Highly connected, non-redundant micro-RNAs in breast cancer molecular subtypes transcriptional networks:
from network topology to functional control

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- Are there highly connected and non-redundant miR in different breast cancer subtypes?

  (YES)

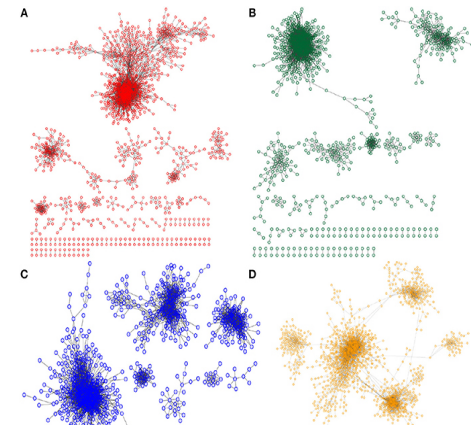- Is the set of these "commodore miR" different in each subtype?
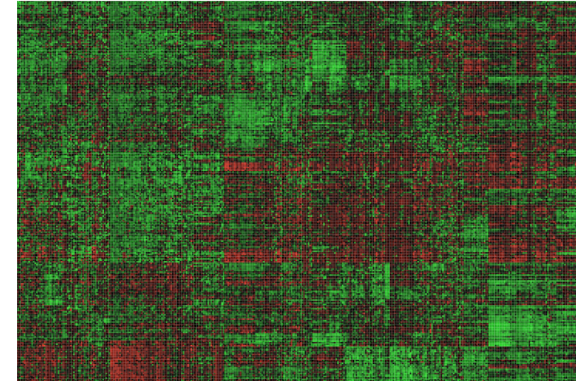
  (YES)

- Are they linked to different biological functions?
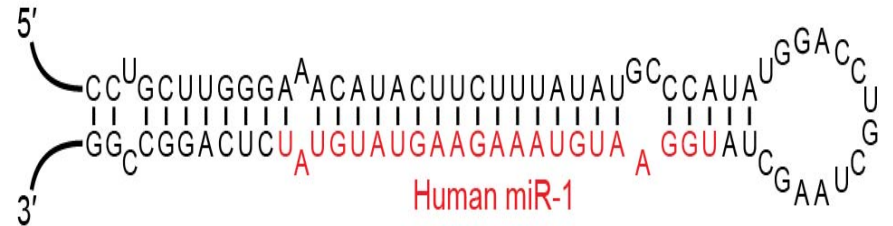
  (YES)

Transcription in breast cancer

- Breast cancer is heterogeneous

- Transcriptional patterns are diverse

- Molecular subtypes [1,2]

- Differences in co-expression networks [3,4]

