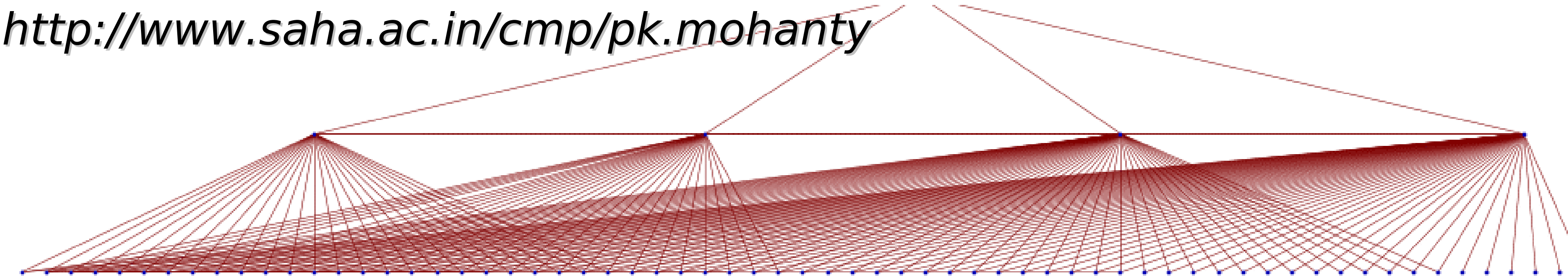
Building Blocks of Cellular Functions

24th Nov, 2009
TIFR, Mumbai

Pradeep K. Mohanty
(TCMP Division, SINP)
E-mail : pk.mohanty@saha.ac.in
http://www.saha.ac.in/cmp/pk.mohanty



Collaboration....

- **Sushmita Mookherjee**
- **Nitai P. Bhatacharyya**
- **Mithun Sinha**
- **Saikat Mukherjee**

Saha Institute of
Nuclear Physics, Kolkata-64

Ref : *OJB* ***10****(2), 280, 2009*

Outline

- What are miRNAs ?
- miRNA interaction…..
- miRNA co-target network
- miRNA clusters
- Implication to genetic diseases

Question : *a broader prospective*

Objects(T)

Molecules(B)

Atom(108)

p, e, n (3)

Cells (T)

Proteins (M)

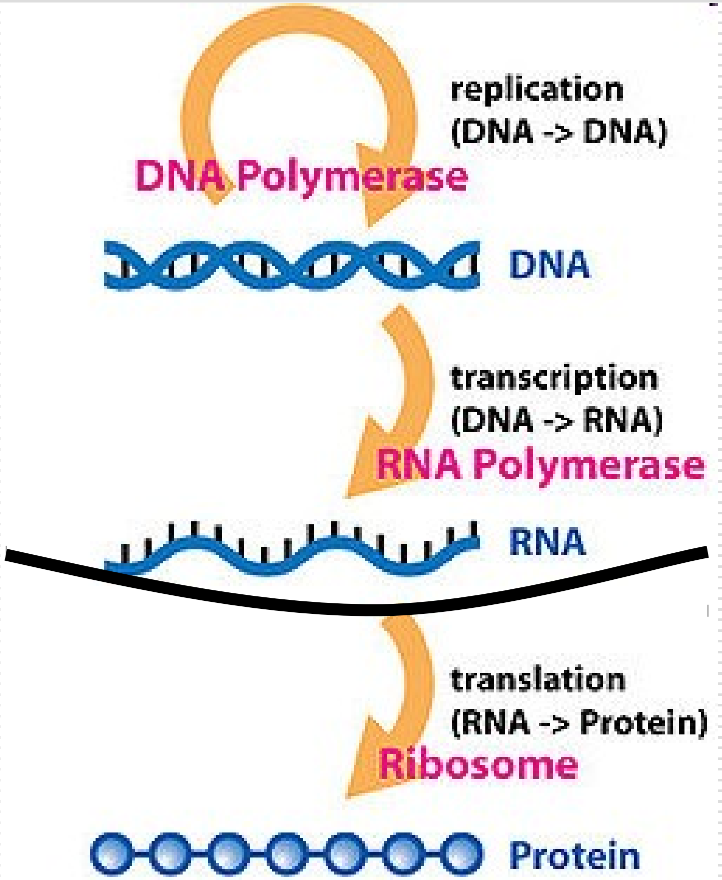
Genes(30K)

miRNA (~1K)

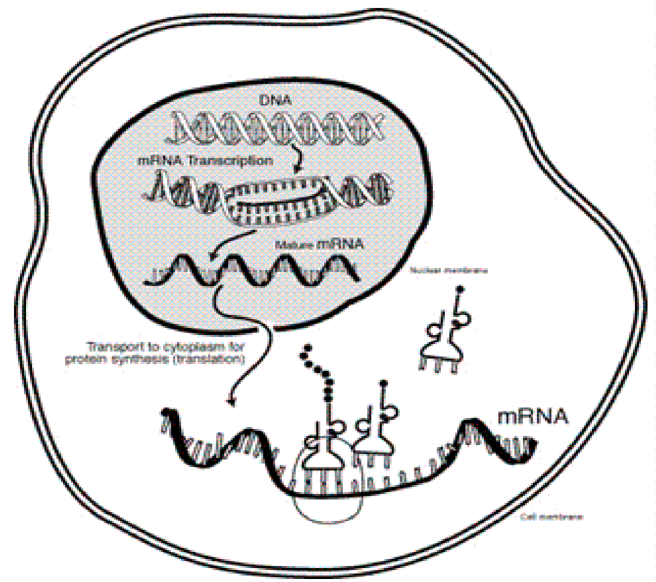
miRNA clusters(~70)

Take Home msg : miRNA clusters are building blocks of bio-functions

The central dogma



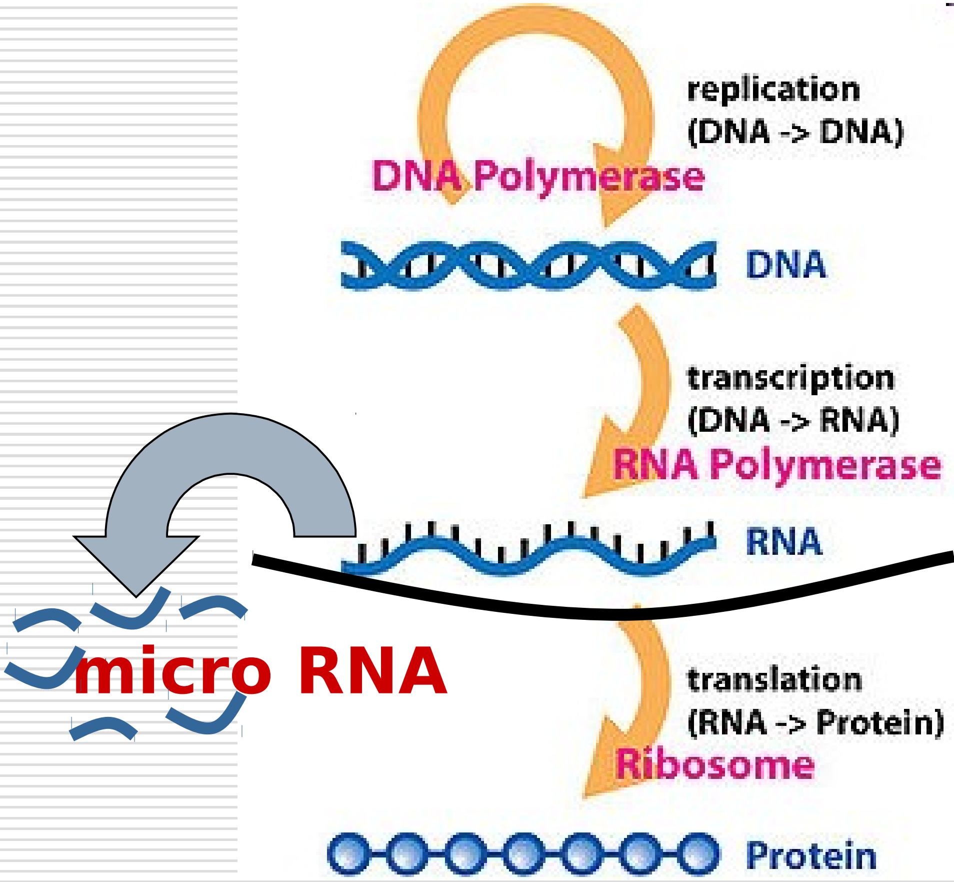
mRNA ~1kbp



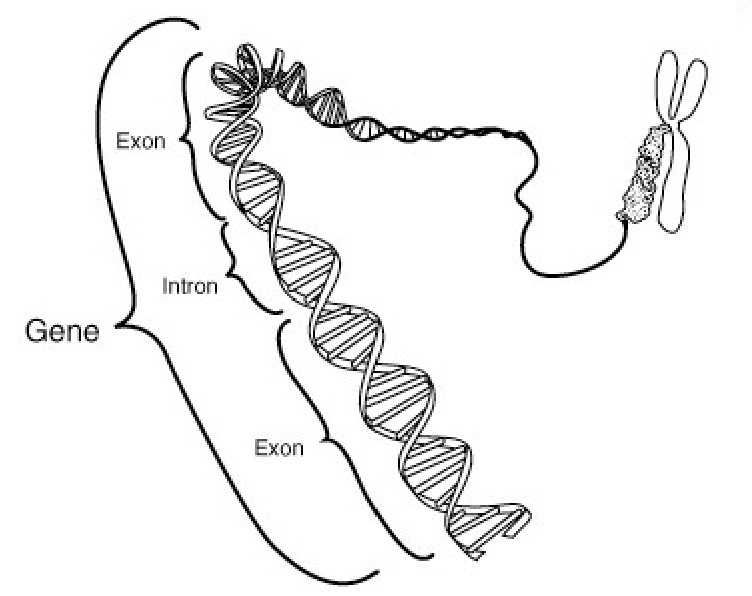
- To function, cells need proteins
- Proteins are produced inside the cell

Short RNA (~20 bp)

- miRNA
  =short RNAs ~20 bp
- Byproducts of transcription ?
- No (2001)



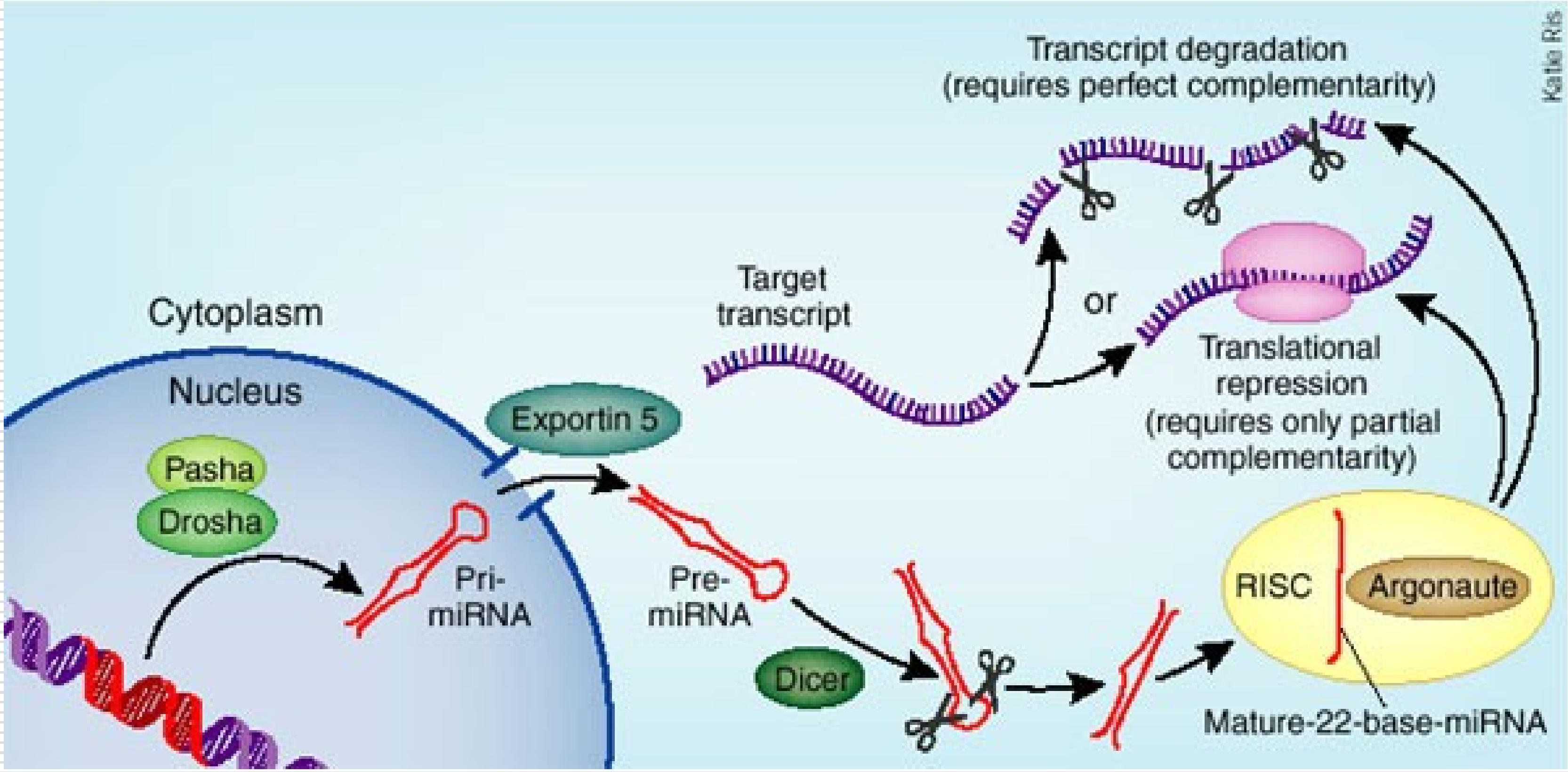
DNA fact-book



- DNA =.22B bases
- Width 2.2-2.6 nm
- Base= nucleotide uni

  =.33 nm
- Length = 7.2 cm
- Body= 6B bp/cell x10T cells
- Total length= 70 round trips to sun

miRNA : (*how and where*)



- Hair-pin
- Seed
- Intergenic

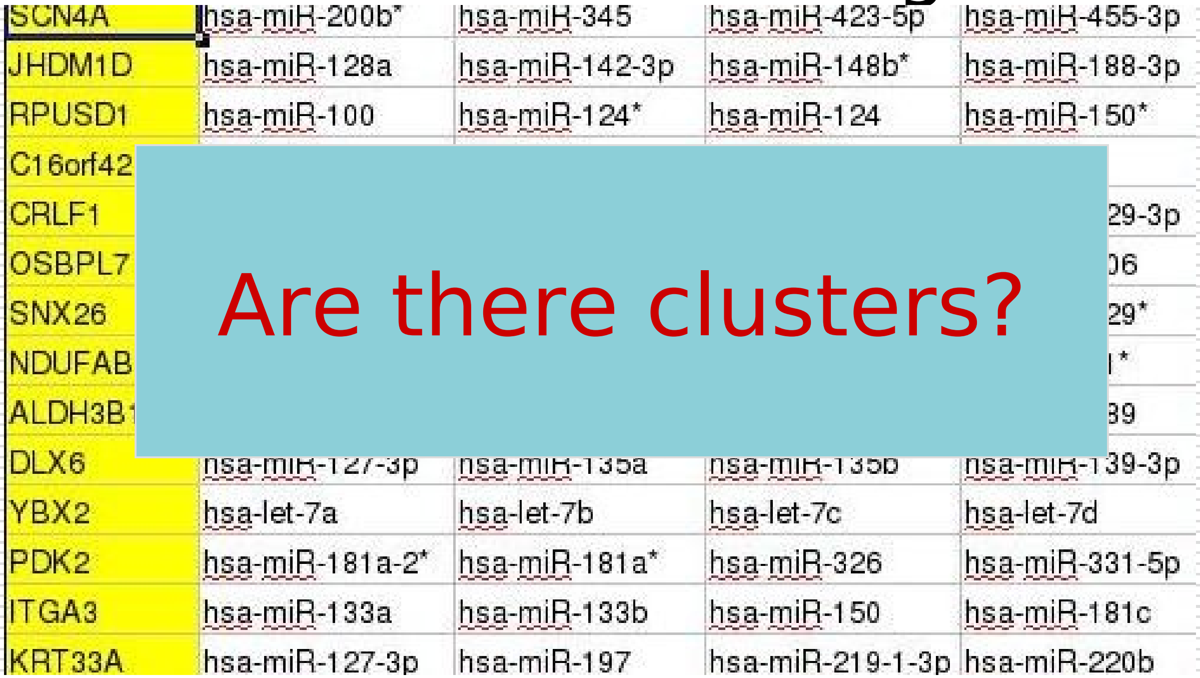
Location of miRNA in DNA

What do miRNAs do ?

