The Novel Biological Phenomenon - Expression of Evolutionarily Novel Genes in Tumors

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Hypothesis

Tumors provide conditions for the expression of evolutionarily novel genes that originate in DNA of germ cells.

Kozlov 1979, 1996, 2010

Two approaches to study the hypothesis:

1 – to study evolutionary novelty of established tumor-specific sequences and/or genes
2 – to study tumor specificity of established evolutionarily novel genes

Baranova et al., 2001; Krukovskaya et al., 2005; Kozlov et al., 2006; Polena et al., 2007; Samusik et al., 2011; Polev et al., 2011

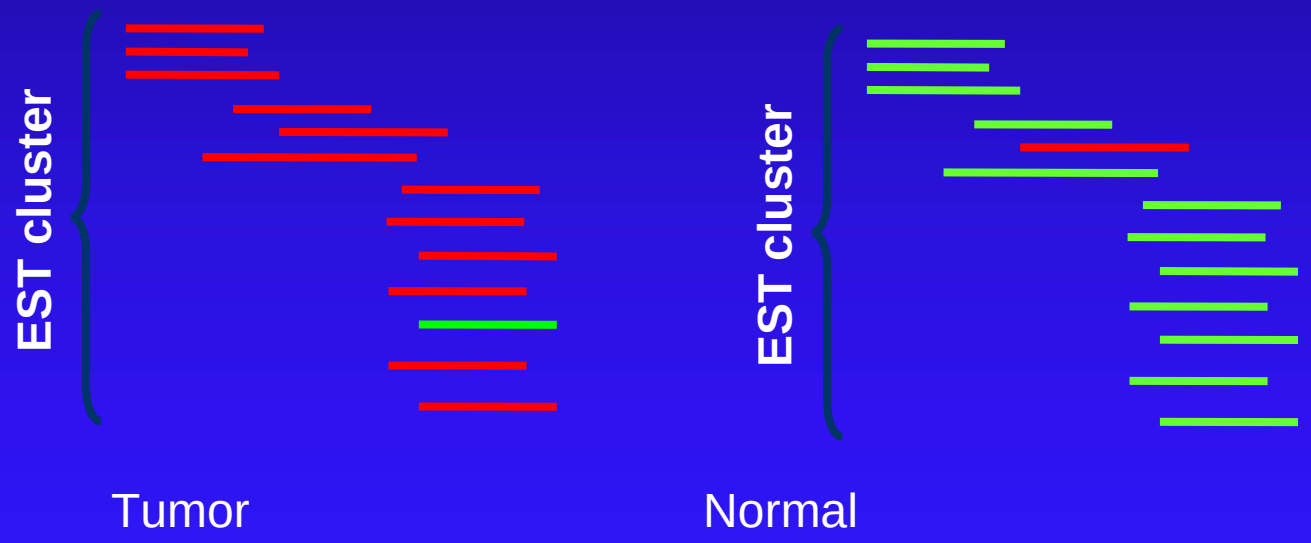
Two specificities were studied: tumor specificity of expression and evolutionary novelty

1. The specificity of tumor expression was studied using computational differential display approach (CDD) and cDNA panels from human normal and tumor tissues

2. Evolutionary novelty was studied with different molecular biological and bioinformatics approaches: Southern hybridization on evolutionary panels, molecular phylogenetic analysis, chained alignments of genomes, conservation analysis database analysis

CDD algorithm uses cDNA libraries annotation to determine EST cluster tumor specificity

cDNA Libraries	Q-ty
Undefined	1436
Normal	2387
Tumorous	4571
Σ	8394



The Results of Global CDD (UG build 129)

Range (number of ESTs per cluster)	Number of ESTs	Number of clusters	Tumor specific ESTs, %	Number of tumour related clusters at threshold, %			
				> 90 %		100%	
				observed	expected	observed	expected
1-2	59111	44373	42%	18342	23073	18342	23073
3-4	45400	13401	35%	1880	1884	1880	1884
5-8	53569	8742	37%	567	279	567	172
9-16	**63421**	**5407**	**39%**	**168**	**5**	**99**	**4**
17-32	**83968**	**3607**	**41%**	**45**	**0**	**17**	**0**
33-64	**176845**	**3762**	**43%**	**16**	**0**	**2**	**0**
65-128	**349008**	**3790**	**45%**	**10**	**0**	**2**	**0**
129-256	**460493**	**2588**	**47%**	**8**	**0**	**0**	**0**
257-512	**339482**	**975**	**50%**	**3**	**NA**	**0**	**NA**
513-1024	**208171**	**303**	**53%**	**1**	**NA**	**0**	**NA**
1025-2048	130524	96	57%	0	NA	0	NA
2049-4096	95180	36	60%	0	NA	0	NA
4097-8192	49804	10	66%	0	NA	0	NA
8193-16384	14725	1	67%	0	NA	0	NA