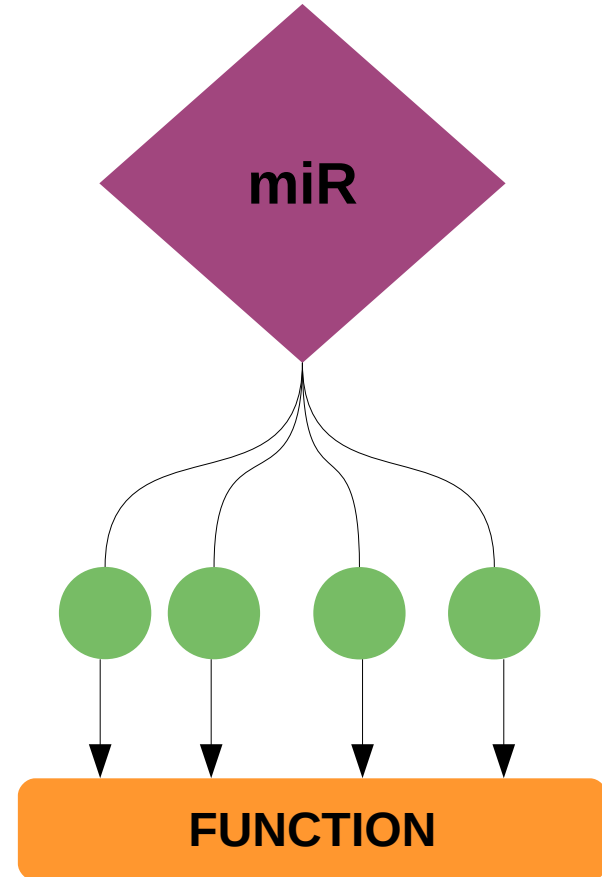# Micro - RNA

- AKA miR

- non- coding RNA

- Gene expression regulation

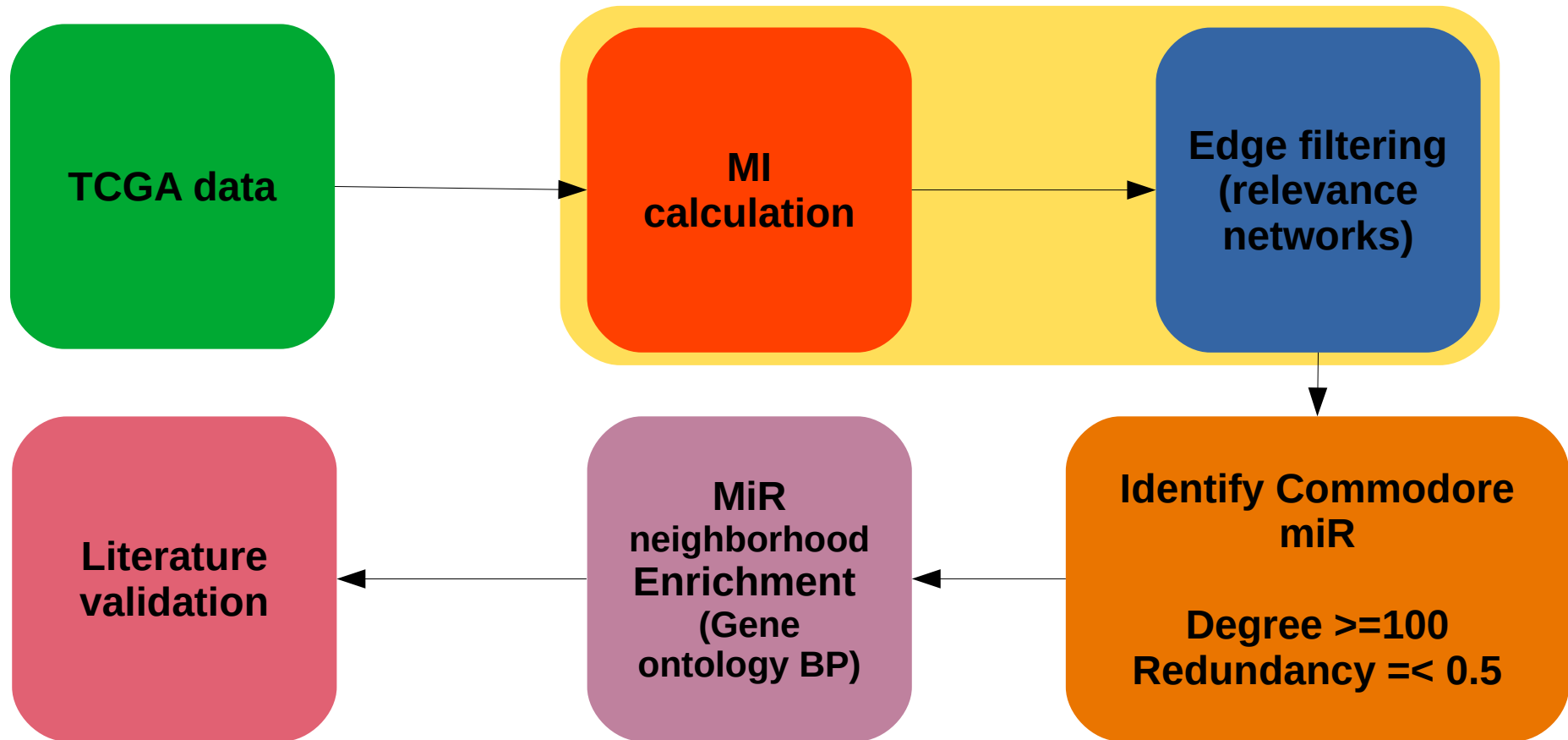- Roles in cancer

