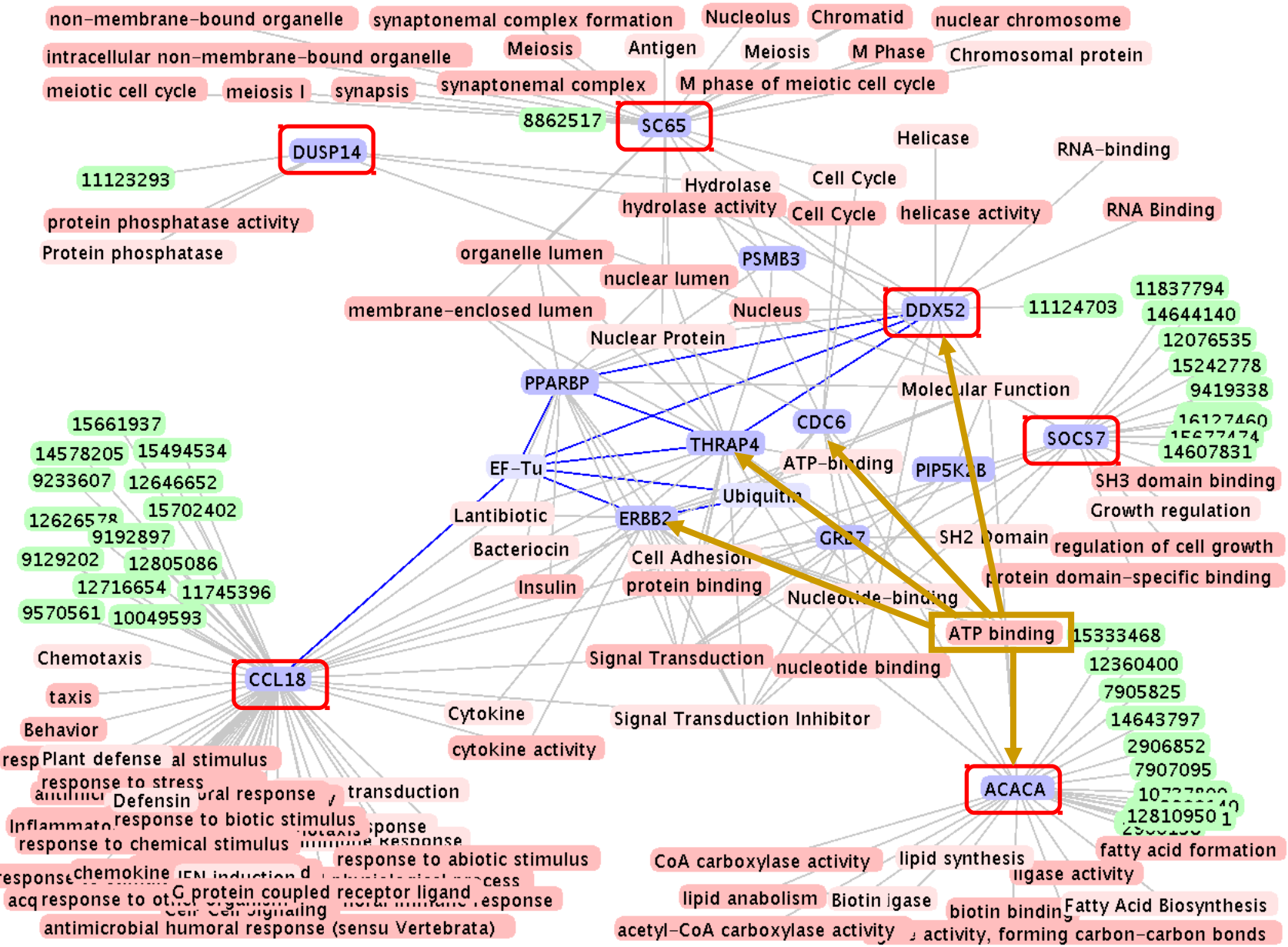

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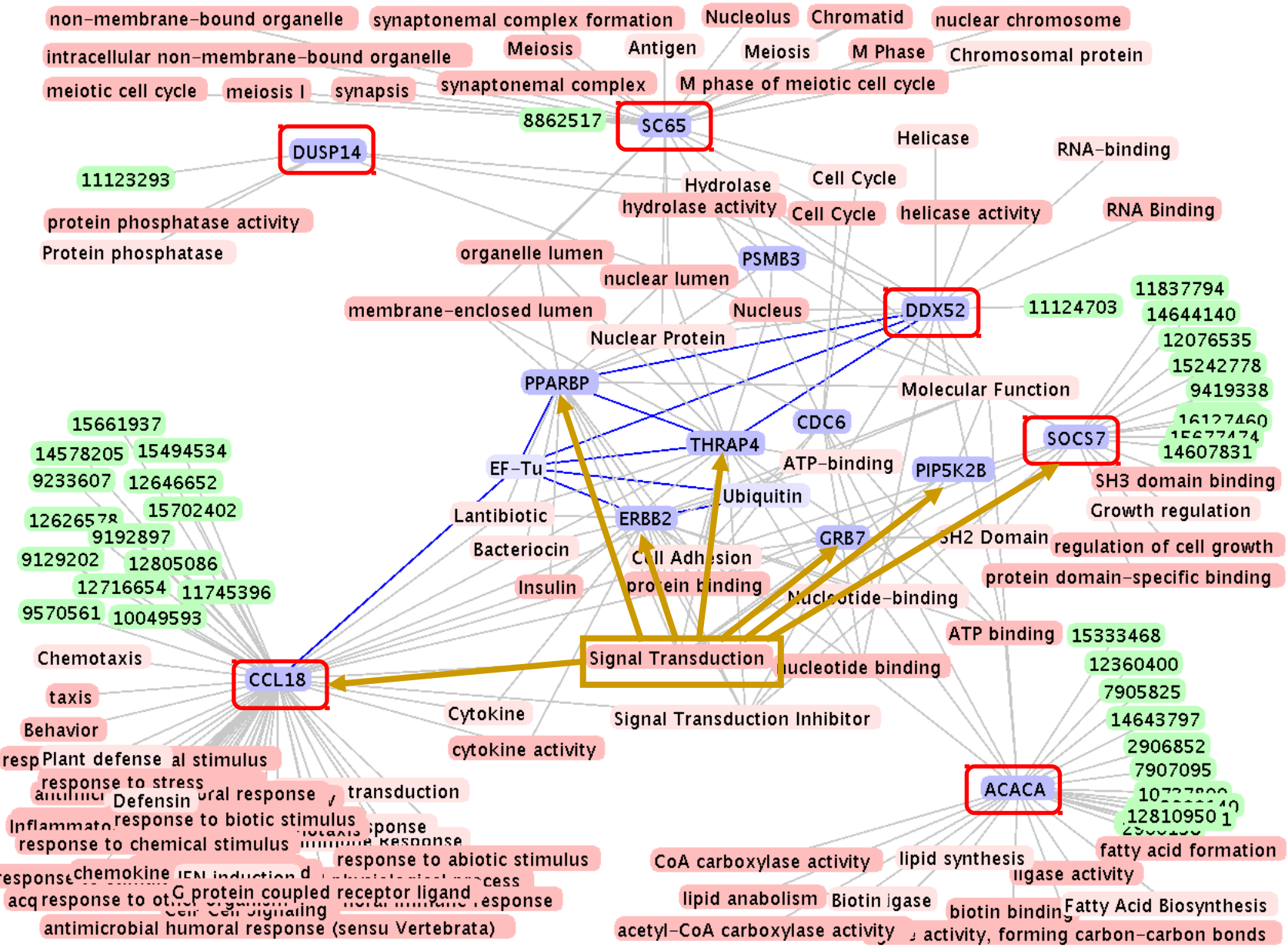