FEBS Letters, 508 (2001), 143-148

Characteristics of Tumor-Related Cluster Set Discovered by CDD

Baranova et al., 2001

- 251 clusters with 90% tumor specificity and 120 clusters with 100% tumor specificity were identified
- Contains several known tumor markers (MAGE family)
- Does not contain known oncogenes
- About half of this cluster set corresponds to transcribed sequences which do not have any known function (noncoding RNAs)

The first approach through the discovery of tumor-specifically expressed sequences by global CDD

UniGene build 129:
2681 tumor + 1087 normal cDNA libraries
$2.2*10^6$ ESTs; 90,000 clusters

↓ CDD

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↓ 56 clusters were experimentally analyzed on cDNA panels

For experimental confirmation of tumor specificity CLONTECH, BioChain and BMC Multiple Tissue cDNA panels containing sets of normalized first-strand cDNA from different human tumors and normal tissues were used

Normal panel: 43 samples from 29 normal and 8 fetal tissues

Tumor panel: 63 samples from 28 tumors of different histogenesis

cDNA panels from normal human tissues

N	Human MTC Panel I	N	Human Immune MTC Panel	N	Human Digestive MTC Panel
1	Brain	1	Bone Marrow	1	Cecum
2	Heart	2	Fetal Liver	2	Colon, ascending
3	KIdney	3	Limph Node	3	Colon, descending
4	Liver	4	Peripheral Blood Leukocite	4	Colon, transverse
5	Lung	5	Spleen	5	Deodenum
6	Pancreas	6	Thymus	6	Esophagus
7	Placenta	7	Tonsil	7	Ileocecum
8	Skeletal Muscle			8	Ileum
N	Human MTC Panel II	N	Human Fetal MTC Panel	9	Jejunum
1	Colon	1	Brain	10	Liver
2	Ovary	2	Heart	11	Rectum
3	Peripheral Blood Leukocyte	3	Kidney	12	Stomach
4	Prostate	4	Liver		
5	Small Intestine	5	Lung		
6	Spleen	6	Skeletal Muscle		
7	Testis	7	Spleen		
8	Thymus	8	Thymus		