- They usually down-regulate gene expression

Data (predicted)

- About 90% of human genome are predicted as miRNA targets



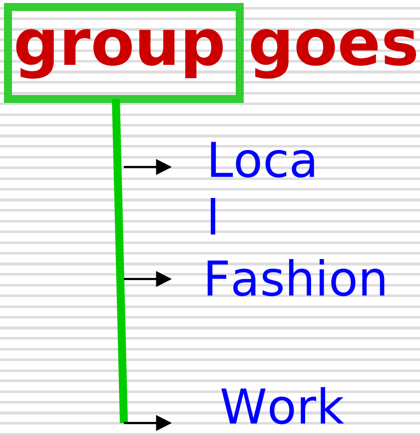
SCN4A	hsa-miR-200b*	hsa-miR-345	hsa-miR-423-5p	hsa-miR-455-3p
JHDM1D	hsa-miR-128a	hsa-miR-142-3p	hsa-miR-148b*	hsa-miR-188-3p
RPUSD1	hsa-miR-100	hsa-miR-124*	hsa-miR-124	hsa-miR-150*
C16orf42				
CRLF1				29-3p
OSBPL7				06
SNX26				29*
NDUFAB				l*
ALDH3B1				39
DLX6	hsa-miR-127-3p	hsa-miR-135a	hsa-miR-135b	hsa-miR-139-3p
YBX2	hsa-let-7a	hsa-let-7b	hsa-let-7c	hsa-let-7d
PDK2	hsa-miR-181a-2*	hsa-miR-181a*	hsa-miR-326	hsa-miR-331-5p
ITGA3	hsa-miR-133a	hsa-miR-133b	hsa-miR-150	hsa-miR-181c
KRT33A	hsa-miR-127-3p	hsa-miR-197	hsa-miR-219-1-3p	hsa-miR-220b

Are there clusters?

miRBase (http://microrna.sanger.ac.uk/ version 10) for *Homo sapience*, **711 miRNAs** and **34525** predicted **targets**.

P1	Hena Ani Suju Due Pinky
P2	Pinky Rita
P3	Ani Uma Hena Suju
P4	Kriti Gouri
P5	Suju Soma Ani Ritu

Women in group goes to parlors ?



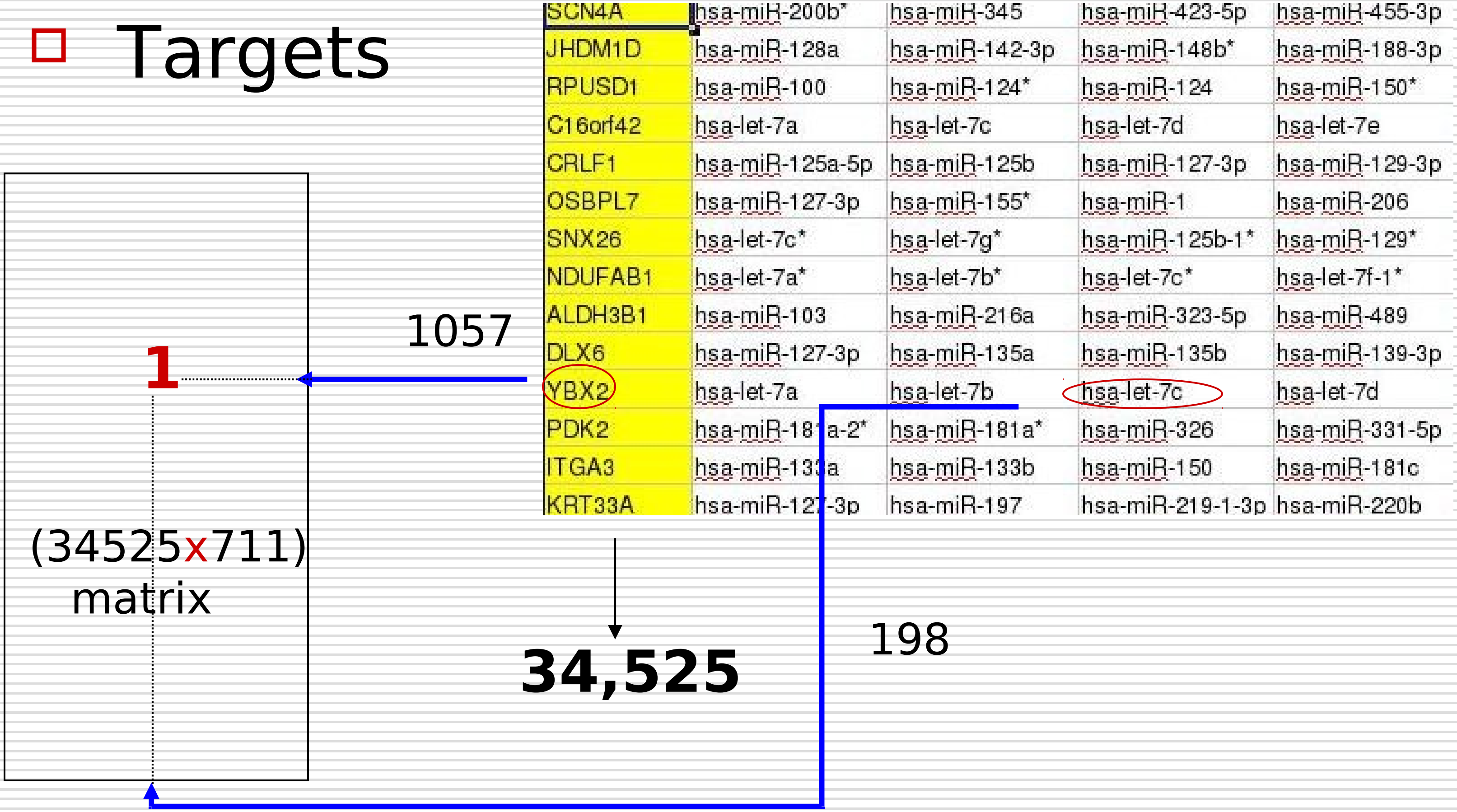
Local = Genomic

Fashion = Sequence Similarity

Work = Function

Data (miRBase http://microrna.sanger.ac.uk/, *version 10*)

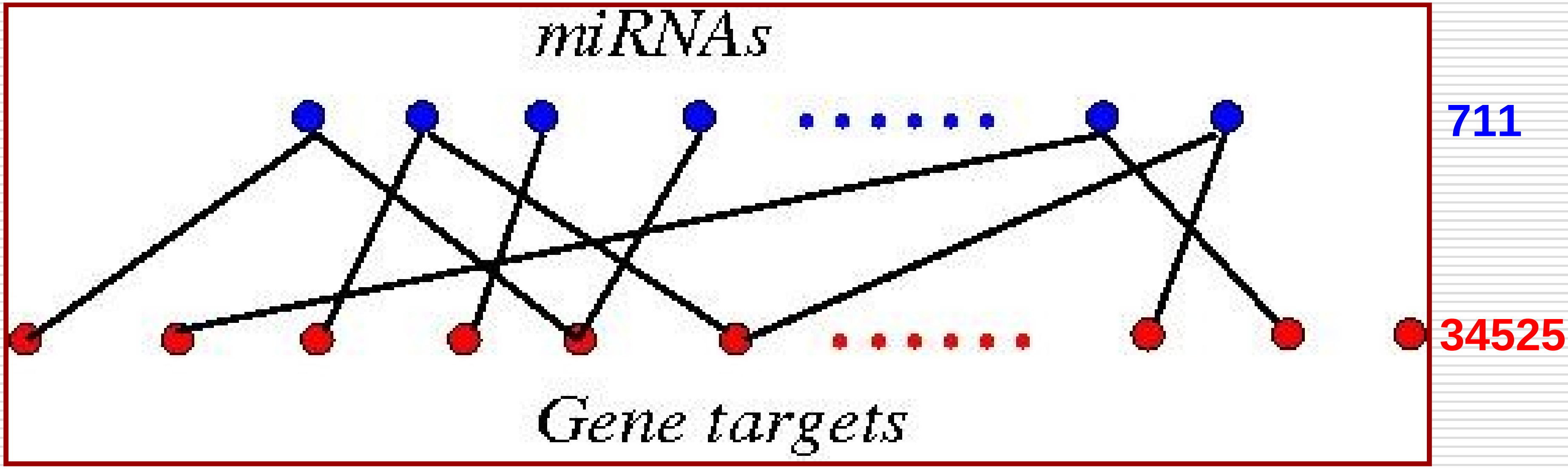
- Targets



SCN4A	hsa-miR-200b*	hsa-miR-345	hsa-miR-423-5p	hsa-miR-455-3p
JHDM1D	hsa-miR-128a	hsa-miR-142-3p	hsa-miR-148b*	hsa-miR-188-3p
RPUSD1	hsa-miR-100	hsa-miR-124*	hsa-miR-124	hsa-miR-150*
C16orf42	hsa-let-7a	hsa-let-7c	hsa-let-7d	hsa-let-7e
CRLF1	hsa-miR-125a-5p	hsa-miR-125b	hsa-miR-127-3p	hsa-miR-129-3p
OSBPL7	hsa-miR-127-3p	hsa-miR-155*	hsa-miR-1	hsa-miR-206
SNX26	hsa-let-7c*	hsa-let-7g*	hsa-miR-125b-1*	hsa-miR-129*
NDUFAB1	hsa-let-7a*	hsa-let-7b*	hsa-let-7c*	hsa-let-7f-1*
ALDH3B1	hsa-miR-103	hsa-miR-216a	hsa-miR-323-5p	hsa-miR-489
DLX6	hsa-miR-127-3p	hsa-miR-135a	hsa-miR-135b	hsa-miR-139-3p
YBX2	hsa-let-7a	hsa-let-7b	hsa-let-7c	hsa-let-7d
PDK2	hsa-miR-181a-2*	hsa-miR-181a*	hsa-miR-326	hsa-miR-331-5p
ITGA3	hsa-miR-133a	hsa-miR-133b	hsa-miR-150	hsa-miR-181c
KRT33A	hsa-miR-127-3p	hsa-miR-197	hsa-miR-219-1-3p	hsa-miR-220b

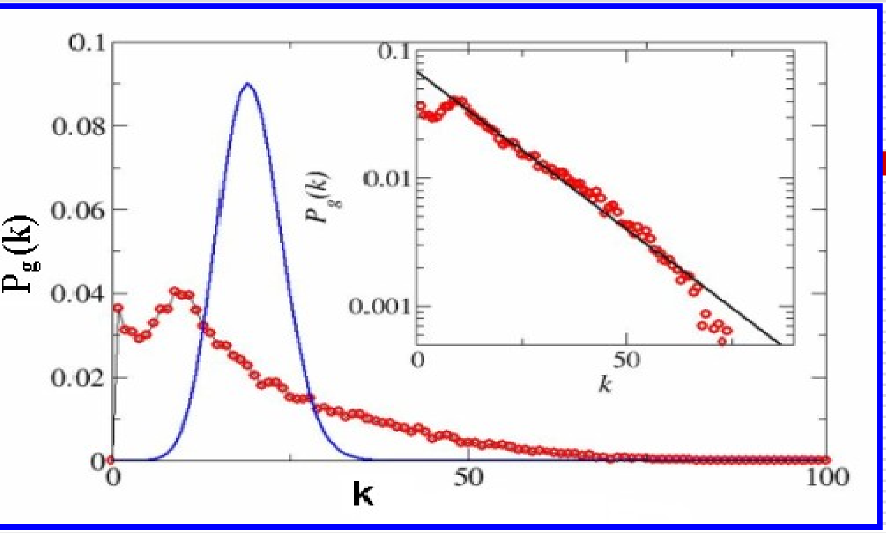
Q. Are there groups of miRNAs ?

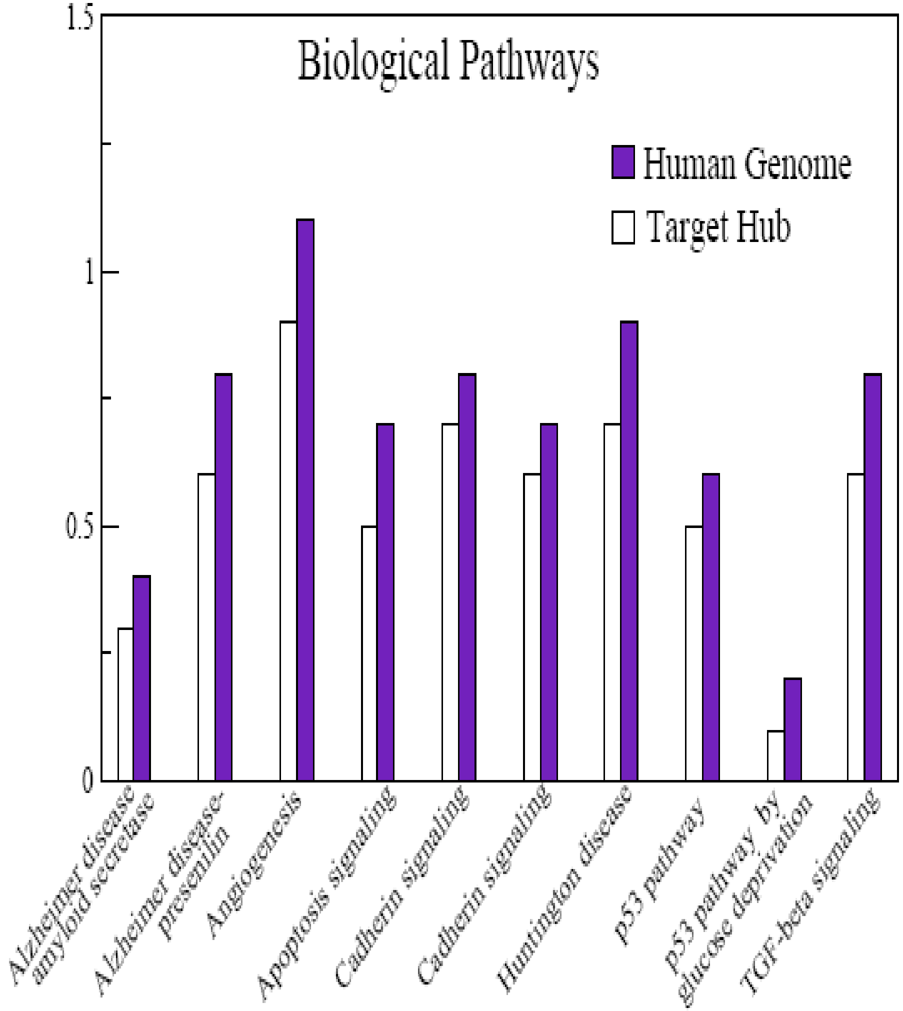
miRNA-Gene Network



miRNA-Gene form a *bi-partite network*
Two genes or two miRNAs are never connected

Target Hubs :



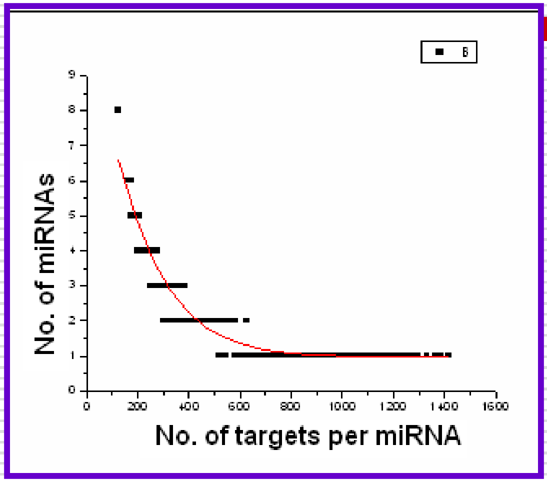


Distribution of genes $P_g(k)$= fraction of genes targeted by k number of miRNAs

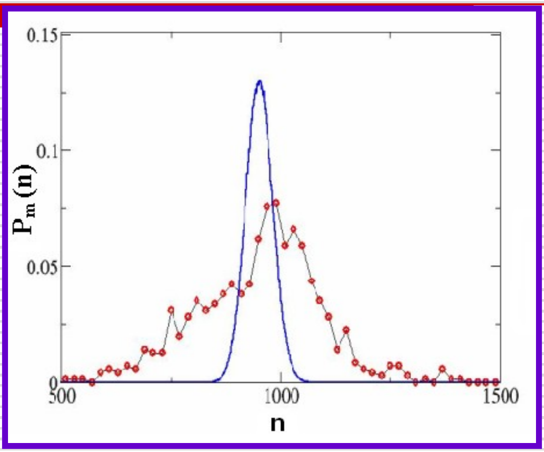
- Exp distribution with k*=20
- Hub = genes targeted by >20 miRNA
- Genes in hub, rich in binding sites (3'-UTR)
- Functional classification of genes in hub

PANTHER,(http://www.pantherdb.org/).

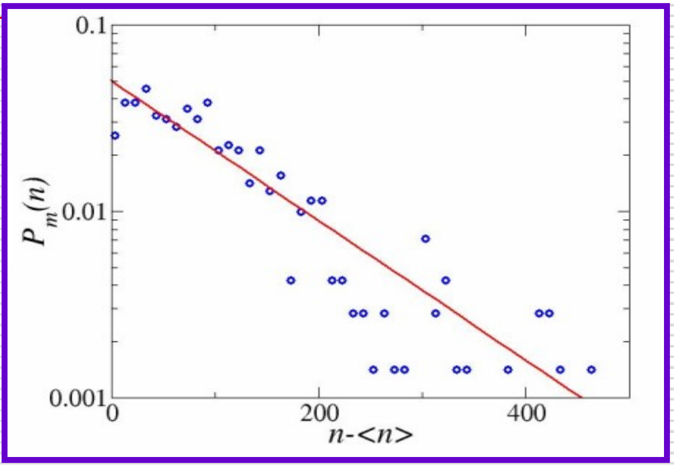
miRNA Hub : *miRNAs those target more than 1067 genes*



miRNA hub considering the number of targets per miRNA



Distribution of miRNAs P_m (n), i.e. the fraction of miRNA (red-circles) which target n genes is compared with corresponding random graph. Note **<n>=951**.



For n-<n>, the distribution P_m (n) decays **exponentially** with a typical scale **n*=116** .