- Potential pharma targets
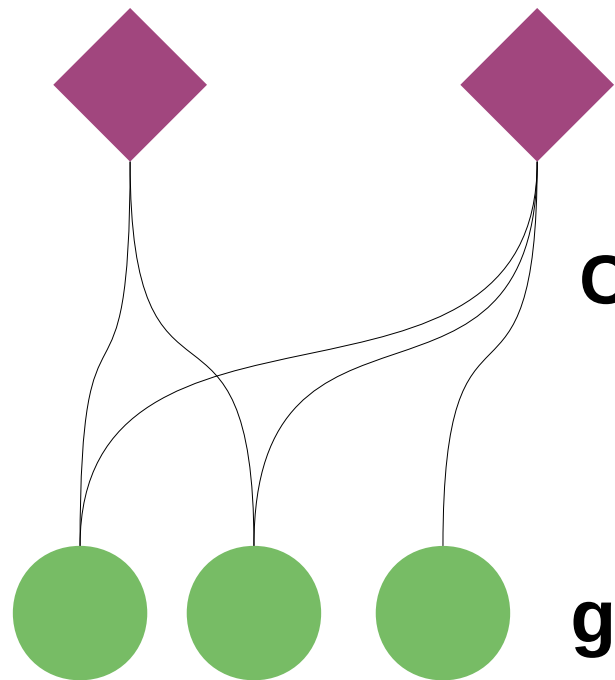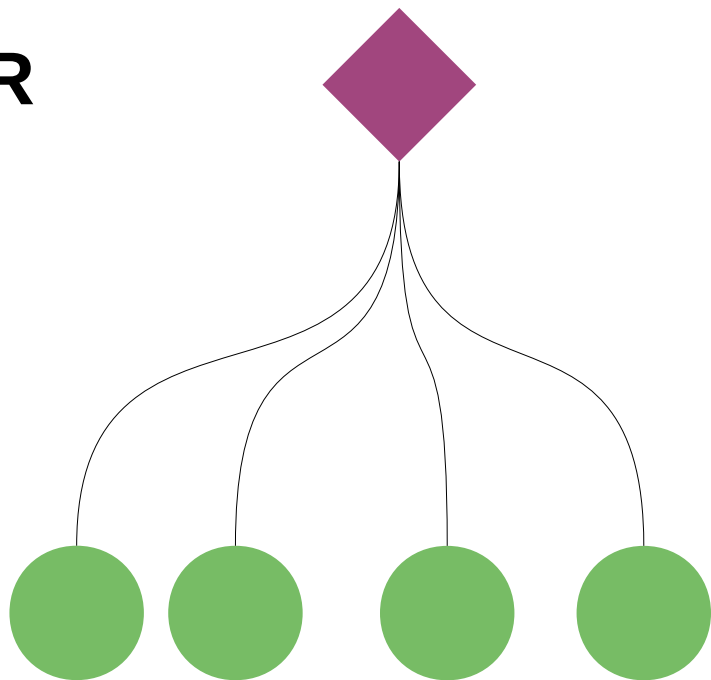

Human miR-1

"Commodore miRs"