cDNA panels from different human tumors

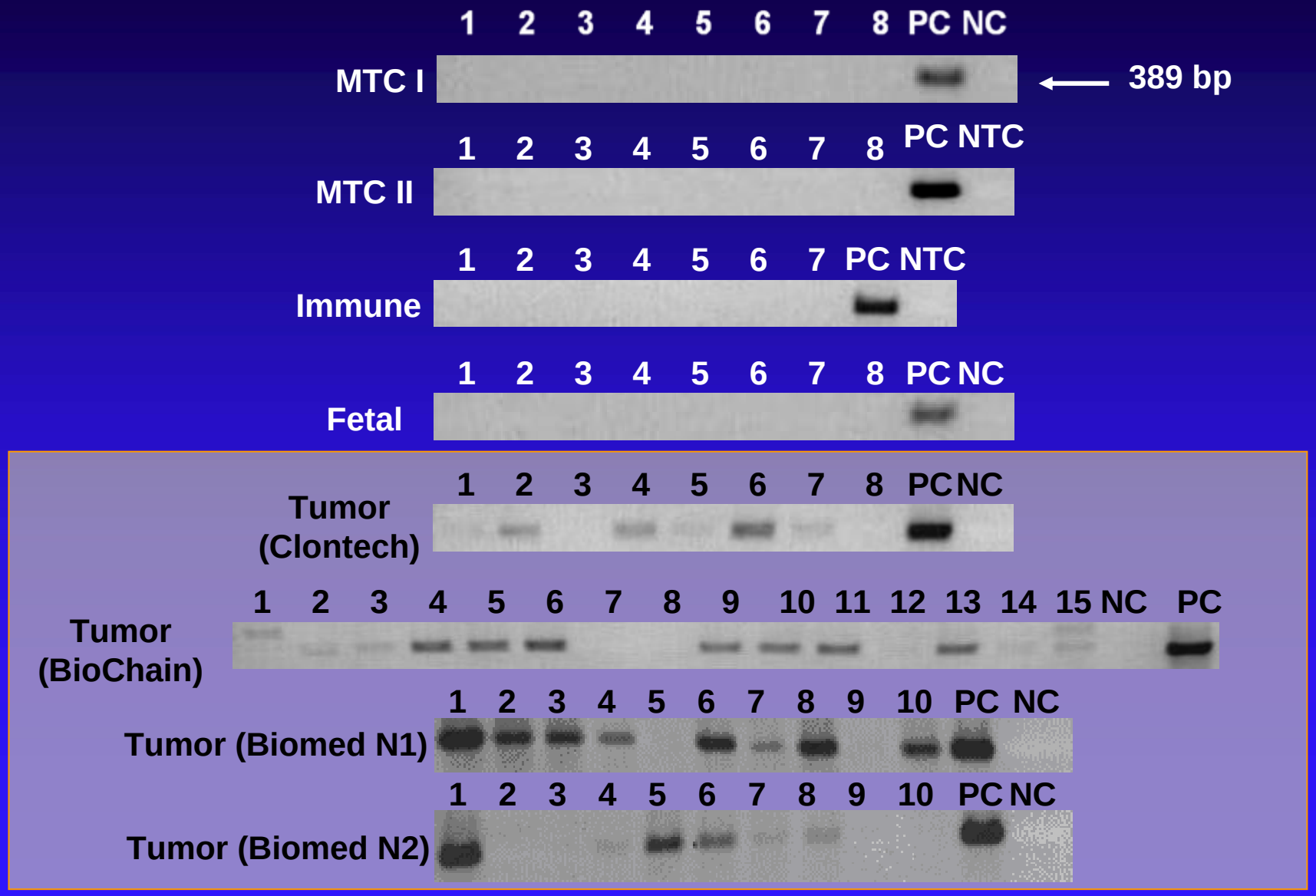
N	Tumor cDNA Panel (BioChain)
1	Brain Astrocytoma
2	Breast Invasive Ductal Carcinoma
3	Lung Squamous Cell Carcinoma
4	Esophagus Adenocarcinoma
5	Stomach Adenocarcinoma
6	Small Intestine Adenocarcinoma
7	Colon Adenocarcinoma
8	Hepatocellular Carcinoma
9	Kidney Clear Cell Carcinoma
10	Bladder Transitional Cell Carcinoma
11	Uterus Adenocarcinoma
12	Fallopian tube Medullary Carcinoma
13	Ovary Mucinous Adenocarcinoma
14	Testis Seminoma
15	Ureter Papillary Transitional Cell Carcinoma

N	Human Tumor MTC Panel (Clontech)
1	Breast carcinoma
2	Lung carcinoma LX-1
3	Colon Adenocarcinoma CX-1
4	Lung Carcinoma GI-117
5	Prostatic Adenocarcinoma
6	Colon Adenocarcinoma GI-112
7	Ovarian Carcinoma
8	Pancreatic Adenocarcinoma

N	Tumor cDNA Panel (Biomed N1)
1	Lung carcinoma
2	Ovarian carcinoma
3	Uterine carcinoma
4	Cervical carcinoma
5	Ovarian and cervical carcinoma
6	Testicular carcinoma

N	Tumor cDNA Panel (Biomed N2)
1	II stage lymphoma
2	III stage lymphoma
3	IV stage lymphoma
4	Brain astrocytoma
5	Head-neck meningioma
6	Breast cancers

Results of PCR experiments with Hs.202247 cluster specific primers



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Nine *in silico* tumor-specific clusters experimentally confirmed as tumor-specific