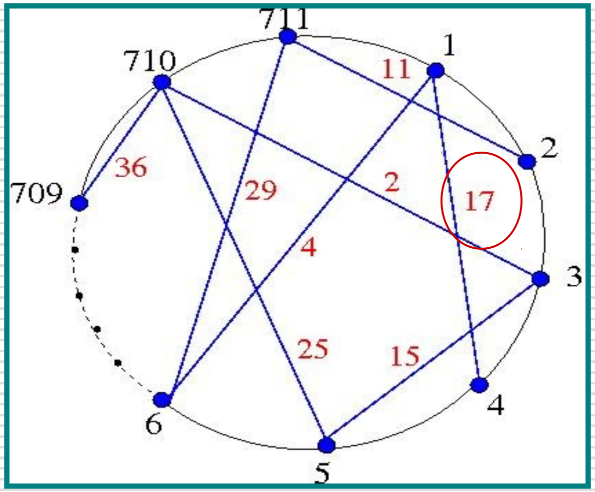
miRNA hubs: We define **hubs** are the miRNAs which target more than **<n>+n*=1067** genes. Further studies reveal that miRNAs in the hub co-target maximum number of genes and form miRNA clusters.

miRNA-miRNA Network

- Two miRNA are connected
  if they have common target
- Weight = #of common targets

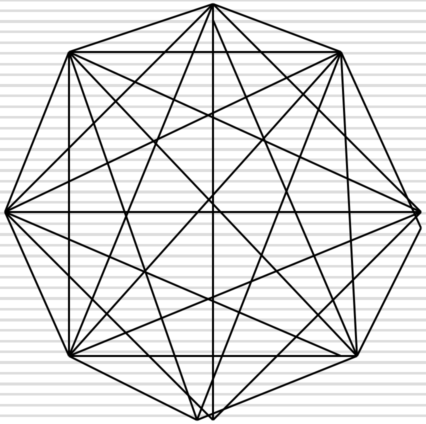
Adjacency matrix (weighted):

$$\begin{array}{c|ccccccc} & 1 & 2 & 3 & 4 & 5 & 6 & \ldots\ldots\ldots\ldots711 \\ 1 & 0 & 0 & 0 & 17 & 0 & 4 & \ldots\ldots\ldots\ldots \\ 2 & 0 & 0 & 0 & 0 & 0 & 0 & \ldots\ldots\ldots\ldots \\ 3 & 0 & 0 & 0 & 0 & 15 & 0 & \ldots\ldots\ldots\ldots \\ 4 & .. & \ldots & \ldots & \ldots. & & & \\ 5 & .. & \ldots & \ldots & \ldots & & & \\ 6 & .. & \ldots. & \ldots & \ldots & & & \\ .. & \ldots & \ldots & \ldots & \ldots & & & \\ .. & \ldots & \ldots & \ldots & \ldots. & & & \\ 711 & & & & & & & \end{array}$$



miRNA network (*schematic*).

miRNA-miRNA Co-target Network



0 41 45 36 51 56 47 45 46 64 48 37 46……
41 0 36 27 33 35 20 36 20 33 30 33 25…….
45 36 0 34 39 47 33 68 36 49 36 33 46……
36 27 34 0 25 40 24 44 46 35 36 33 28……
..
.. **Actual Matrix** (711 × 711)
..
..
..
61 28 33 37 69 59 30 42 52 44 41 40 53….

=C

- Fully connected, undirected, weighted network.
- miR-17 & miR-20b = **1253** (max), *identical seed* ***AAAGUGC***
- miR-944 &miR-346)=1 (min)
- ***most of the links could be erased***.

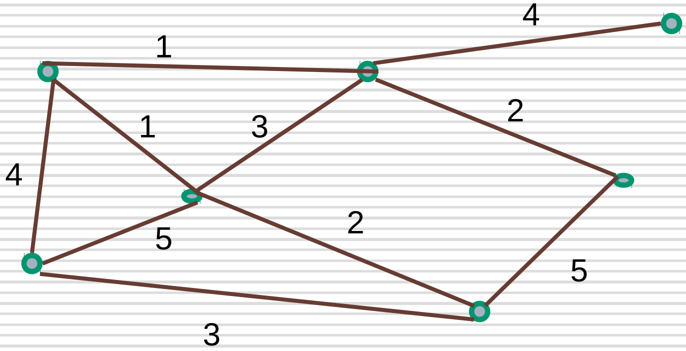
Erase “enough” such that ……………..

- all *not-so important links* are lost

  (thus network is simple)

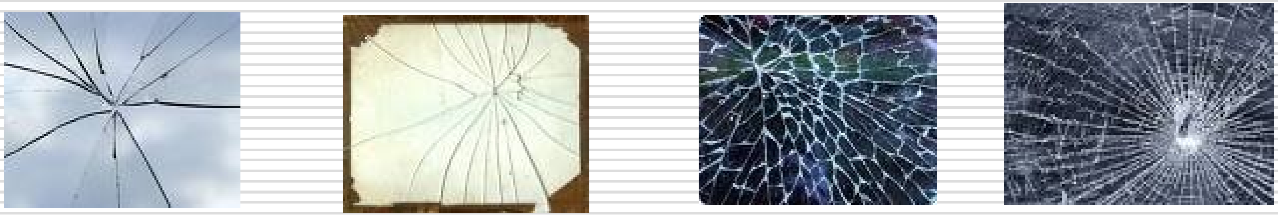
- *important links* are not erased

  (functions are preserved !!)



Erase all links having weight <q (Nq)	**No of Disconnected Sub-graphs**
1	1
2	1
3	3
4	5

Representation of miRNA network



Actual steps:

- Erase all links with weight < *q*
- New adjacency matrix :

$$C_{ij}^{q} = \begin{cases} 0 & \text{if } C_{ij} < q \\ 1 & \text{otherwise} \end{cases}$$

- Count number of disconnected sub graphs (   )

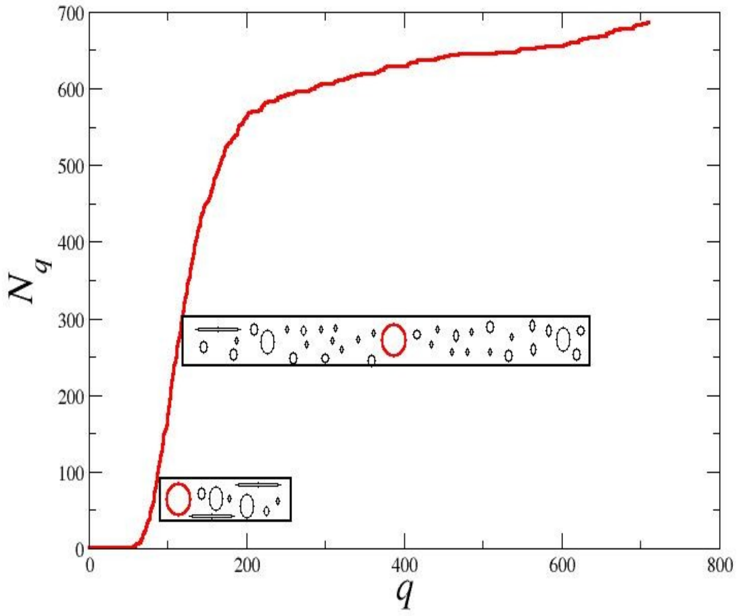
N_q

- = Number of diagonal blocks of .
- N_q Vary *q* and find as a function of *q* C_{ij}^{q}

N_q

And the result…

- **Small *q* :** link with little weight are erased (network is not affected)
- **Large *q* :** high-weight links (probably the important ones) are erased
- **Optimal *q=q** :** when one starts loosing important connections



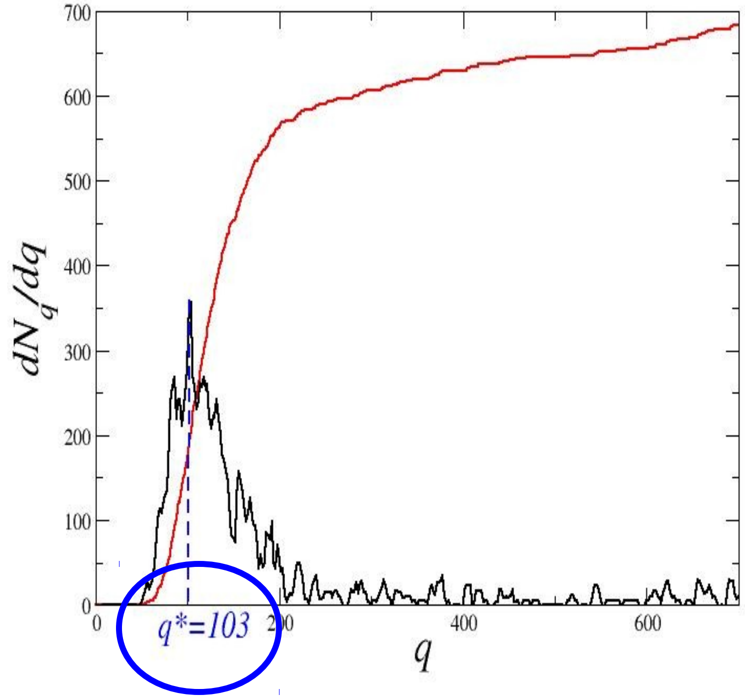
Why Nq changes rapidly at q* ?

Change in N_q

- $\frac{dN_q}{dq}$ measures change in N_q

- *Maximum at say q=q**

- *q*= 103*



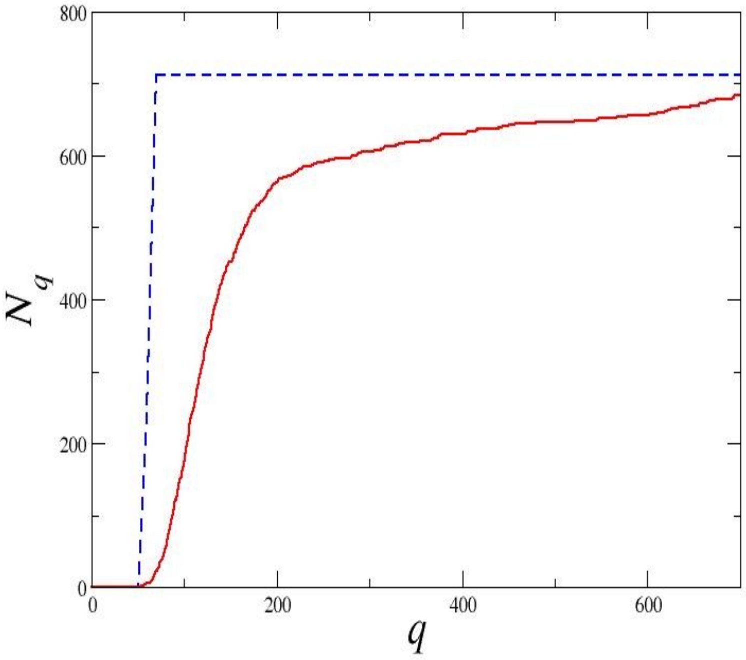
Comparison with a random graph

C=

0 41 45 36 51 56 47 45 46 64 48 37 46……
41 0 36 27 33 35 20 36 20 33 30 33 25…….
45 36 0 34 39 47 33 68 36 49 36 33 46……
36 27 34 0 25 40 24 44 46 35 36 33 28……
..
.. **Actual Matrix** (711 × 711)
..
..
..
61 28 33 37 69 59 30 42 52 44 41 40 53……

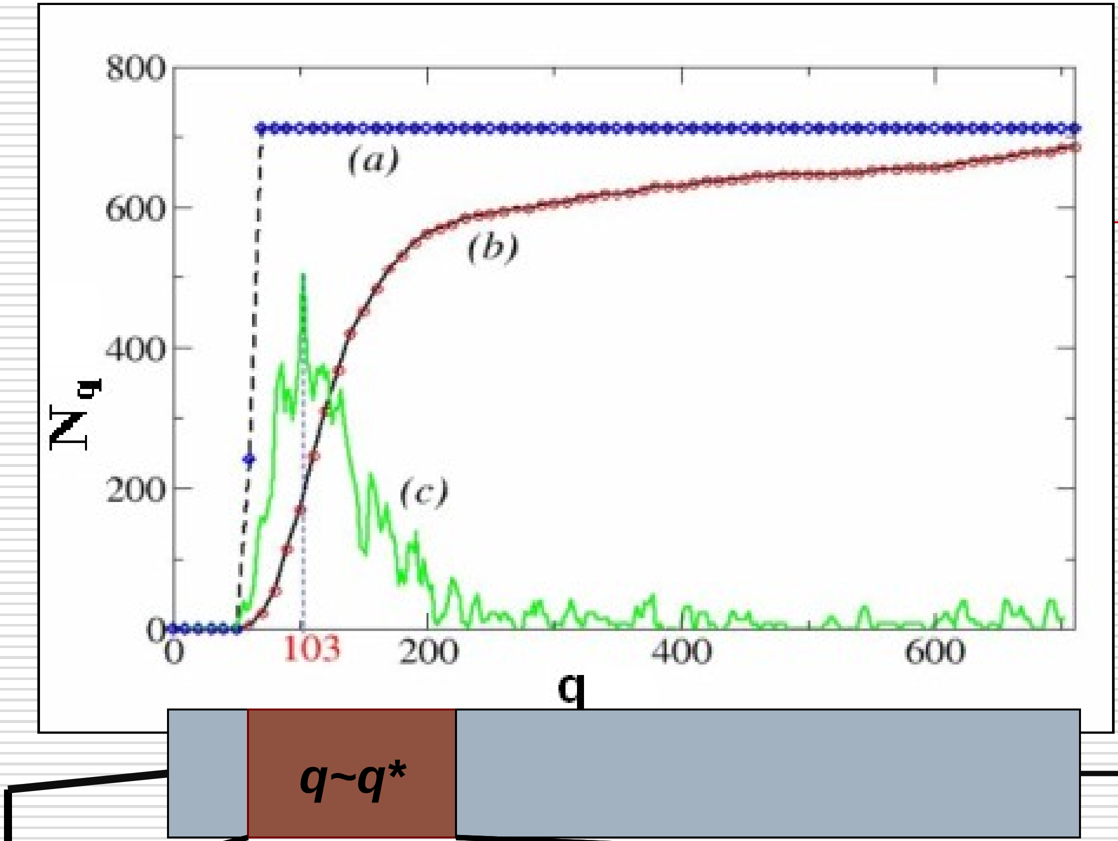
- Another matrix R, so that

$$\sum_{i}^{N}\sum_{j=i+1}^{N} R_{ij} = \sum_{i}^{N}\sum_{j=i+1}^{N} C_{ij}$$



The miRNA co-target network is not JUST another random graph !!

Optimally relevant miRNAs



(a) → Random symmetric graph with 711 nodes and total weight 676265.

(b) → miRNA co-target network

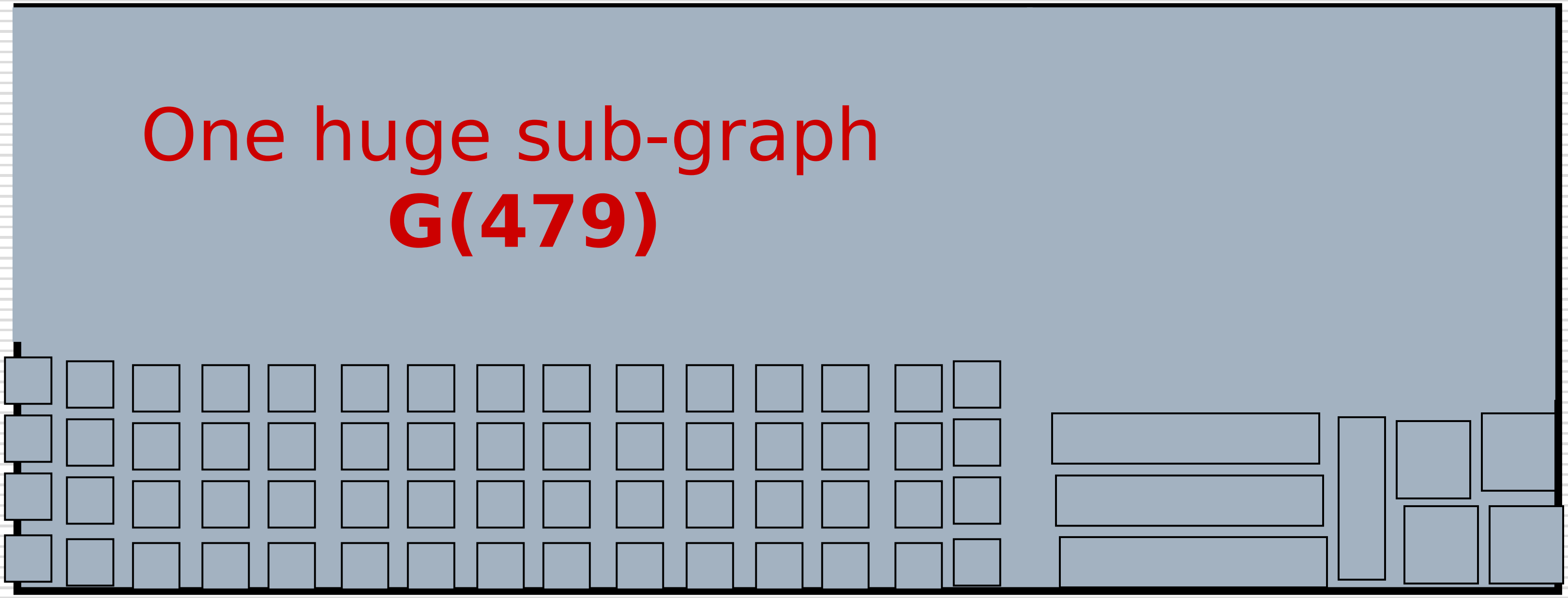
(c) → dN_q/dq

Relevant connections are not erased !! miRNAs form clusters due to **possible functional similarity**. Optimal cut-off q*=103 (where dNq/dq is maximum)

Network is quite **“stiff”,** not affected until threshold q* is reached)

Important connections are erased. Sub-graphs are due to **seed sequence similarity** ?