- Gene – miR bipartite networks

- Highly connected, non-redundant miRs

- Can control many genes → many associated functions by themselves

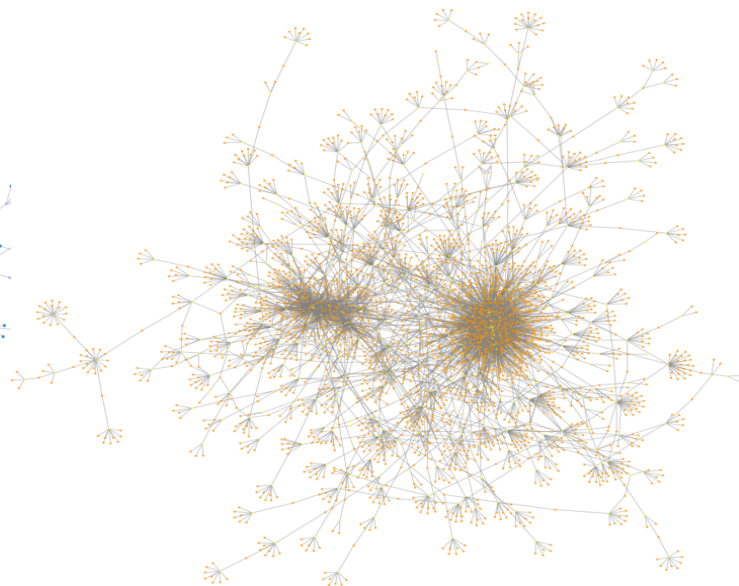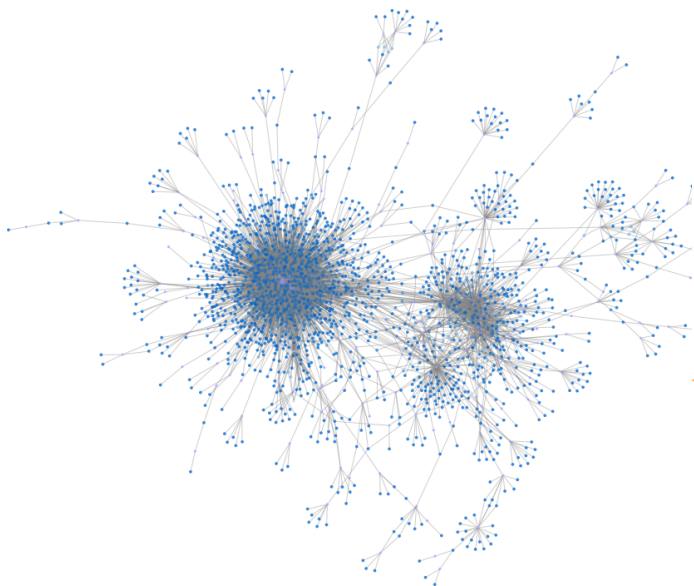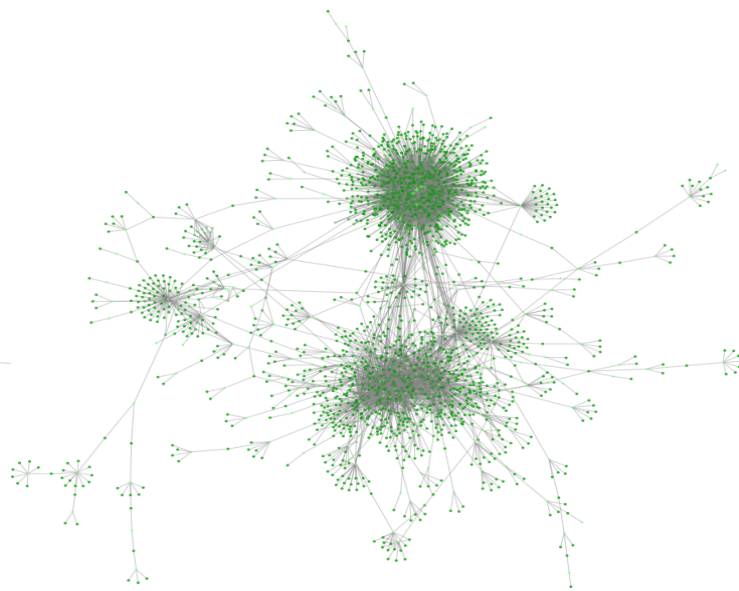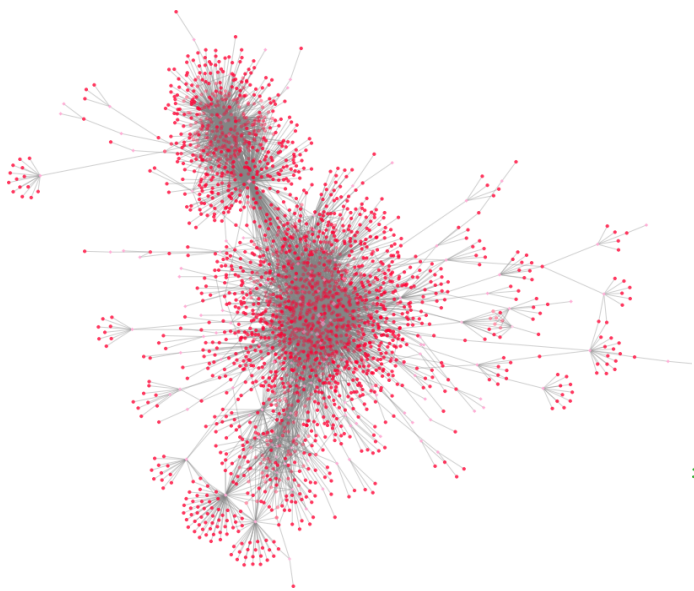[5]