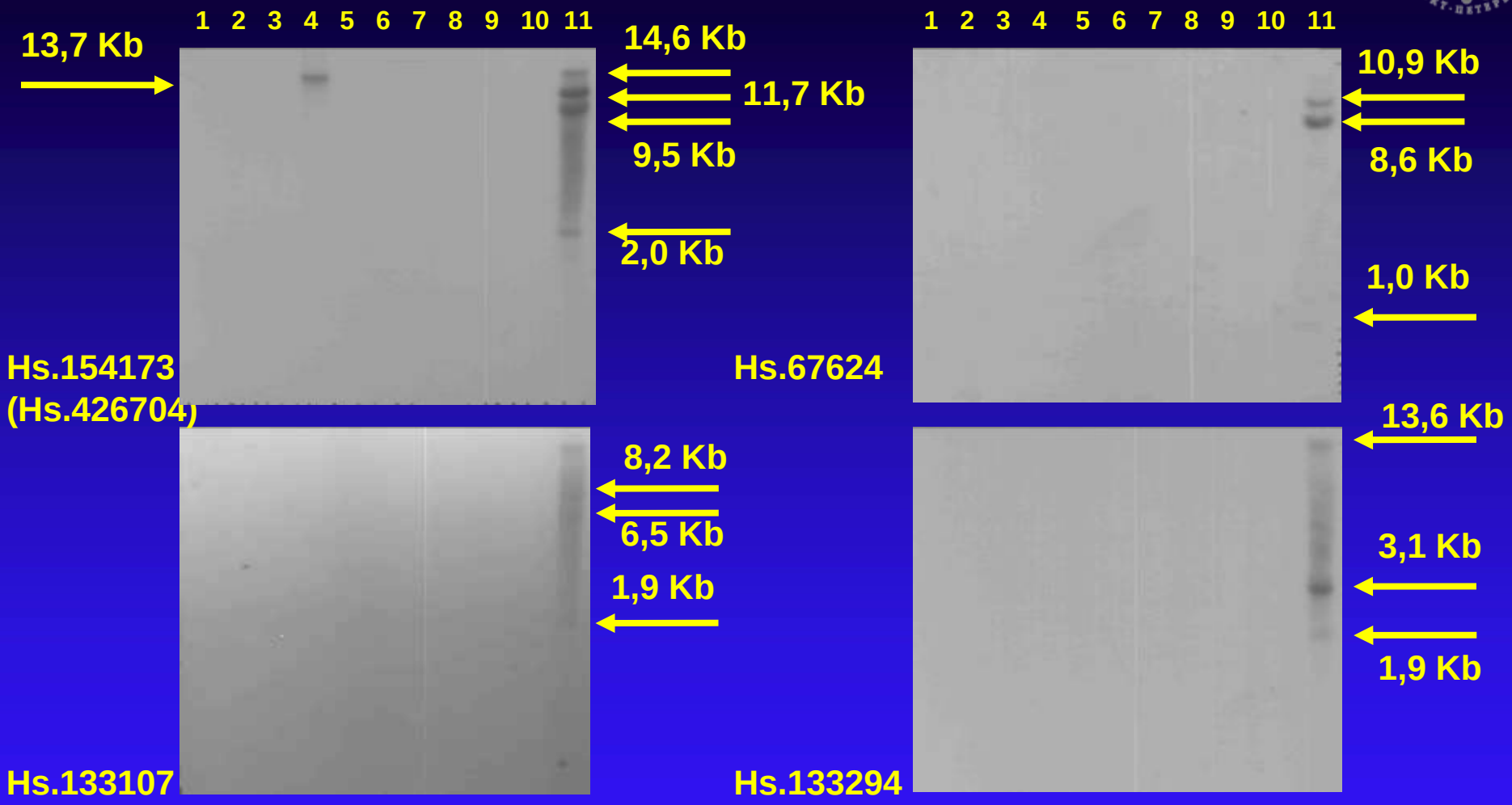
Expression of 9 tumor-specific clusters in different tumors