Optimal : $q^*=103$, $N_q=166$



One huge sub-graph

G(479)

128 single miRNA

37 small clusters (104)

G(479) is the important sub-graph

Proof : G(479) is crucial

- Take a disease :(Autism)
- Associated miRNAs (*from experiments*)=29

  miR-484 miR-21 miR-212 miR-598 miR-95 miR-129-3p miR-129-5p miR-431 miR-7 miR-15a miR-27a miR-15b miR-148b miR-132 miR-128a miR-93 miR-106a miR-539 miR-652 miR-550 miR-432 miR-193b miR-181d miR-146b-3p miR-146b-5p miR-140-3p miR-140-5p miR-381 miR-106b
- Ask how many are in G (479)? Ans : 24 = **83%**
- Ask the same for other diseases:

Schizophrenia	**86%**	Heart failure	**83%**	Diabetes	**76%**
Overian Cancer	**76%**	AML	**76%**	Breast Cancer	**82%**
Colon Cancer	**68%**	Lung Cancer	**72%**	Pancreas Cancer	**73%**
Prostate Cancer	**86%**	Stomach Cancer	**72%**	HNC	**85%**
Thyroid Cancer	**78%**	CLL	**83%**	Glioblastoma	**82%**

How are miRNAs organized in *G*(479) ?

G(479)

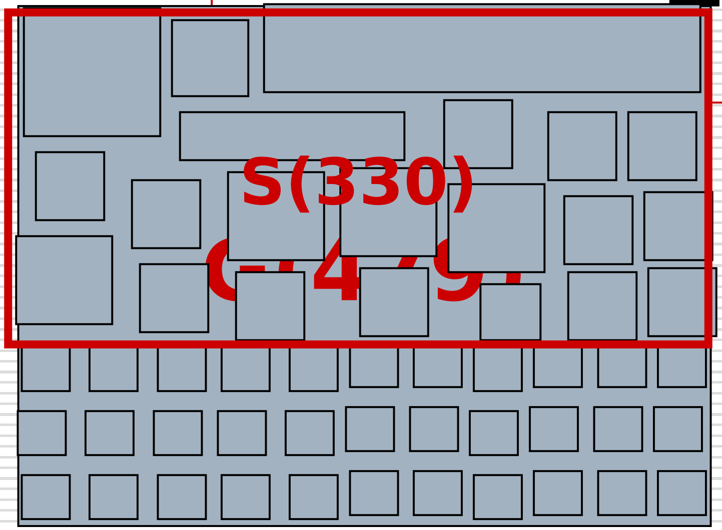
Increase q to ~160 (*find clusters*)

-those which are clustered
at q=160 must be in
clustered form at q=103

How are miRNAs organized in *G*(479) ?

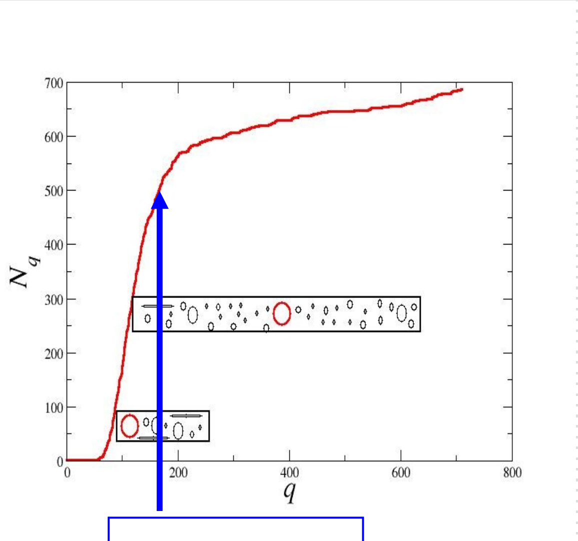
- G (479)= 149 single miRNA

  \+ 70 clusters (330)



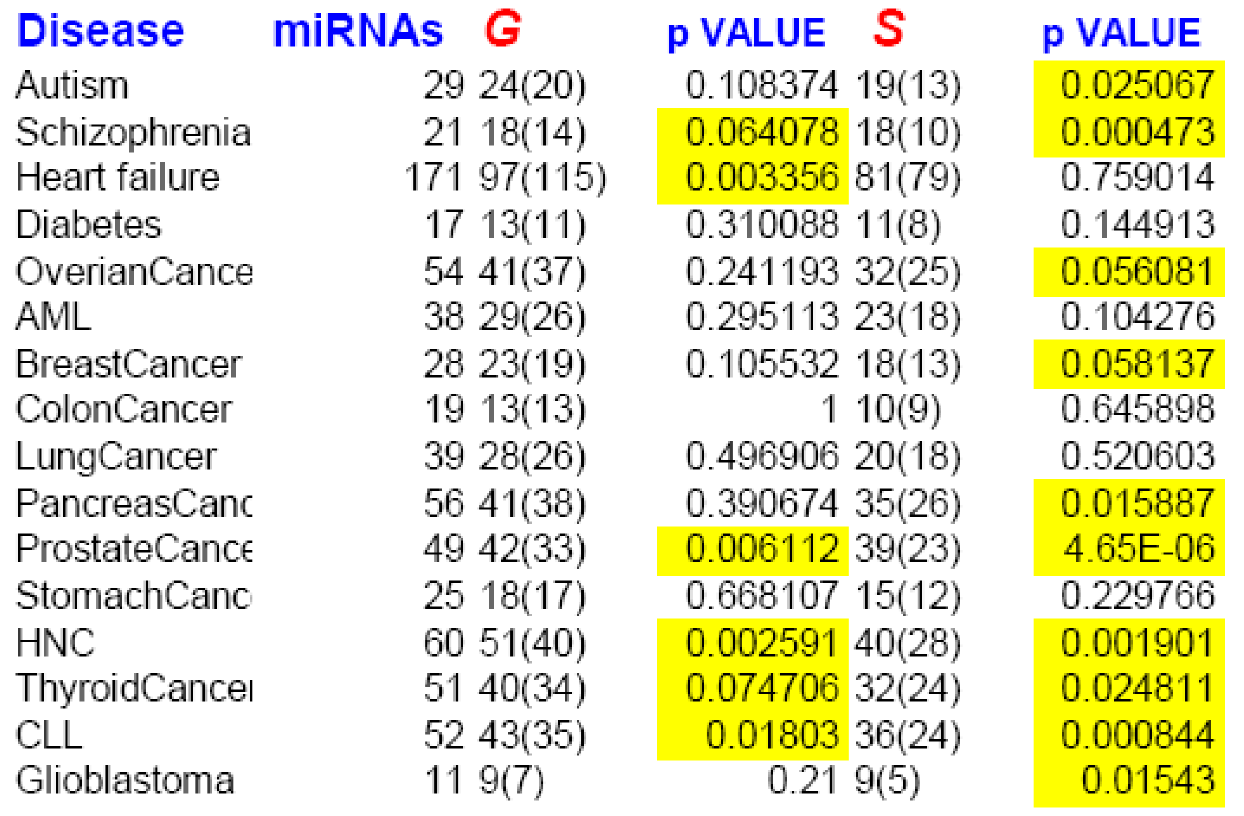
70 clusters (330)

149 single miRNA



q=160

Smaller is better than larGer ?



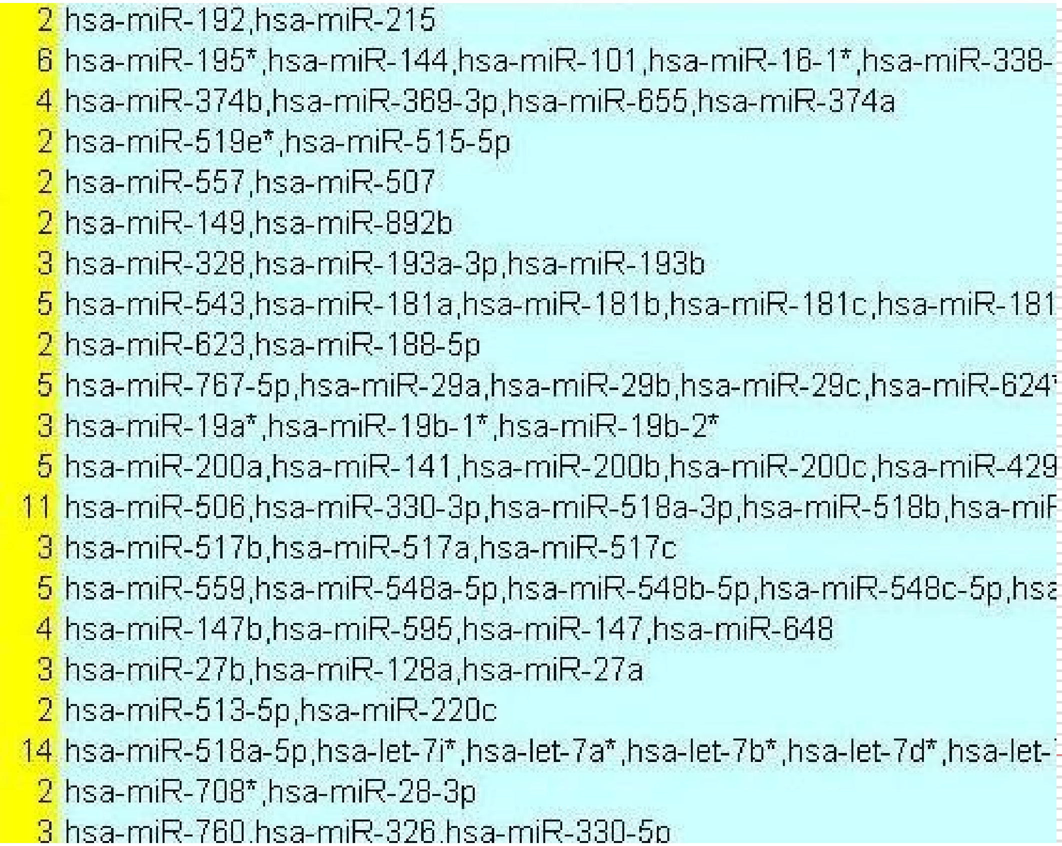
Disease	**miRNAs**	***G***	**p VALUE**	***S***	**p VALUE**
Autism	29	24(20)	0.108374	19(13)	0.025067
Schizophrenia	21	18(14)	0.064078	18(10)	0.000473
Heart failure	171	97(115)	0.003356	81(79)	0.759014
Diabetes	17	13(11)	0.310088	11(8)	0.144913
OverianCance	54	41(37)	0.241193	32(25)	0.056081
AML	38	29(26)	0.295113	23(18)	0.104276
BreastCancer	28	23(19)	0.105532	18(13)	0.058137
ColonCancer	19	13(13)	1	10(9)	0.645898
LungCancer	39	28(26)	0.496906	20(18)	0.520603
PancreasCanc	56	41(38)	0.390674	35(26)	0.015887
ProstateCance	49	42(33)	0.006112	39(23)	4.65E-06
StomachCanc	25	18(17)	0.668107	15(12)	0.229766
HNC	60	51(40)	0.002591	40(28)	0.001901
ThyroidCance	51	40(34)	0.074706	32(24)	0.024811
CLL	52	43(35)	0.01803	36(24)	0.000844
Glioblastoma	11	9(7)	0.21	9(5)	0.01543

Yes.

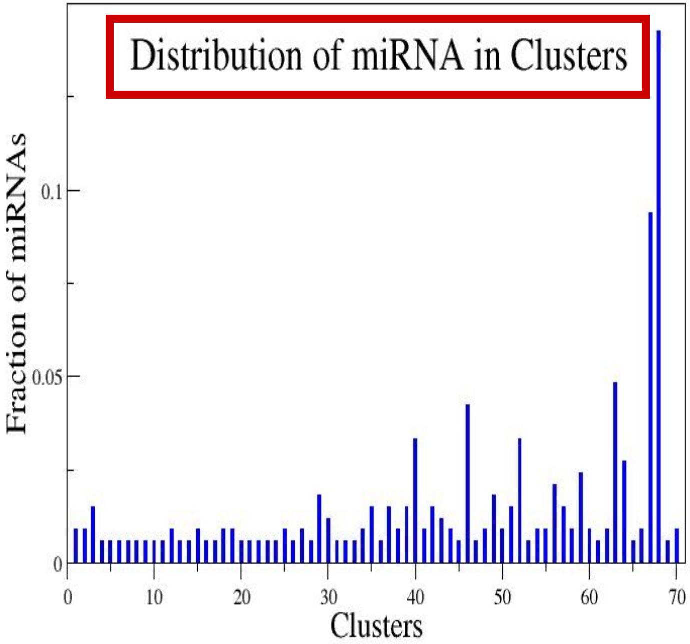
Further study ….

….only with S(330)

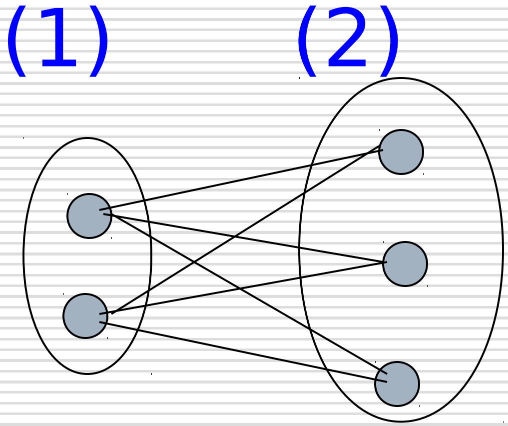
What are the clusters in S(330)



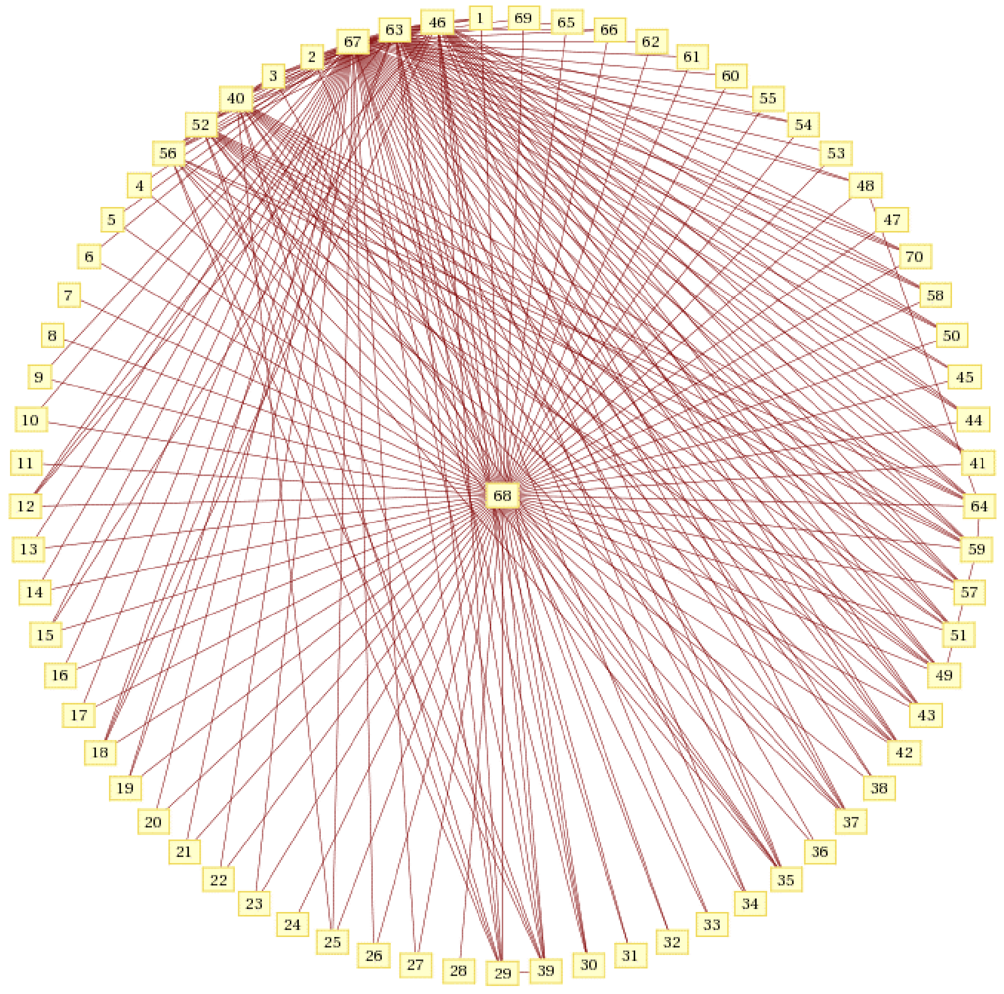
2	hsa-miR-192,hsa-miR-215
6	hsa-miR-195*,hsa-miR-144,hsa-miR-101,hsa-miR-16-1*,hsa-miR-338-
4	hsa-miR-374b,hsa-miR-369-3p,hsa-miR-655,hsa-miR-374a
2	hsa-miR-519e*,hsa-miR-515-5p
2	hsa-miR-557,hsa-miR-507
2	hsa-miR-149,hsa-miR-892b
3	hsa-miR-328,hsa-miR-193a-3p,hsa-miR-193b
5	hsa-miR-543,hsa-miR-181a,hsa-miR-181b,hsa-miR-181c,hsa-miR-181
2	hsa-miR-623,hsa-miR-188-5p
5	hsa-miR-767-5p,hsa-miR-29a,hsa-miR-29b,hsa-miR-29c,hsa-miR-624
3	hsa-miR-19a*,hsa-miR-19b-1*,hsa-miR-19b-2*
5	hsa-miR-200a,hsa-miR-141,hsa-miR-200b,hsa-miR-200c,hsa-miR-429
11	hsa-miR-506,hsa-miR-330-3p,hsa-miR-518a-3p,hsa-miR-518b,hsa-mi
3	hsa-miR-517b,hsa-miR-517a,hsa-miR-517c
5	hsa-miR-559,hsa-miR-548a-5p,hsa-miR-548b-5p,hsa-miR-548c-5p,hsa
4	hsa-miR-147b,hsa-miR-595,hsa-miR-147,hsa-miR-648
3	hsa-miR-27b,hsa-miR-128a,hsa-miR-27a
2	hsa-miR-513-5p,hsa-miR-220c
14	hsa-miR-518a-5p,hsa-let-7i*,hsa-let-7a*,hsa-let-7b*,hsa-let-7d*,hsa-let-
2	hsa-miR-708*,hsa-miR-28-3p
3	hsa-miR-760,hsa-miR-326,hsa-miR-330-5p



Network of clusters



- Weight of link (1) and (2) = sum of (*six*) we

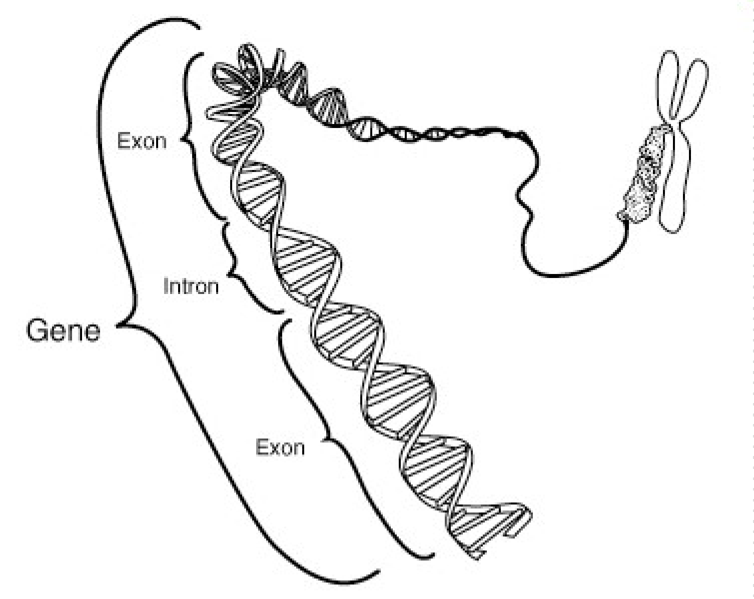


Cluster with more miRNA have more links (as expected)

Biological relevance ?