Find cdre-miRs in subtypes
Compare them and their functions

```
┌─────────────┐        ┌─────────────────────────────────────────────────┐
│             │        │  ┌─────────────┐            ┌─────────────────┐  │
│  TCGA data  │───────▶│  │     MI      │───────────▶│  Edge filtering │  │
│             │        │  │ calculation │            │   (relevance    │  │
│             │        │  │             │            │    networks)    │  │
└─────────────┘        │  └─────────────┘            └─────────────────┘  │
                       └─────────────────────────────────────┬───────────┘
                                                             │
                                                             ▼
┌─────────────┐        ┌──────────────────┐        ┌──────────────────────┐
│             │        │      MiR         │        │  Identify Commodore  │
│ Literature  │◀───────│  neighborhood    │◀───────│        miR           │
│ validation  │        │   Enrichment     │        │                      │
│             │        │  (Gene           │        │   Degree >=100       │
│             │        │   ontology BP)   │        │   Redundancy =< 0.5  │
└─────────────┘        └──────────────────┘        └──────────────────────┘
```

TCGA data → **MI calculation** → **Edge filtering (relevance networks)**

Identify Commodore miR
Degree >=100
Redundancy =< 0.5
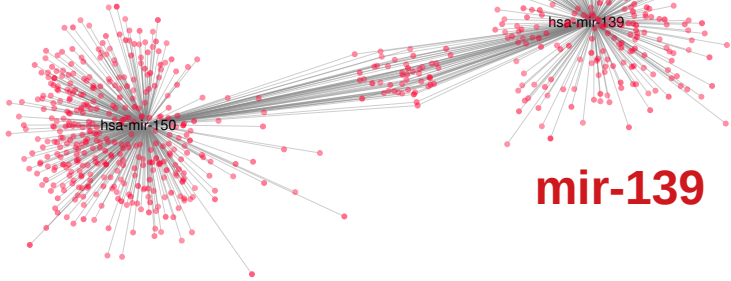
→ **MiR neighborhood Enrichment (Gene ontology BP)** → **Literature validation**