Tumor localization	Hs.426704	Hs.128594	Hs.133107	Hs.202247	Hs.633957	Hs.389457	Hs.285026	Hs.516444	Hs.150166
Brain astrocytoma	0/1	0/1	0/1	0/1	0/1	0/1	1/1	0/1	1/1
Breast	4/8	1/8	8/8	6/8	7/8	4/7	3/7	1/7	6/7
Respiratory system	3/6	3/6	6/6	6/6	5/6	2/4	3/4	4/4	4/4
Esophagus	1/1	0/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
Stomach	0/2	0/2	2/2	2/2	2/2	1/2	1/2	0/2	2/2
Pancreas	1/1	0/1	1/1	0/1	0/1	N/A	N/A	N/A	N/A
Liver	1/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
Small intestine	1/1	0/1	1/1	1/1	1/1	1/1	1/1	0/1	1/1
Colon	0/3	0/3	3/3	1/3	3/3	0/1	0/1	1/1	0/1
Kidney	0/1	0/1	1/1	1/1	1/1	1/1	0/1	0/1	1/1
Bladder	1/1	0/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
Ureter	0/1	0/1	1/1	1/1	1/1	0/1	0/1	0/1	0/1
Female genital system	4/15	6/15	13/15	13/15	15/15	6/14	4/14	0/14	12/14
Prostate	1/1	0/1	1/1	1/1	1/1	N/A	N/A	N/A	N/A
Testis	2/2	2/2	1/2	2/2	2/2	2/2	1/2	1/2	0/2
Lymphomas	2/7	6/7	7/7	7/7	7/7	7/7	0/7	0/7	7/7
Non-malignant neoplasms	Breast cyst , head	Head	Breast cyst , head	Breast cyst , head	Breast cyst , head	Head	Breast cyst, head	Head	Breast cyst, head
Normal tissues	-	PBL, testis, thymus	Lymph node, spleen, thymus	-	Heart, liver	Sm. Intestine, spleen, testis	Bone marrow	Thymus	Heart, kidney, lung

In some tumors, all studied clusters are expressed

Some clusters are expressed in almost all studied tumors

Southern Hybridization of Tumor-Specific Fragments with Genomic DNA from Different Animal Species (Hind III)



1 Lamprey
2 Fish
3 Frog

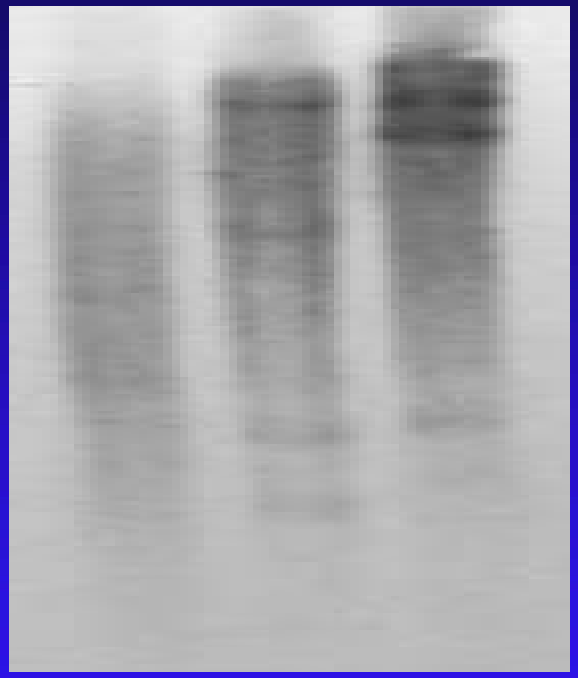
4 Chicken
5 Pigeon
6 Mouse

7 Rat
8 Guinea Pig
9 Sheep

10 Horse
11 Human

Southern Hybridization of Hs.154173 (Hs.426704) Fragment with Genomic DNA from Different Primate Species (Hind III)