Why cluster ?

Some obvious answers :



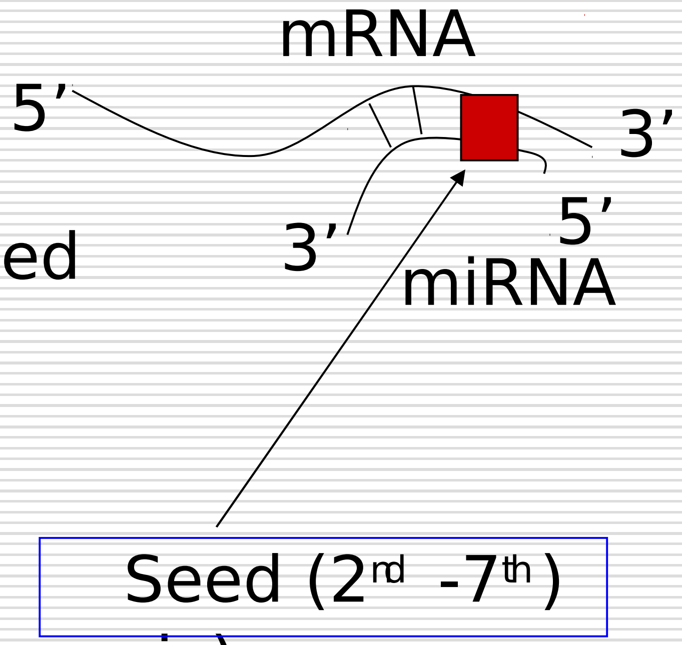
- Inter-genomic ?

  If miRNAs come from the introns of the same gene ?

Ans :11 of 70 (within 10Kbp)

- Seed similarity ?

  Two miRNA having similar seed are likely to cluster



- Ans : 18 of 70

(5 clusters =

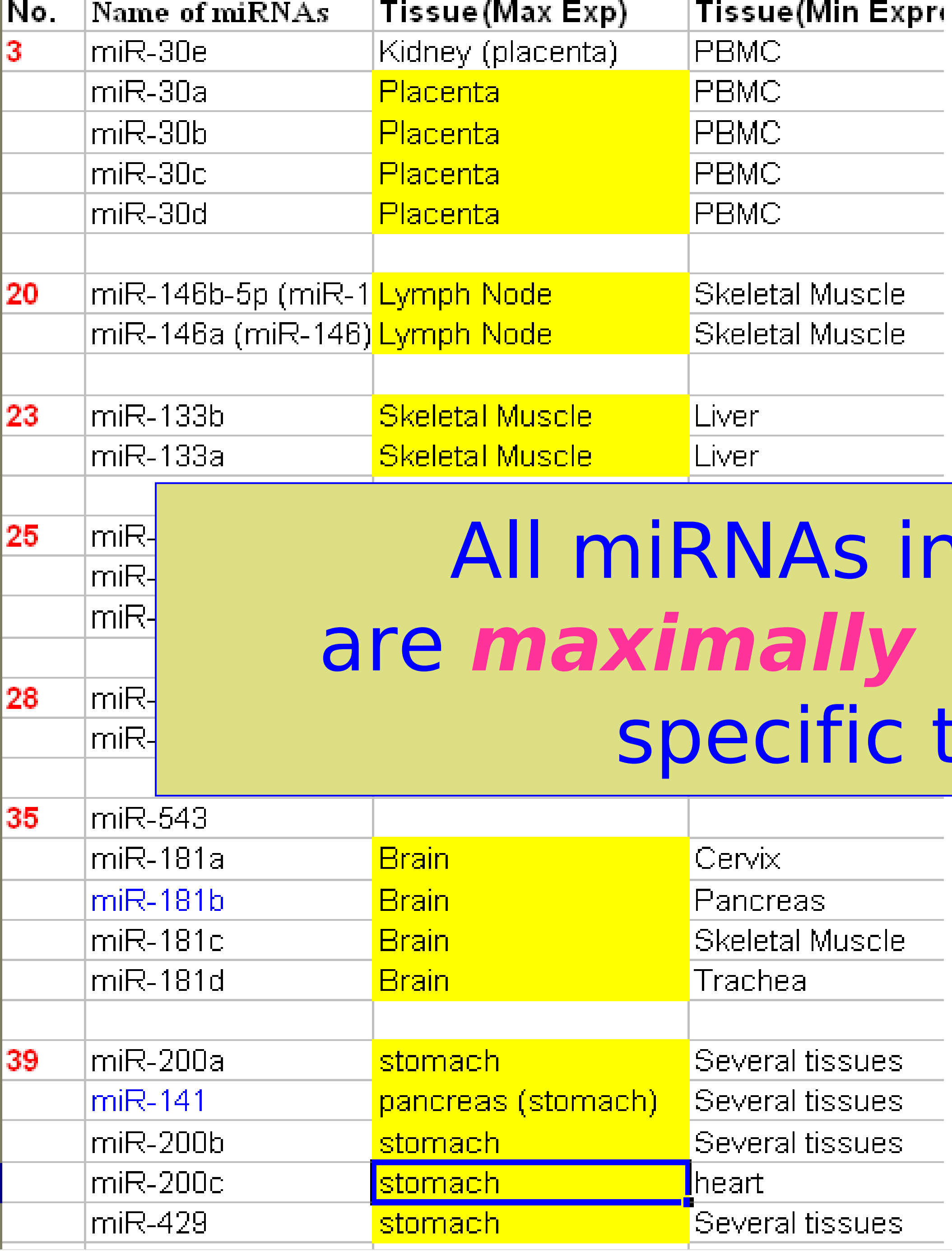
both seed seq. and inter-genomic)

Basis of clustering !!

- 47 of 70 has at least one relevant pathway
- (a)Seed sequence 18
- (b) Inter-genic 11
- Common (a),(b) 5

- Clustering due to seed sequence is unlikely
- Intergenic : may be
- Mostly : Functional, Functional !!

Tissue specificity



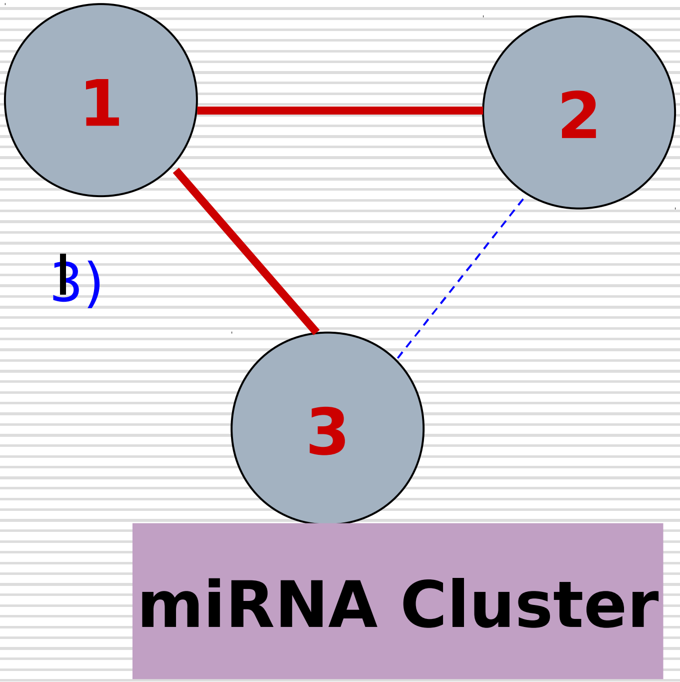
No.	Name of miRNAs	Tissue(Max Exp)	Tissue(Min Expr
3	miR-30e	Kidney (placenta)	PBMC
	miR-30a	Placenta	PBMC
	miR-30b	Placenta	PBMC
	miR-30c	Placenta	PBMC
	miR-30d	Placenta	PBMC
20	miR-146b-5p (miR-1	Lymph Node	Skeletal Muscle
	miR-146a (miR-146)	Lymph Node	Skeletal Muscle
23	miR-133b	Skeletal Muscle	Liver
	miR-133a	Skeletal Muscle	Liver
25	miR-		
	miR-		
	miR-		
28	miR-		
	miR-		
35	miR-543		
	miR-181a	Brain	Cervix
	miR-181b	Brain	Pancreas
	miR-181c	Brain	Skeletal Muscle
	miR-181d	Brain	Trachea
39	miR-200a	stomach	Several tissues
	miR-141	pancreas (stomach)	Several tissues
	miR-200b	stomach	Several tissues
	miR-200c	stomach	heart
	miR-429	stomach	Several tissues

All miRNAs in a cluster are ***maximally*** expressed in specific tissue.

Are clusters pathway specific ?

A= Target genes of 1U2U3

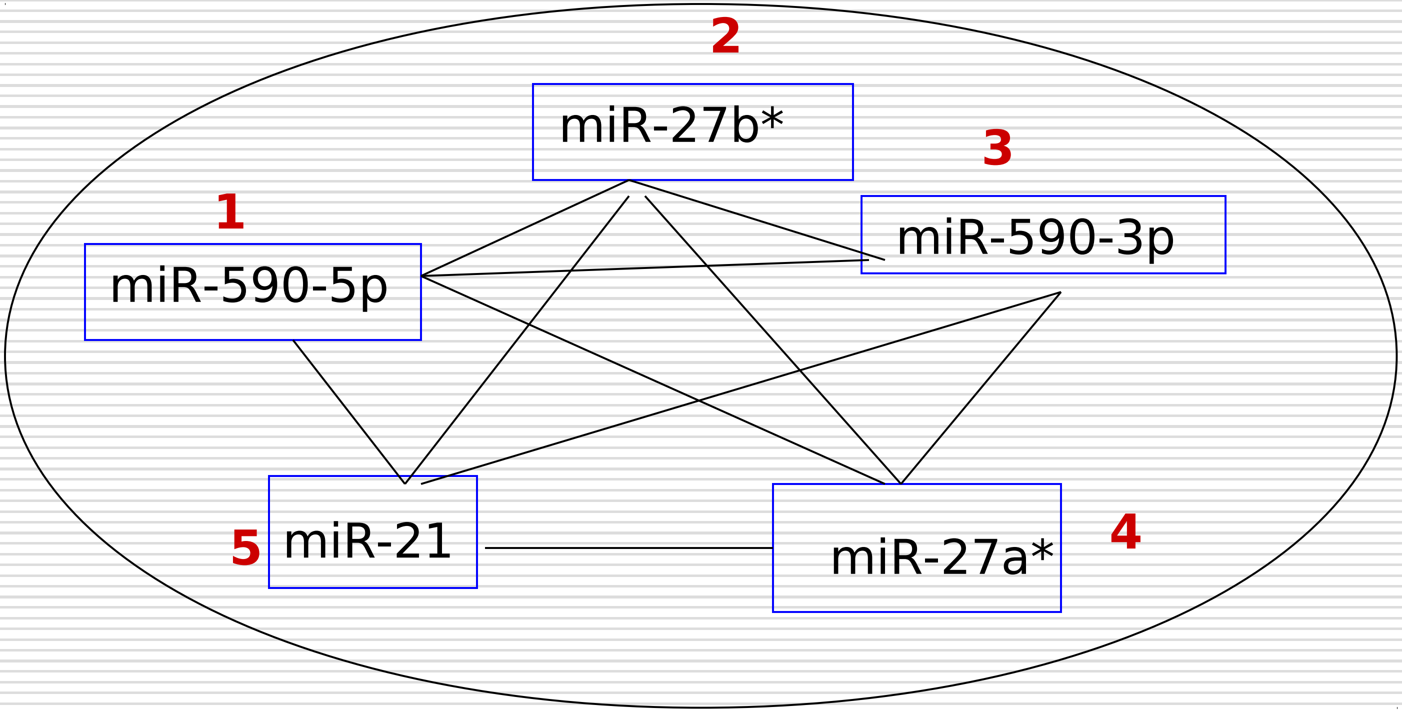
B= Target gene of (1 I 2) U (1 I 3) U(2 I 3)



Compare significant pathways for **B** compared to **A**

Example :

A= Target genes of 1U2U3U4U5**= 1395**



B= target gene of (1 | 2) U (1 |3) U(1 |4) U (of all pairs) **=139**

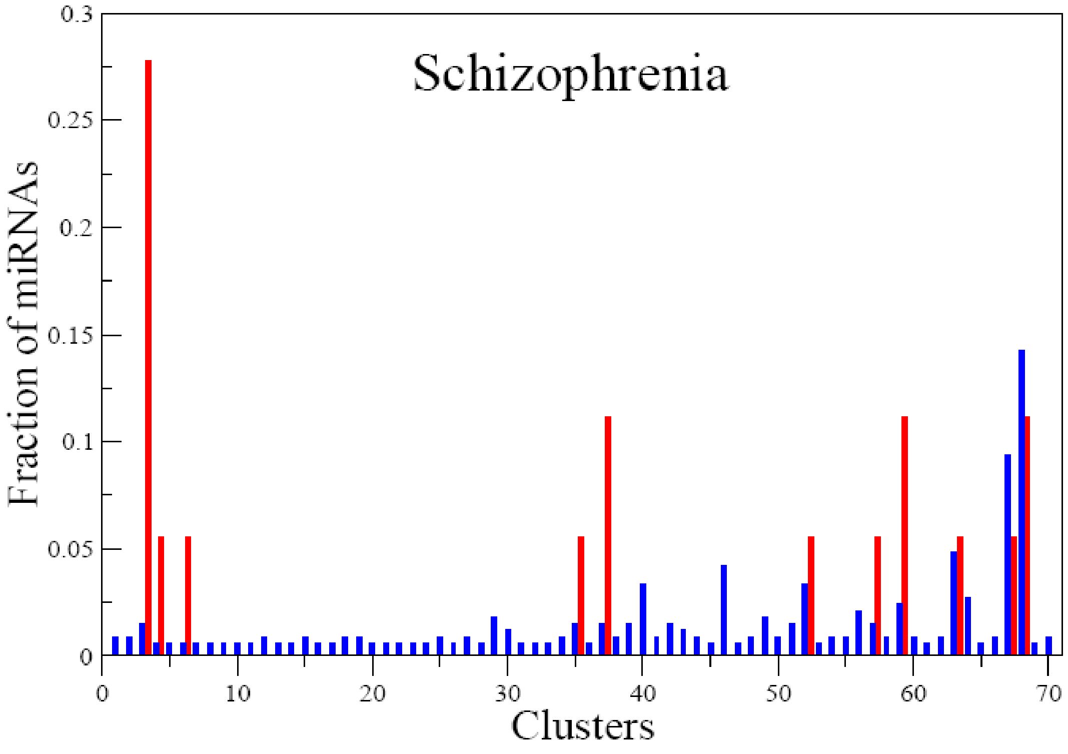
Compare significant pathways for **B** compared to **A**

The significant pathways (**Table-I**)....