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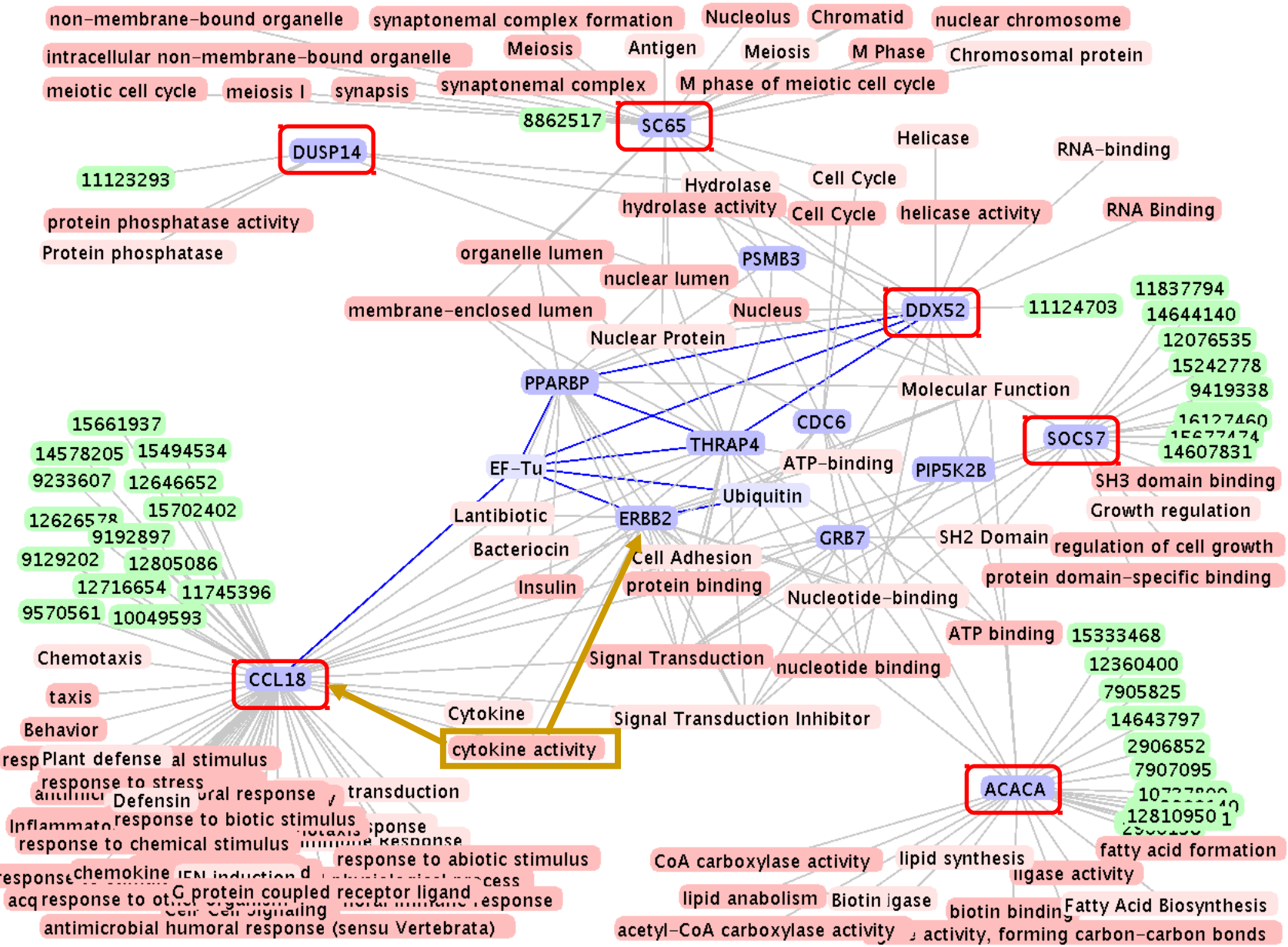

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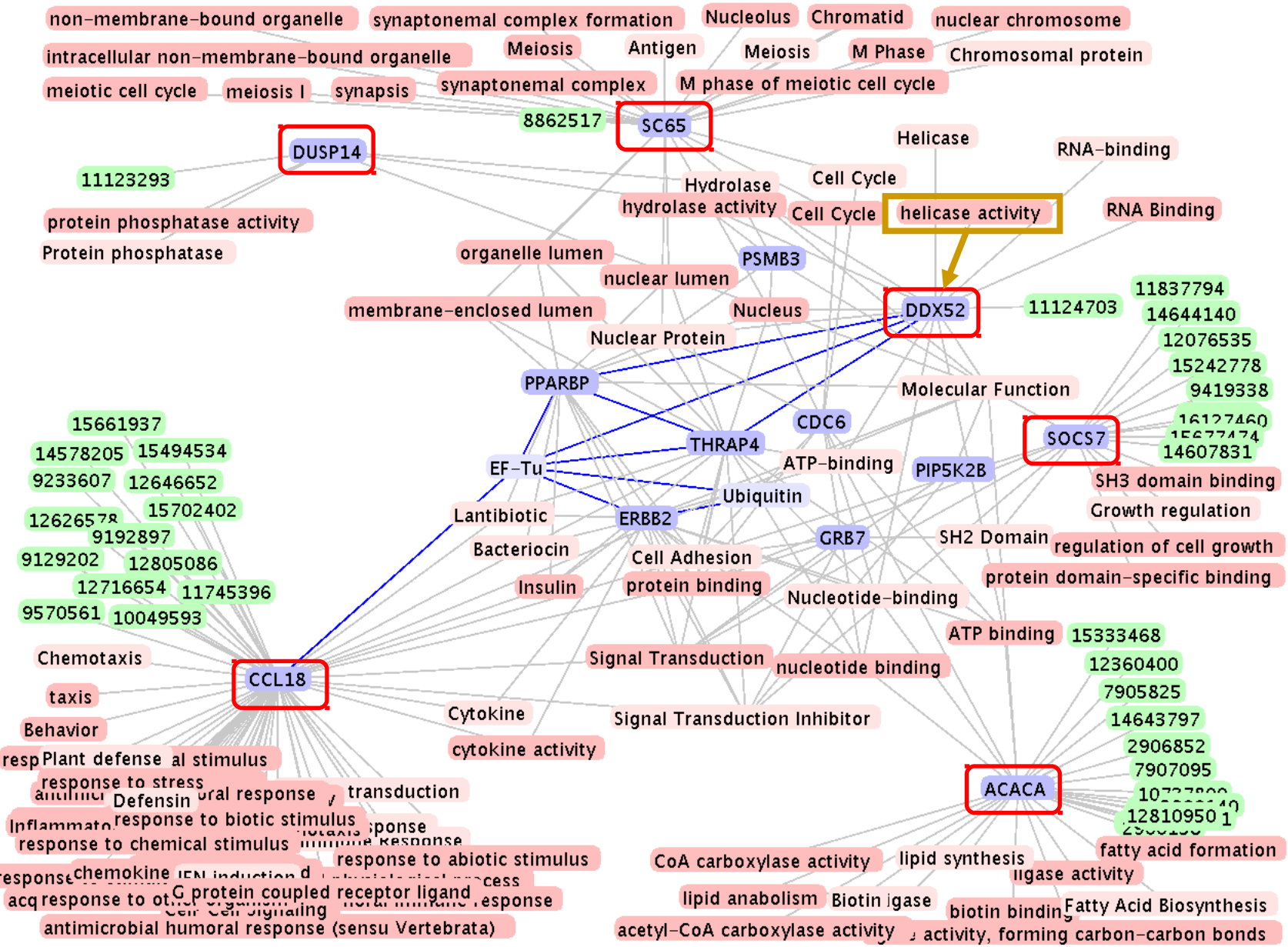