Comparable:
- MI threshold
- No. connected nodes
- No. edges
- No. connected components
- Degree distribution
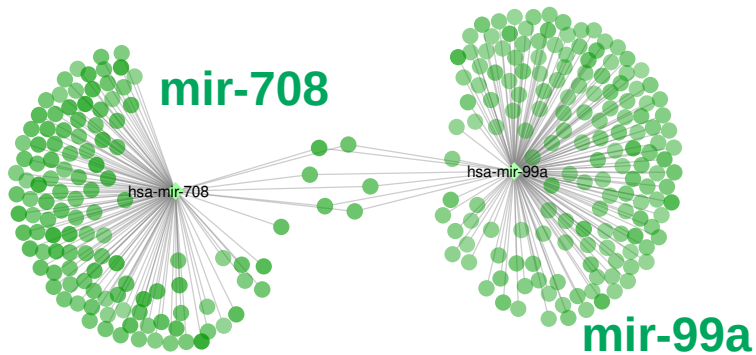
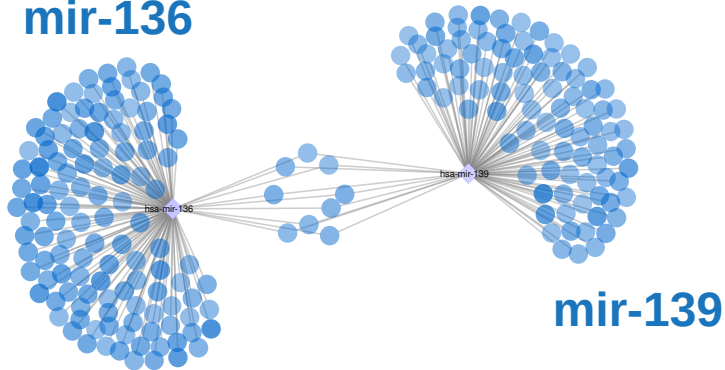| name	subtype	degree	Redundancy
hsa-mir-136	Luminal A	2	0.0000
	Luminal B	53	0.6466
	Basal	**128**	**0.3238**
	HER2-enriched	6	0.0000
hsa-mir-139	**Luminal A**	**294**	**0.4452**
	Luminal B	52	0.1169
	Basal	**101**	**0.0319**
	HER2-enriched	18	0.0000
hsa-mir-150	**Luminal A**	**437**	**0.2930**
	Luminal B	470	0.7762
	Basal	898	0.6652
	HER2-enriched	397	0.5169
hsa-mir-708	Luminal A	1	0.0000
	Luminal B	**122**	**0.3150**
	Basal	13	0.2821
	HER2-enriched	8	0.0357
hsa-mir-99a	Luminal A	485	0.6560
	Luminal B	**164**	**0.2245**
	Basal	6	0.0000
	HER2-enriched	11	0.3636

Functional enrichment

Subtype	Cdre-miR	Biological Processes
luma	hsa-mir-139	113
luma	Hsa-mir-150	170
lumb	hsa-mir-708	36
lumb	hsa-mir-99a	46
basal	hsa-mir-136	102
basal	hsa-mir-139	19