Clusters of of miRNAs	**Biological Pathways**
miR-125b, miR-125a-5p	PDGF signaling pathway (P00047)
miR-543,miR-181a,miR-181b,miR-181c, miR-181d	Wnt signaling pathway (P00057), p38 MAPK pathway (P05918), p53 pathway feedback loops 2 (P04398)
miR-27b,miR-128a,miR-27a	Heterotrimeric G-protein signaling pathway-Gi alpha and Gs alpha mediated pathway (P00026), Metabotropic glutamate receptor group III pathway (P00039), Heterotrimeric G-protein signaling pathway-Gq alpha and Go alpha mediated pathway (P00027), Thyrotropin-releasing hormone receptor signaling pathway(P04394), Metabotropic glutamate receptor group II pathway (P00040)
miR-27b*,miR-590-3p,miR-590-5p,miR-21, miR-27a*	Androgen/estrogene/progesterone biosynthesis(P02727), FAS signaling pathway (P00020), Apoptosis signaling pathway (P00006)
miR-363*,miR-25,miR-32,miR-363,miR-367,miR-92a,miR-92b,miR-566	Oxidative stress response(P00046), Angiogenesis(P00005**)**, Alzheimer disease-presenilin pathway (P00004), p38 MAPK pathway (P05918), 5HT4 type receptor mediated signaling pathway (P04376)
miR-331-3p,miR-146b-3p,miR-18b*,miR-18a*, miR-324-5p,miR-874,miR-324-3p, miR-10a, miR-10b	Huntington disease (P00029), Alpha adrenergic receptor signaling pathway (P00002), Axon guidance mediated by netrin (P00009), Heterotrimeric G-protein signaling pathway-Gq alpha and Go alpha mediated pathway (P00027)

Are diseases cluster specific ?

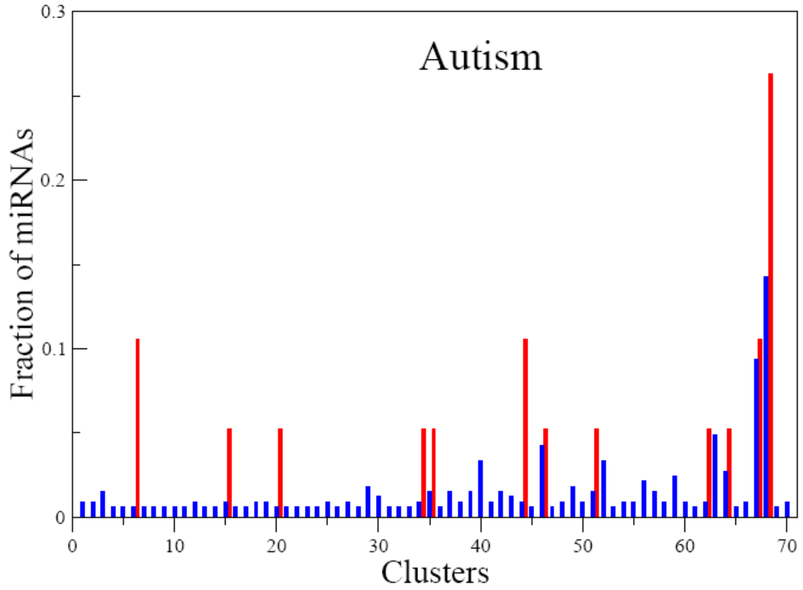
- ☐ Schizophrenia (21)
- ☐ 18 in G
- ☐ 14 in S
- ☐ How are 14 miRNAs distributed in clusters ?



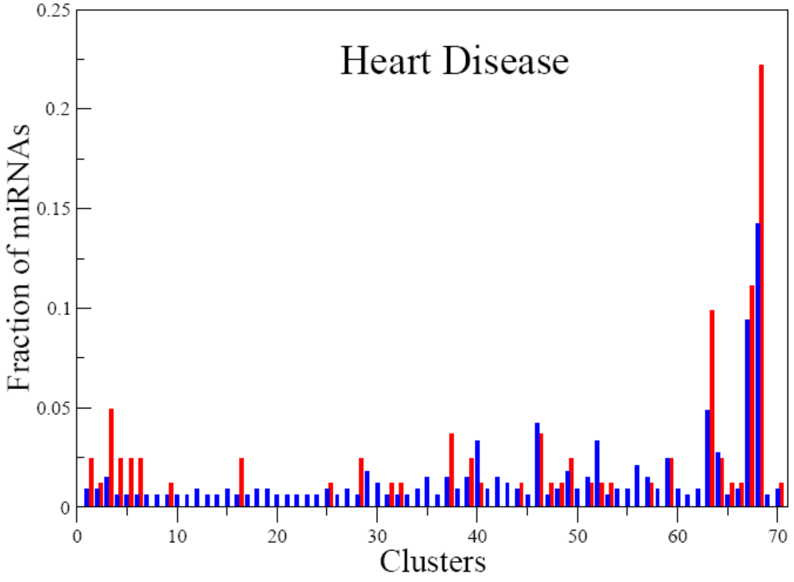
- Schizophrenia: 3, 4, 6, 35, 37, 52, 57, 59

☐**YES :** Schezophrenia (**cluster 3** =miR-30a,b,c,d,e)

Continues….

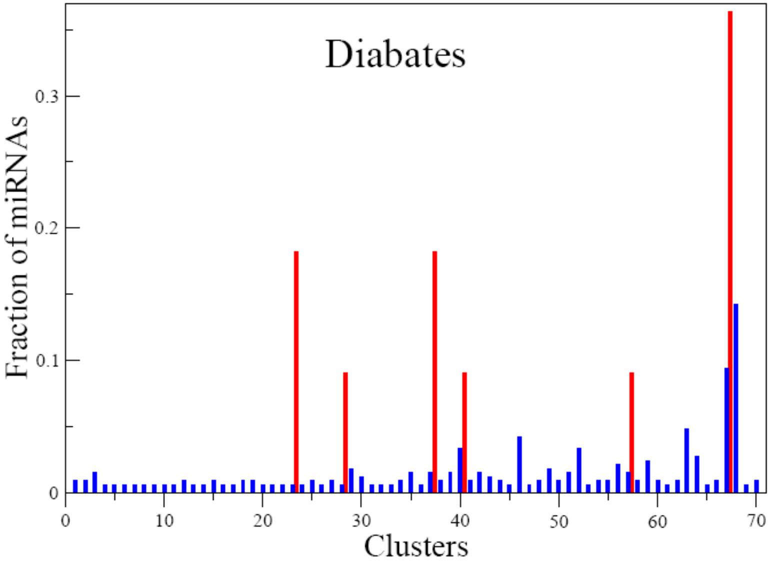


- Autism : 6, 15, 20, 34, 35, 44, 51, 62, 64, 68

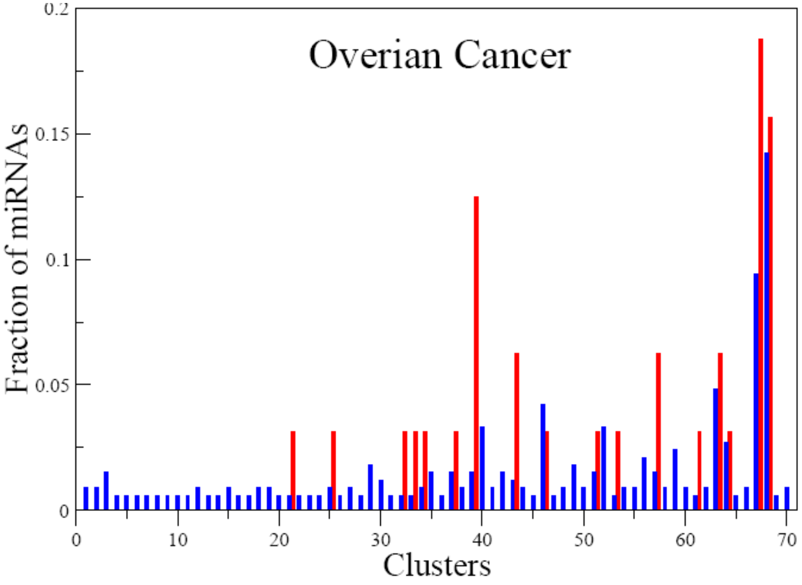


- Heart Disease: 1, 3, 4, 5, 6, 16, 28, 37, 63, 68

Continues….

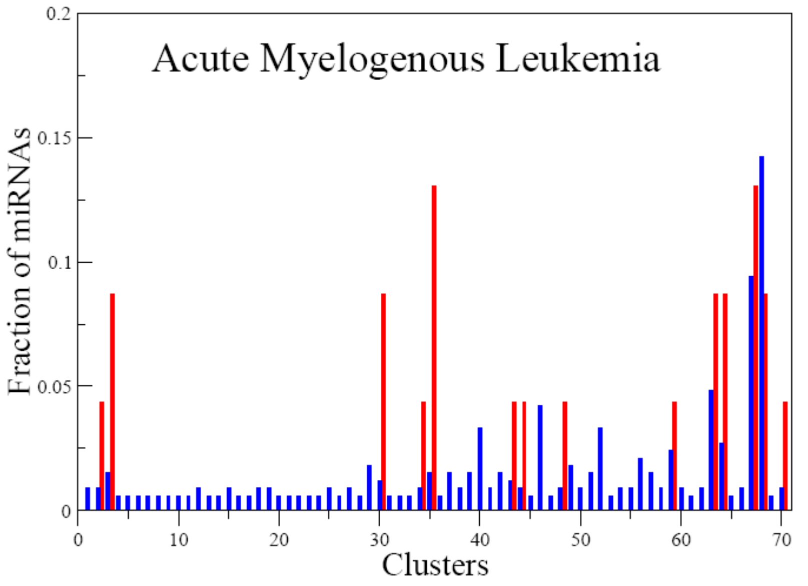


- Diabetes: 23, 28, 37, 40, 57, 67

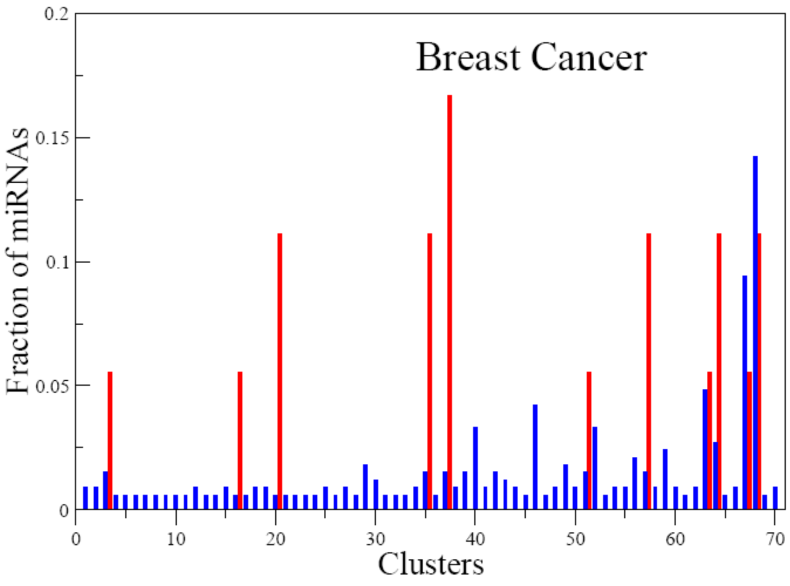


- Overian Cancer :21, 25, 32, 33, 34, 37, 39, 43, 51, 53, 57, 61, 67

Continues….

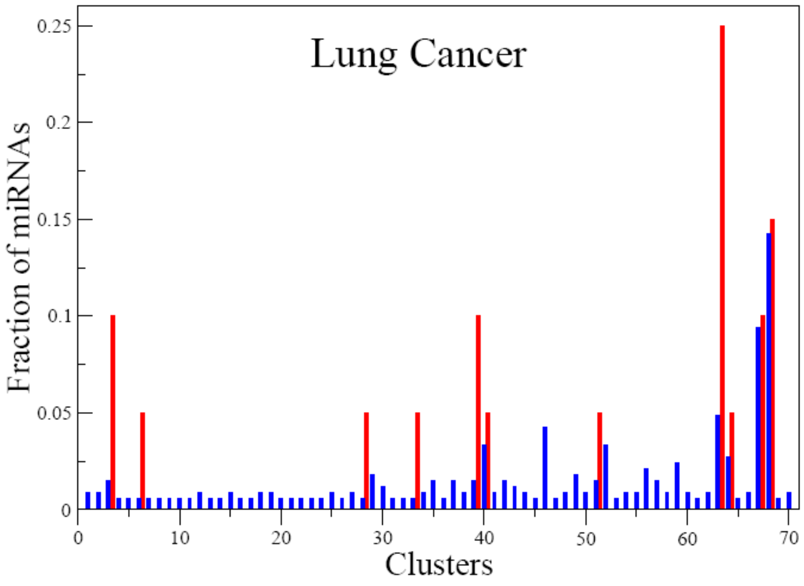


- Acute Myelogenous Leukemia (AML) :2, 3, 30, 34, 35, 43, 44, 48, 59, 63, 64, 67, 70

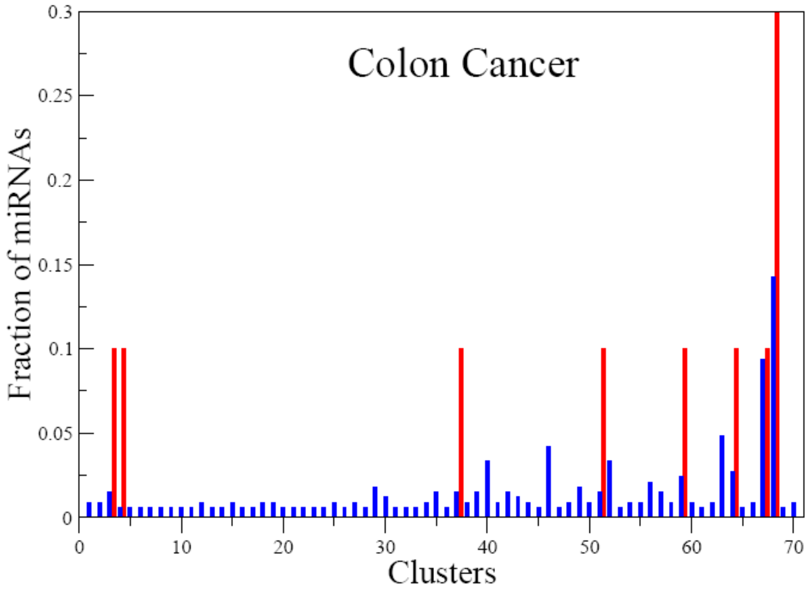


- Breast Cancer: 3, 16, 20, 35, 37, 51, 57, 64

Continues….

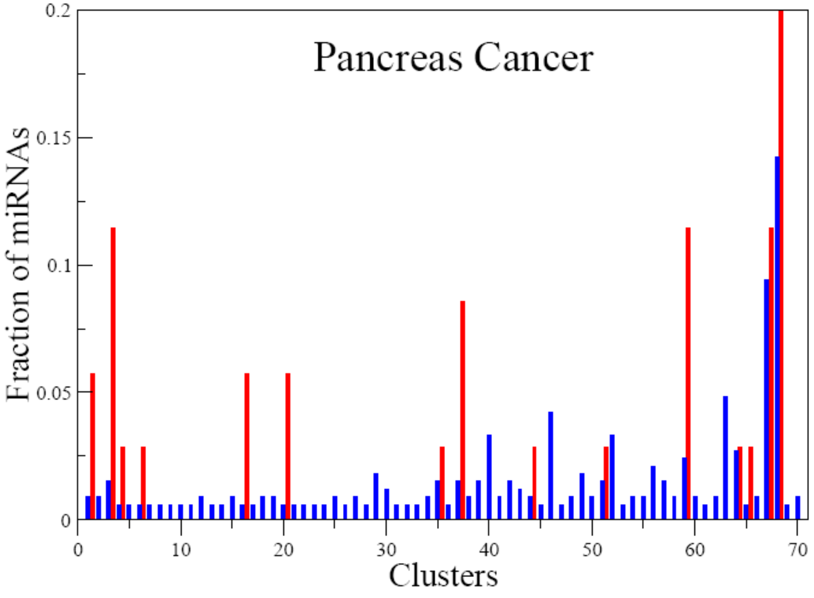


- Lung Cancer :3, 6, 28, 33, 39, 51, 63, 64

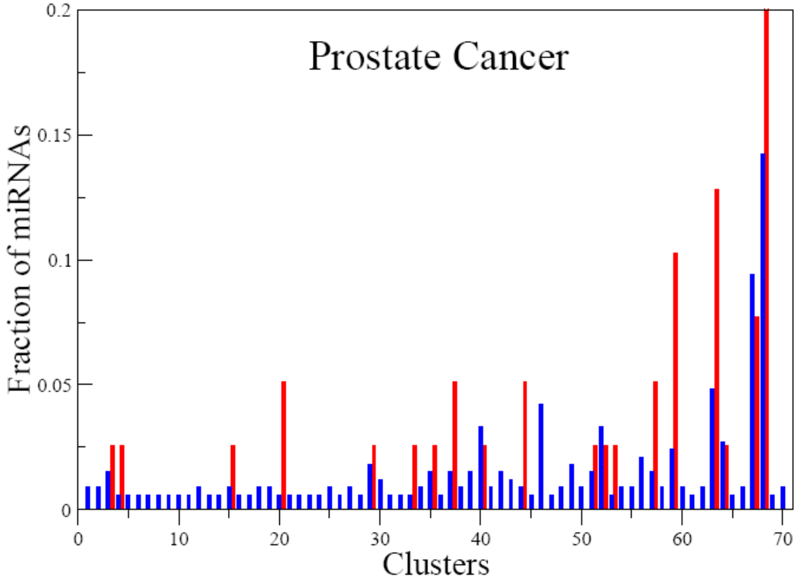


- Colon Cancer: 3, 4, 37, 51, 59, 64, 68

Continues….