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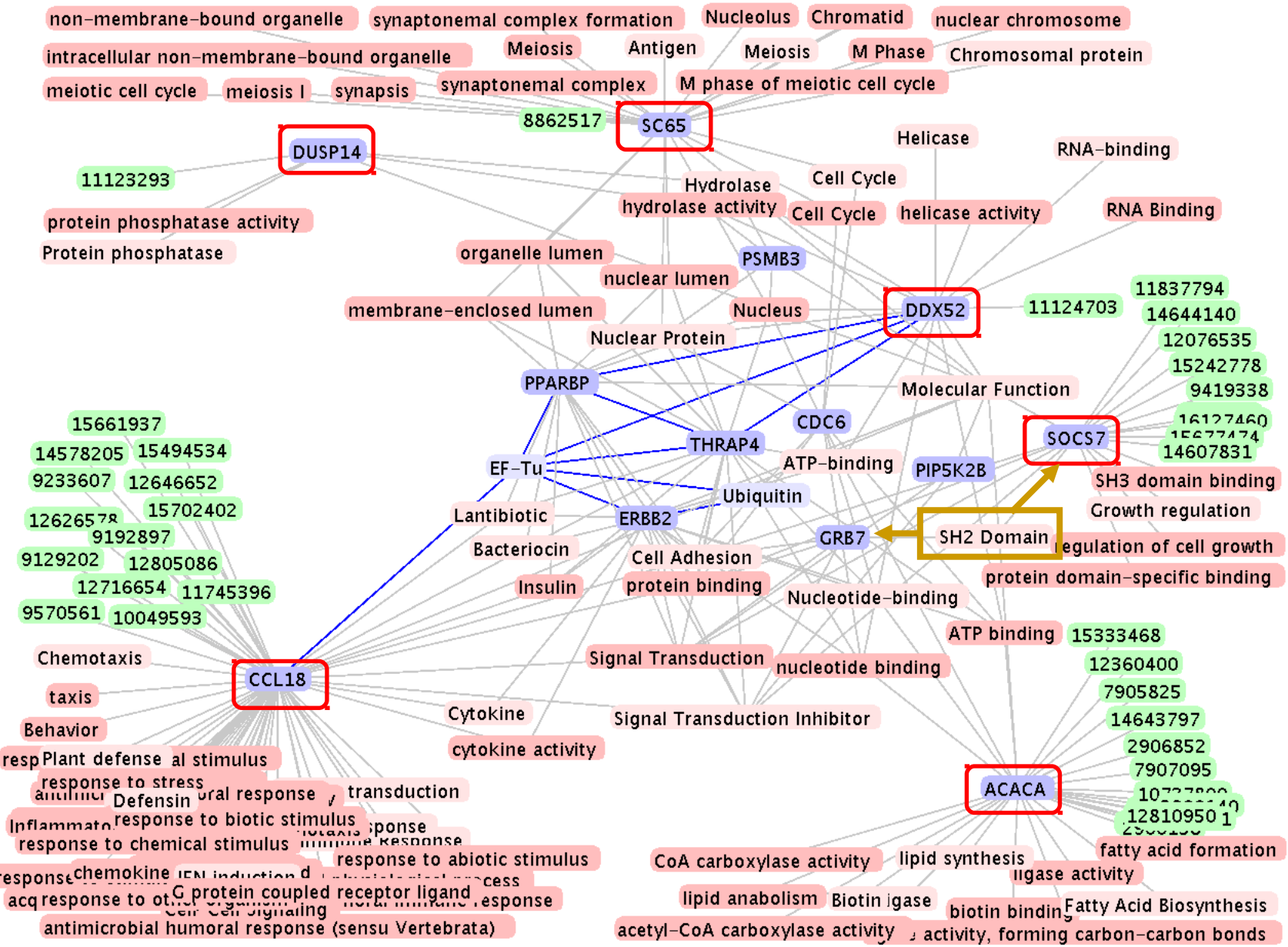

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