lumb_hsa-mir-99a

basal_hsa-mir-139

lumb_hsa-mir-708

basal_hsa-mir-136

luma_hsa-mir-150
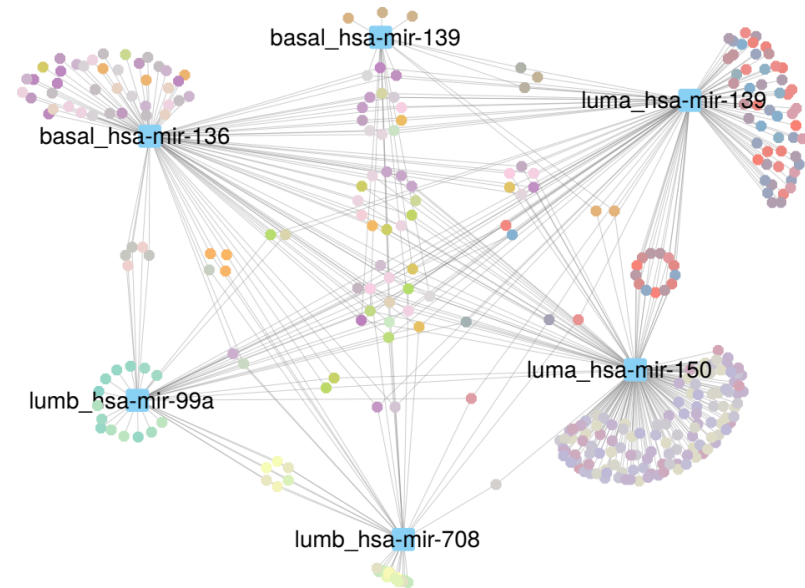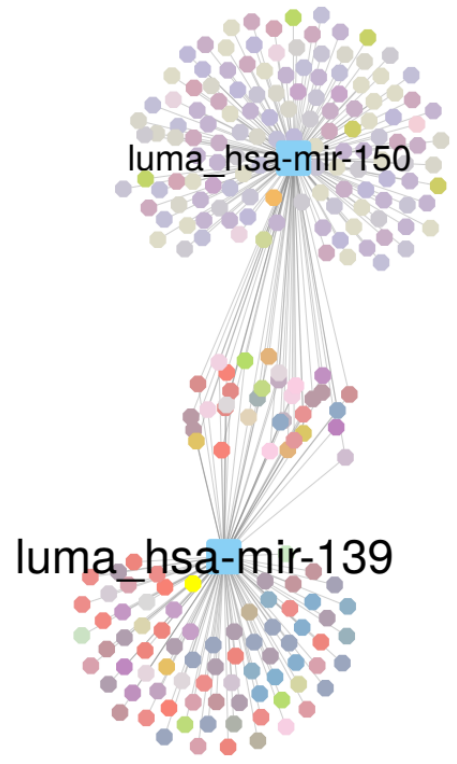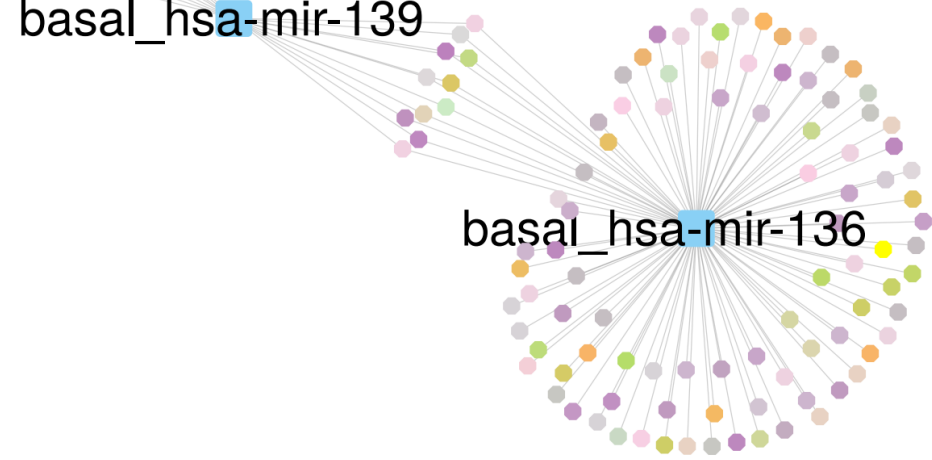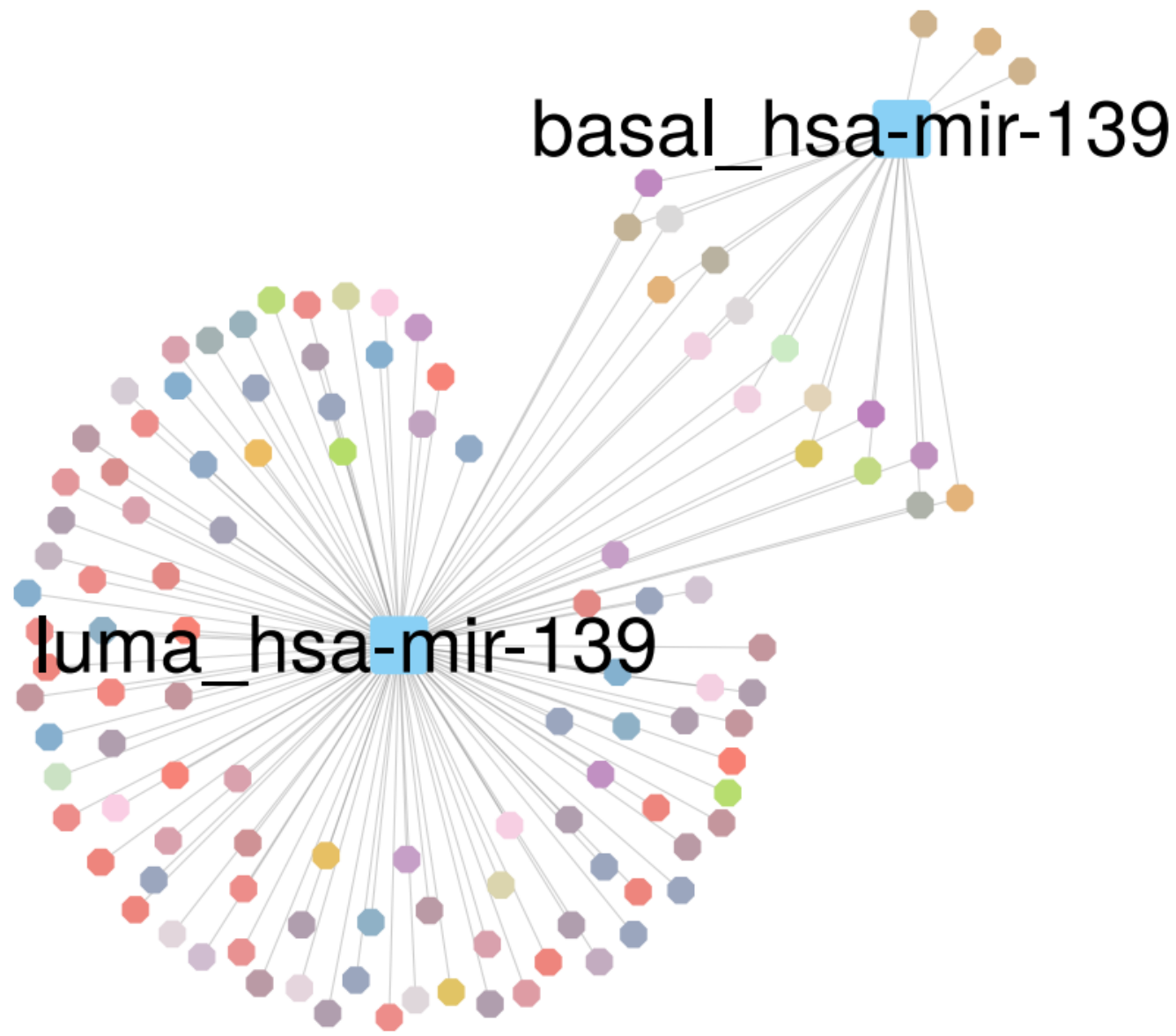
luma_hsa-mir-139