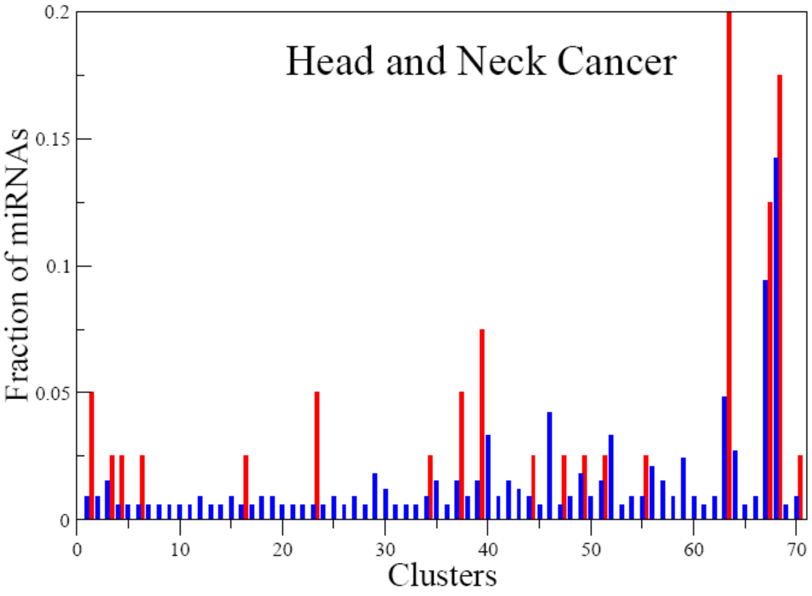


- Pancreas Cancer :1, 3, 4, 6, 16, 20, 37, 44, 59, 65, 68



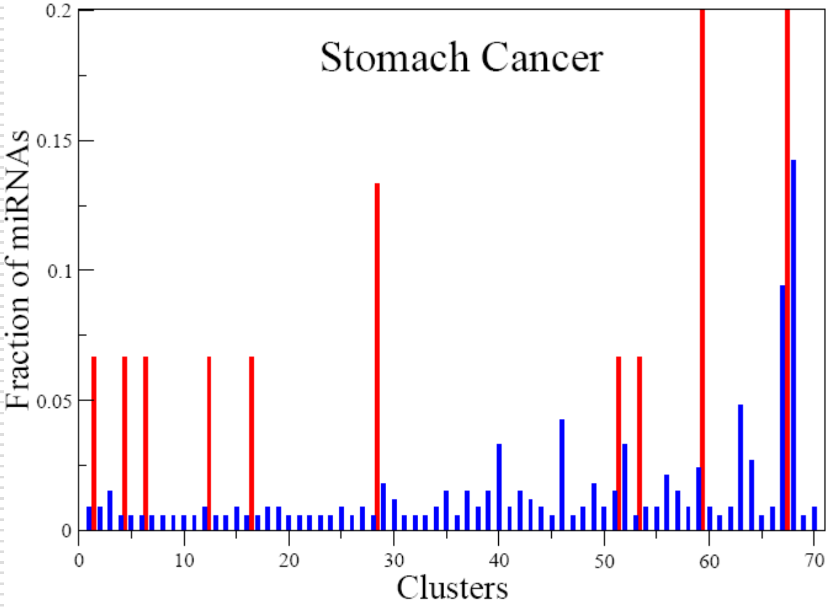
- Prostate Cancer: 4, 15, 20, 33, 37, 44, 53, 57, 59, 63, 68

Continues….



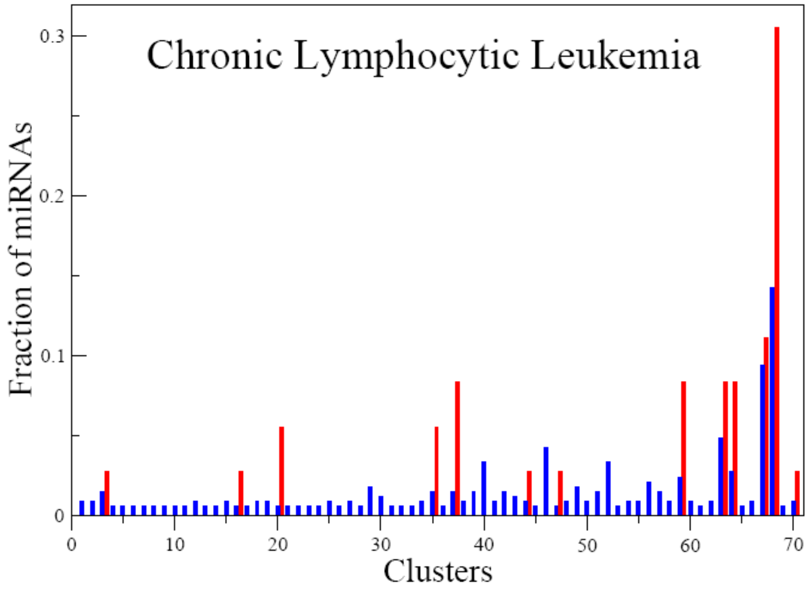
a the random distribution of miRNAs

- Head and Neck Cancer :1, 4, 6, 16, 23, 34, 37, 39, 44, 47, 55, 63, 70

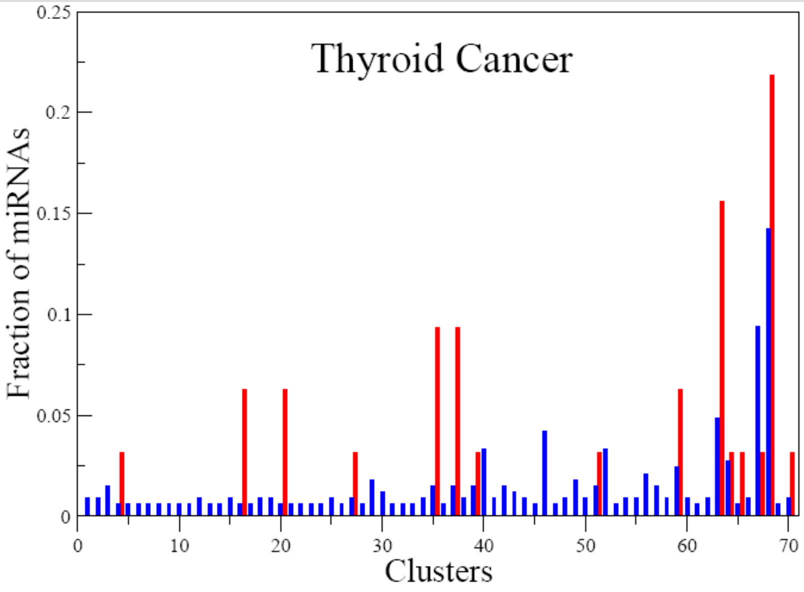


- Stomach Cancer :1, 4, 6, 12, 16, 28, 51, 53, 59, 67

Continues….

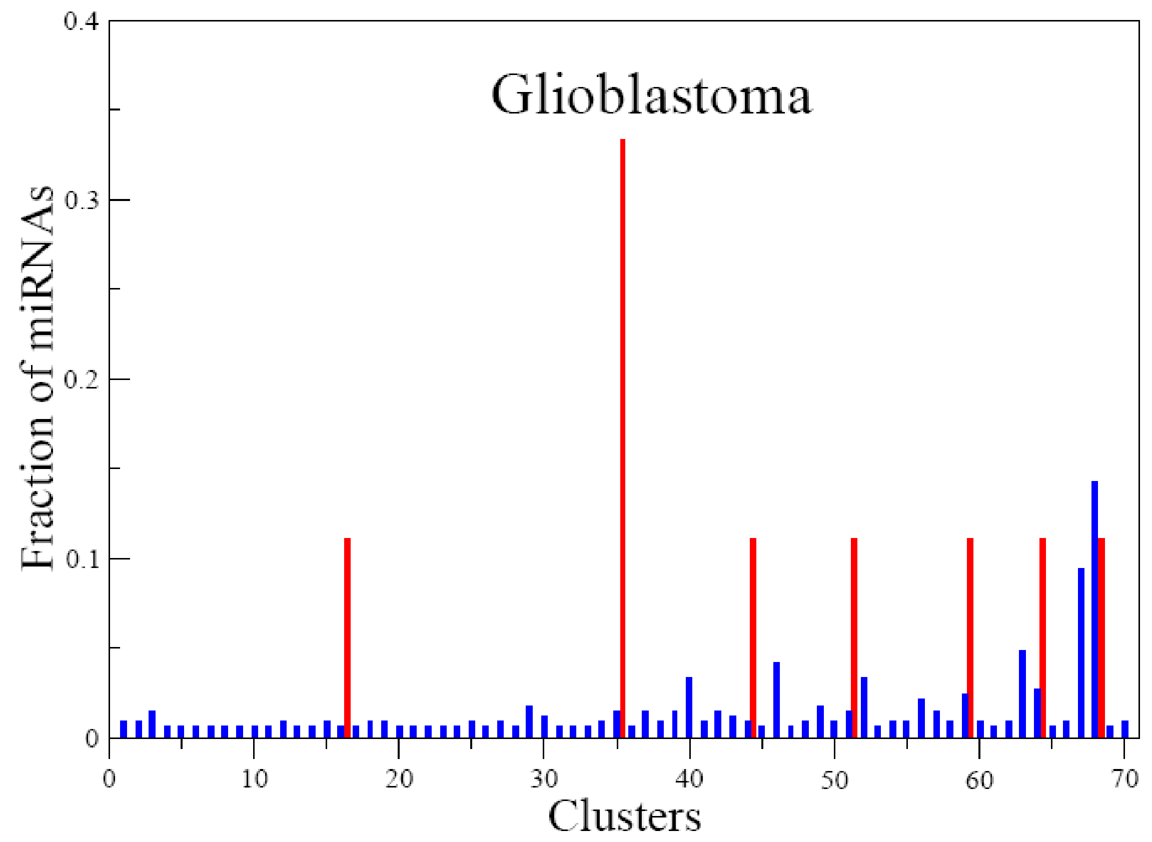


- Chronic Lymphocytic Leukemia :16, 20, 35, 37, 44, 47, 59, 63, 64, 68, 70



- Thyroid Cancer :4, 16, 20, 27, 35, 37, 39, 51, 59, 63, 65, 68, 70

Continues….



- Glioblastoma : 16, 35, 44, 51, 59, 64

Predictions ?

The prediction…………

and verification

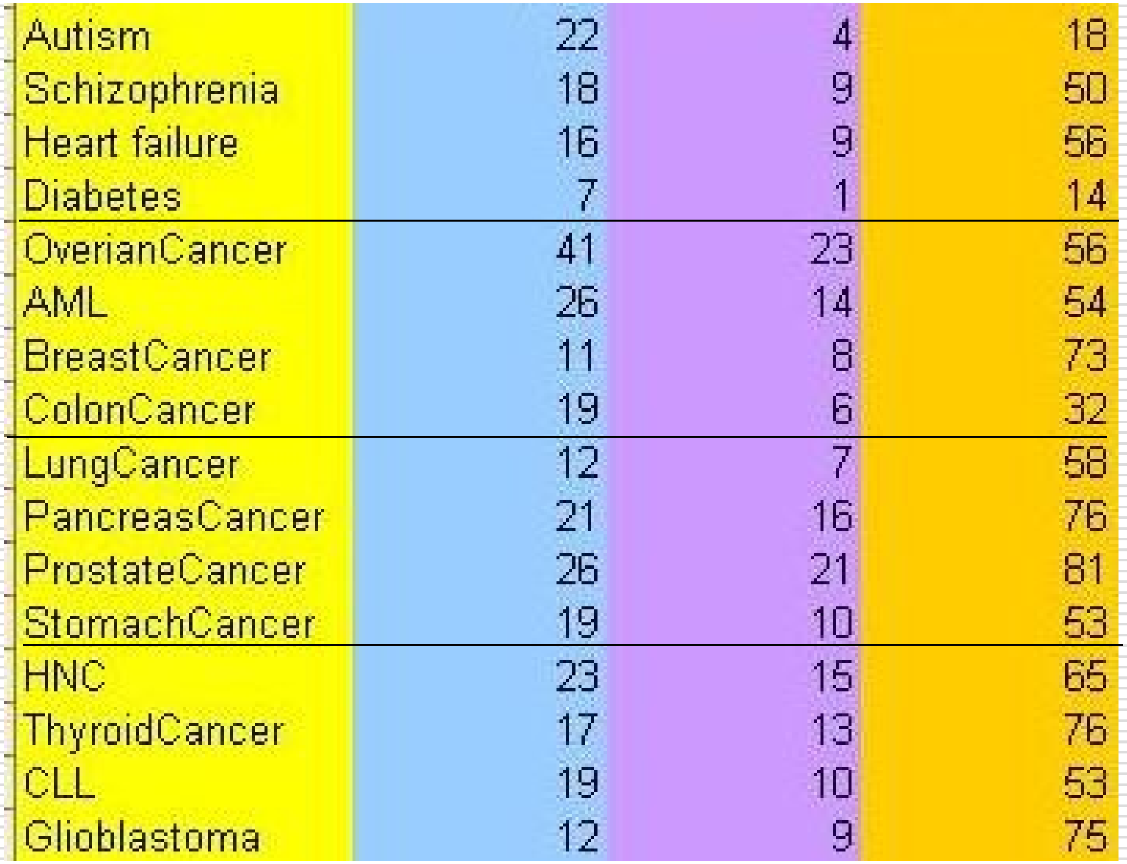
- Take a disease
- Find miRNAs in S(330)
- Find corresponding clusters
- **Prediction :**

  Read pathways (*Q*) from Table-I
- **Test-I** (compare *Q* with micro-array data)
- **Test-II** (compare *Q* published literature)

Test-I (*compare with micro-array data*)

- Example: Breast Cancer
- Find involved genes from publised data (micro-array)
- Find corresponding pathways *P* (using PANTHER)
- Ask what % of predicted pathways (in *Q*) are there in *P* ?

About 60% of predicted pathways match with those predicted from micro-array data.



Autism	22	4	18
Schizophrenia	18	9	50
Heart failure	16	9	56
Diabetes	7	1	14
OverianCancer	41	23	56
AML	26	14	54
BreastCancer	11	8	73
ColonCancer	19	6	32
LungCancer	12	7	58
PancreasCancer	21	16	76
ProstateCancer	26	21	81
StomachCancer	19	10	53
HNC	23	15	65
ThyroidCancer	17	13	76
CLL	19	10	53
Glioblastoma	12	9	75

🟦 Pathways predicted
from
cluster analysis

🟪 Predicted pathways
which matches with
micro-array data

Test-II

- Ask, if predicted pathways (Q) for a disease comes together with the disease in the literature?
- **Example :** Autism predicts wNT pathway
- “Autism and wNT pathway”

  (appear together in 10 published papers)

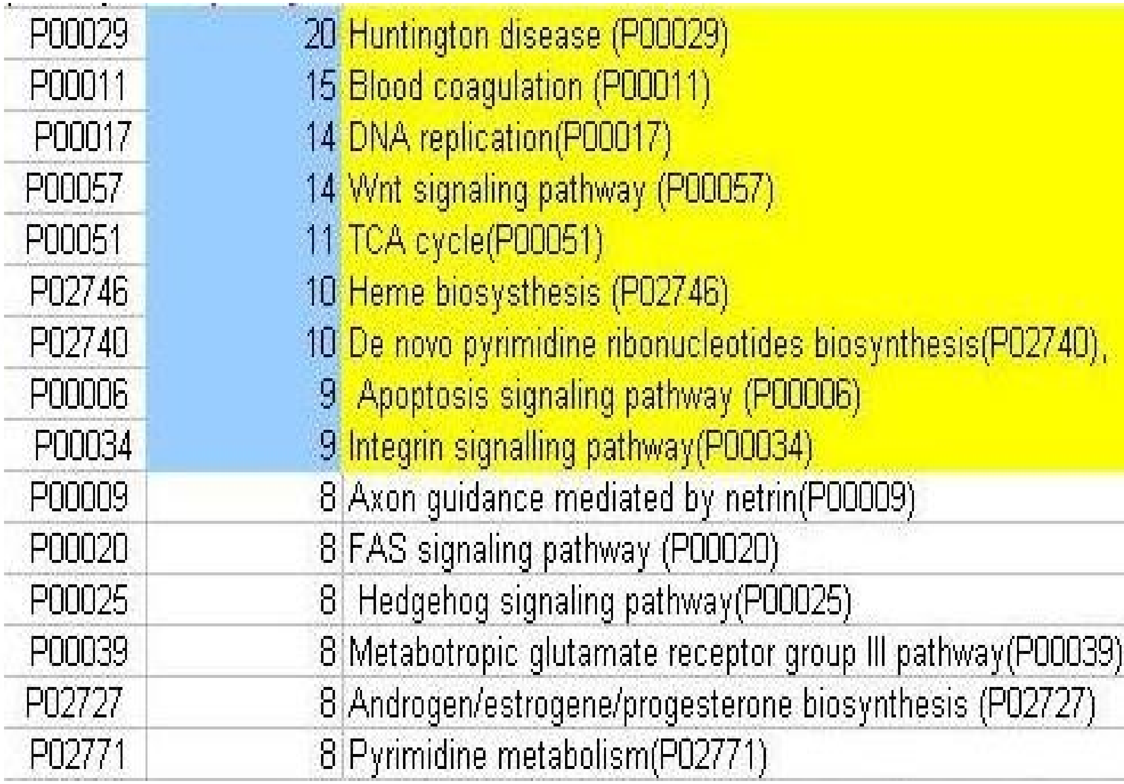
- Other diseases show similar correlation

Thus….

- These **70 clusters** form the building block of biological function ?

Not convinced ?