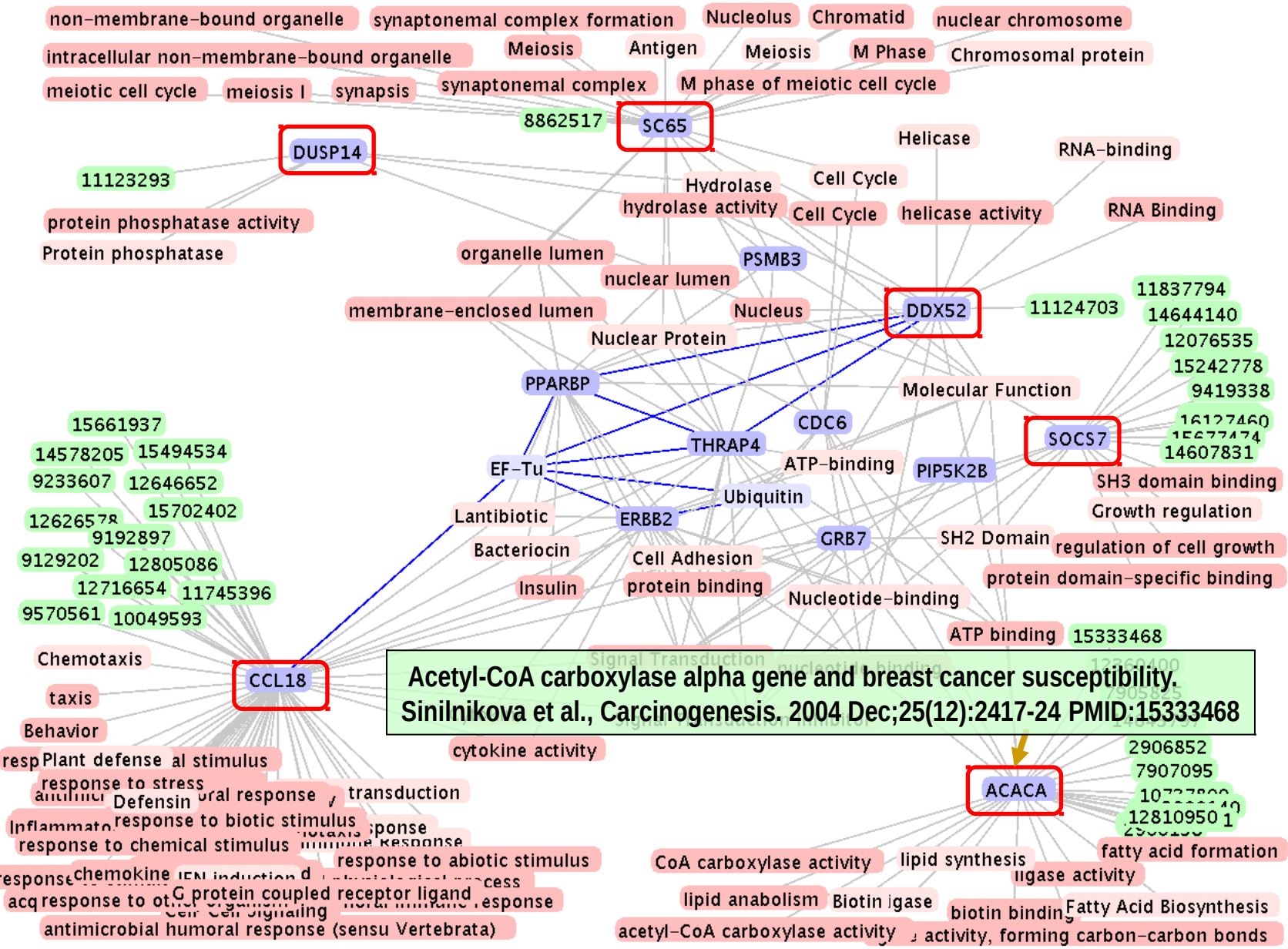

Acetyl-CoA carboxylase alpha gene and breast cancer susceptibility. Sinilnikova et al., Carcinogenesis. 2004 Dec;25(12):2417-24 PMID:15333468

Conclusion

- Semantic networks can be used:
  - to facilitate information integration
  - to extract valuable data
- An application to the analysis of expression values, allowed us:
  - to detect highly amplified zones
  - to highlight several genes potentially implied in breast cancer