Literature validation

subtype	miR	GO representative term	Pubmed mentions	miR mentions
luma	hsa-mir-139	angiogenesis	3	112
basal	hsa-mir-139	angiogenesis	3	112
lumb	hsa-mir-708	cell adhesion	1	37
basal	hsa-mir-136	cell adhesion	5	39
basal	hsa-mir-139	cell adhesion	2	112
luma	hsa-mir-139	negative regulation of apoptotic process	2	112
luma	hsa-mir-139	positive regulation of gene expression	7	112
basal	hsa-mir-136	regulation of signaling receptor activity	1	39
luma	hsa-mir-150	signal transduction	30	240

To wrap up

- cdre-miRs are found in 3 subtypes of breast cancer: luminal (A & B), basal

- cdre-miRs are linked to the expression of different genes across the molecular subtypes

- cdre-miR are linked to several biological functions, many of these unique to each molecular subtype

- Associations between some identified cdre-miRs and important cancer hallmarks have been reported in the literature

- Perspective: Validate their ability to control these at the physiological level

References

1 https://doi.org/10.1038/35021093
2 https://dx.doi.org/10.1200%2FJCO.2008.18.1370
3 https://doi.org/10.3389/fphys.2016.00568
4 https://doi.org/10.3389/fphys.2017.00915
5 https://doi.org/10.1155/2018/9585383

Preprint: https://doi.org/10.1101/652354

Thanks to:

Cátedras CONACYT
CONACYT Ciencia Básica 285544
INMEGEN
NetSci 2019

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References

1 https://doi.org/10.1038/35021093
2 https://dx.doi.org/10.1200%2FJCO.2008.18.1370
3 https://doi.org/10.3389/fphys.2016.00568
4 https://doi.org/10.3389/fphys.2017.00915
5 https://doi.org/10.1155/2018/9585383

Preprint: https://doi.org/10.1101/652354

See also: Our posters, Thursday

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Preprocessing ?
Data types?
Sample size?

Discretization method ?
Estimation method?

Threshold value?
Alternative filtering?

Does the cdre limits hold for any phenotype?

Hypergeometric?
GO-BP only?
Significance value ?
Aggregation methods?

Extract effects systematically