Pathways [no appears in 16 diseases]	**Diseases**	**References**
Huntington disease (P00029) [20]	Schizophrenia and Cancers	1, 2, 3
Wnt signaling pathway (P00057) [14]	Autism, Heart failure, Ovarian cancer,	4, 5, 6
Apoptosis signaling pathway (P00006) [9]	Schizophrenia and cancers	7
Integrin signaling pathway (P00034) [9]	Colon cancer Pancreas cancer	8, 9

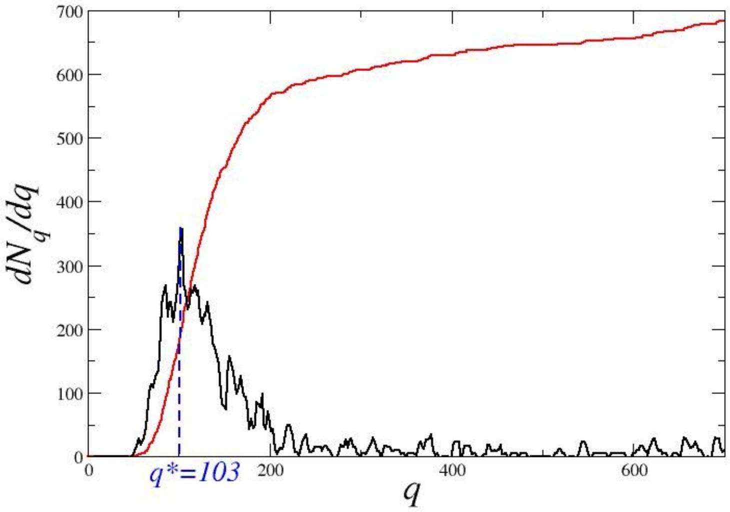


P00029		20	Huntington disease (P00029)
P00011		15	Blood coagulation (P00011)
P00017		14	DNA replication(P00017)
P00057		14	Wnt signaling pathway (P00057)
P00051		11	TCA cycle(P00051)
P02746		10	Heme biosysthesis (P02746)
P02740		10	De novo pyrimidine ribonucleotides biosynthesis(P02740),
P00006		9	Apoptosis signaling pathway (P00006)
P00034		9	Integrin signalling pathway(P00034)
P00009		8	Axon guidance mediated by netrin(P00009)
P00020		8	FAS signaling pathway (P00020)
P00025		8	Hedgehog signaling pathway(P00025)
P00039		8	Metabotropic glutamate receptor group III pathway(P00039)
P02727		8	Androgen/estrogene/progesterone biosynthesis (P02727)
P02771		8	Pyrimidine metabolism(P02771)

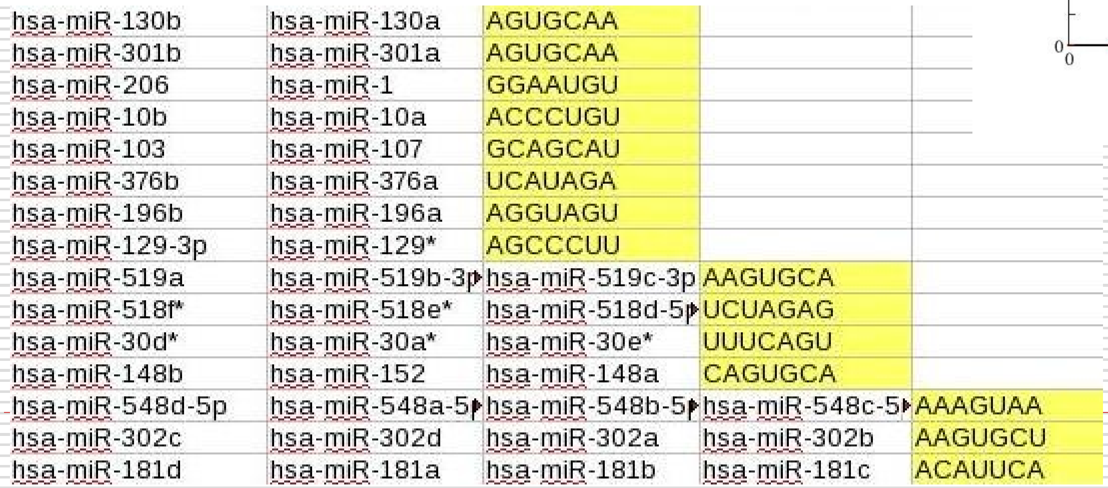
orrêa BB, Xavier M, Guimarães J (2006) Association of **Huntington's disease and schizophrenia-like psychosis in a**
untington's disease pedigree, **Clin Pract Epidemol Ment Health**. 2006 Feb 15;2 :1
HD, neurons undergo accelerated cell death while in general in cancer there is inhibition/decrease in cell death.
rensen et al., (1999) S.A. Sorensen, K. Fenger and J.H. Olsen, Significantly lower incidence of cancer among patients with
untington disease: an apoptotic effect of an expanded polyglutamine tract? *Cancer* **86** (7) (1999), pp. 1342–1346.
assink TH, Piven J, Vieland VJ, Huang J, Swiderski RE, Pietila J, Braun T, Beck G, Folstein SE, Haines JL, Sheffield VC
001) Evidence supporting WNT2 as an autism susceptibility gene, Am J Med Genet 105, 406-413.
ankesteijn WM, van de Schans VA, ter Horst P, Smits JF (2008) The Wnt/frizzled/GSK-3 beta pathway: a novel therapeuti
get for cardiac hypertrophy, Trends Pharmacol Sci. 2008 Apr;29(4):175-80.

Next is what ......?

- Why *cluster* at large *q* ?
- Seed-sequence similarity ?
- 100 % ....



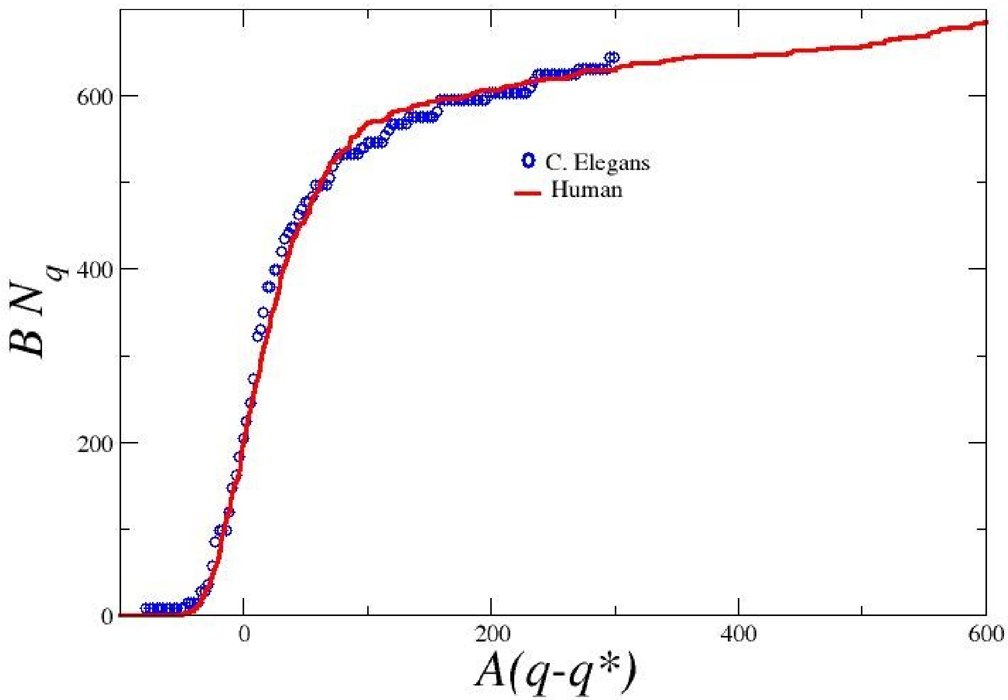
$q=600$



hsa-miR-130b	hsa-miR-130a	AGUGCAA		
hsa-miR-301b	hsa-miR-301a	AGUGCAA		
hsa-miR-206	hsa-miR-1	GGAAUGU		
hsa-miR-10b	hsa-miR-10a	ACCCUGU		
hsa-miR-103	hsa-miR-107	GCAGCAU		
hsa-miR-376b	hsa-miR-376a	UCAUAGA		
hsa-miR-196b	hsa-miR-196a	AGGUAGU		
hsa-miR-129-3p	hsa-miR-129*	AGCCCUU		
hsa-miR-519a	hsa-miR-519b-3p	hsa-miR-519c-3p	AAGUGCA	
hsa-miR-518f*	hsa-miR-518e*	hsa-miR-518d-5p	UCUAGAG	
hsa-miR-30d*	hsa-miR-30a*	hsa-miR-30e*	UUUCAGU	
hsa-miR-148b	hsa-miR-152	hsa-miR-148a	CAGUGCA	
hsa-miR-548d-5p	hsa-miR-548a-5	hsa-miR-548b-5	hsa-miR-548c-5	AAAGUAA
hsa-miR-302c	hsa-miR-302d	hsa-miR-302a	hsa-miR-302b	AAGUGCU
hsa-miR-181d	hsa-miR-181a	hsa-miR-181b	hsa-miR-181c	ACAUUCA

Universality ?

&



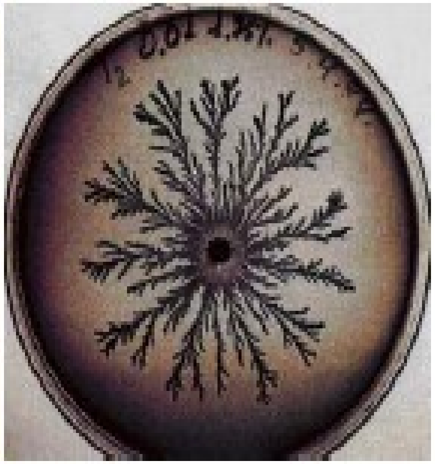
What is the universal structure in miRNA co-target network ?

Universality

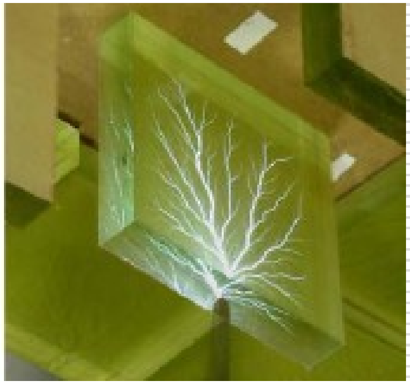

Cu-crystal


Mineral dendrite


Fingering

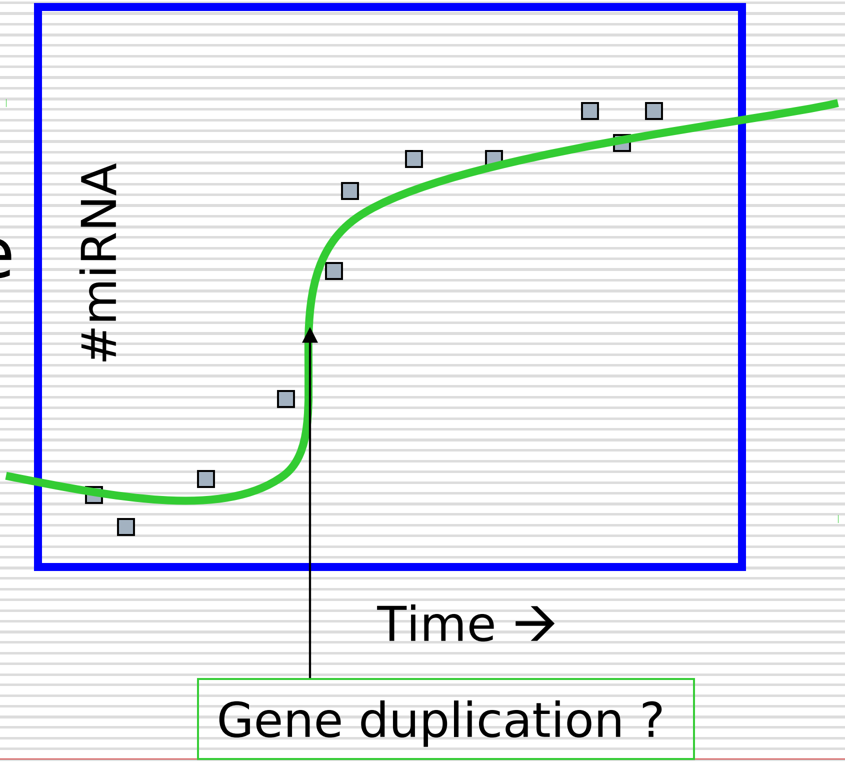

Bacteria colony


Lightening


Lichtenberg Fig

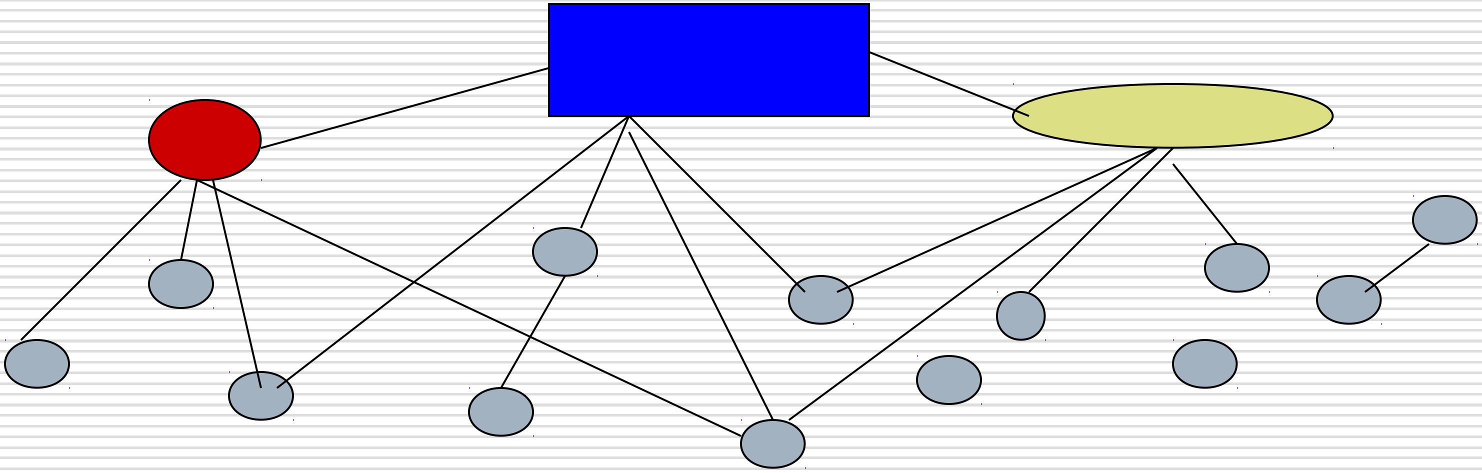
Evolution .....?

- #of miRNA (diff. species) have grown in time ?
- Substantial change during gene-duplication ?



Q. Bio-informatics ?

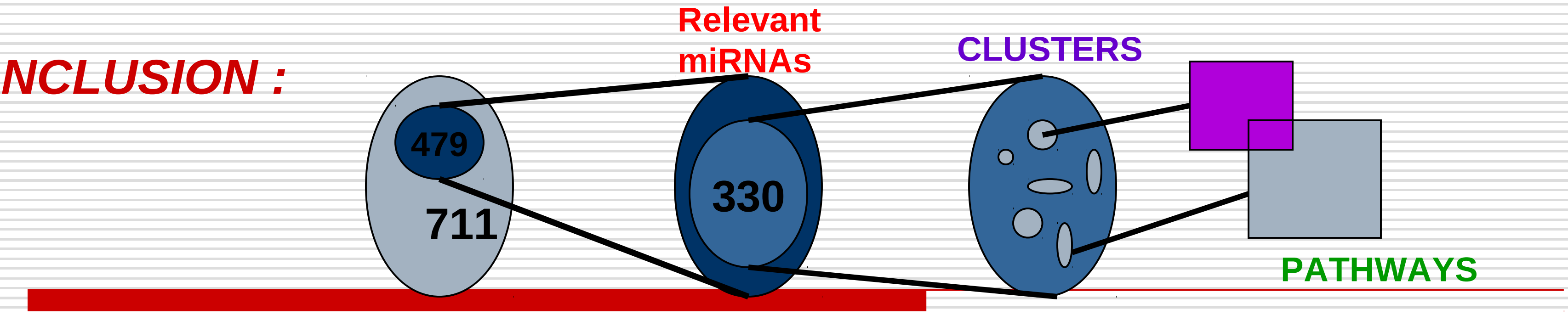
- Transcription Factor
- Pathway network
- Disease correlation



Generic method … ?

- Of finding cluster in undirected weighted network ?

CONCLUSION :



- ***G*****=479 of 711 miRNAs** are found functionally relevant.
- miRNAs associated with genetic diseases belongs to ***G***.
- ***G*** has **70 miRNA clusters** : only a few regulate a

  particular disease.
- miRNA **clusters are pathway specific**(verified)

- **Possibility :** if certain miRNAs are known to regulate any particular **"function",** other miRNAs in corresponding miRNA clusters are likely to regulate the same function.

Databases used :

- miRBase database (http://microrna.sanger.ac.uk/ version 10) for *Homo sapience,* 711 miRNAs and 34525 predicted targets.

- Gene names with ENSEMBLE ID (http://www.ensembl.org/)

- Oncomine research (http://www.oncomine.org/)

- NCBI gene ID (NM numbers), Clone/Gene Id Converter (http://idconverter.bioinfo.cnio.es/) and Ensemble Genome Browser (http://www.ensembl.org/index.html)

- PicTar database (http://pictar.bio.nyu.edu/cgi-bin/PicTar_vertebrate.cgi) for *Homo sapience,* 178 miRNAs and 9152 predicted targets.

- PANTHER database i.e. Panther Classification of genes and proteins (http://www.pantherdb.org/).

Computer Programs developed during this project :

- Perl & C Language

Thank you !!