1 2 3



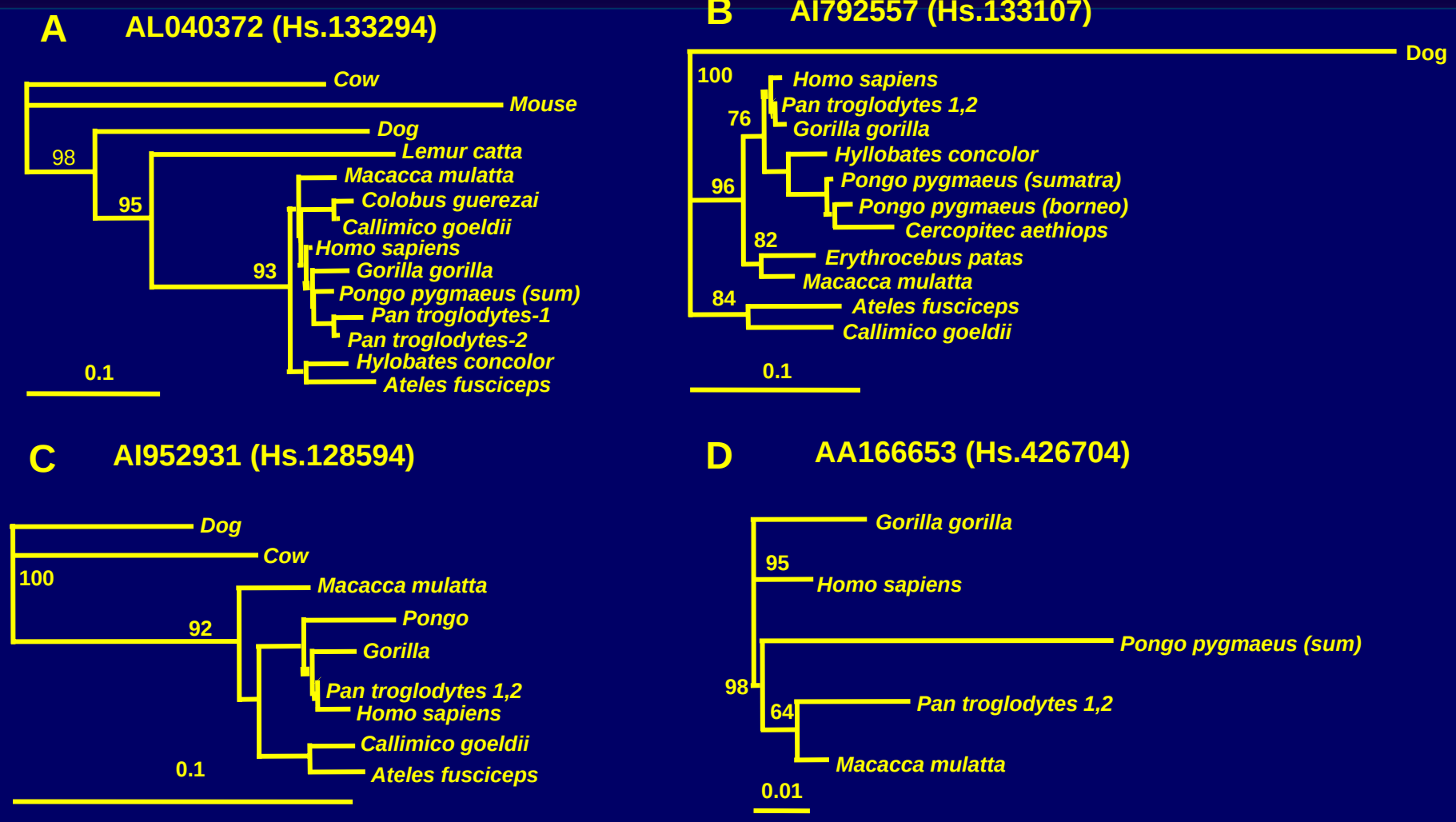
1 Baboon 2 Orangutan 3 Human

Results of PCR experiments* with sequence-specific primers and comparative genomics data obtained by homology analysis** within primates

Superfamily	Species\Transcript (EST Clusters)	AL040372 (Hs.133294)	AA166653 (Hs.426704)	AI952931 (Hs.128594)	AI792557 (Hs.133107)
Platyrrhini (New World monkeys)	*Lemur catta*	+	-	-	-
	Ateles fusciceps	+	-	+	+
	Callimico goeldii	+	-	+	+
Cercopitecoidea (Old World monkeys)	*Colobus guereza*	+	-	-	-
	Erythrocebus patas	+	-	-	+
	Cercopithecus aethiops	+	-	-	+
	Macaca mulatta	(+)**	(+)	(+)	(+)
Hominoidea (Apes and Human)	*Hylobates concolor*	+	-	+	+
	Pongo pygmaeus (sumatran)	+	+	+	+
	Pongo pygmaeus (bornean)	-	-	+	+
	Gorilla gorilla (sample 1)	+	+	+	+
	Gorilla gorilla (sample 2)	-	-	+/-***	+
	Pan troglodytes (sample 1)	+	+	+	(+)
	Pan troglodytes (sample 2)	+	+	+	(+)
	Homo sapiens	+	+	+	+

* DNA samples were ranged according to the existing classification of primates (Napier J. and Napier P., 1985).
** Data in brackets are results of comparative genomics analysis (http://www.hgsc.bcm.tmc.edu/projects).

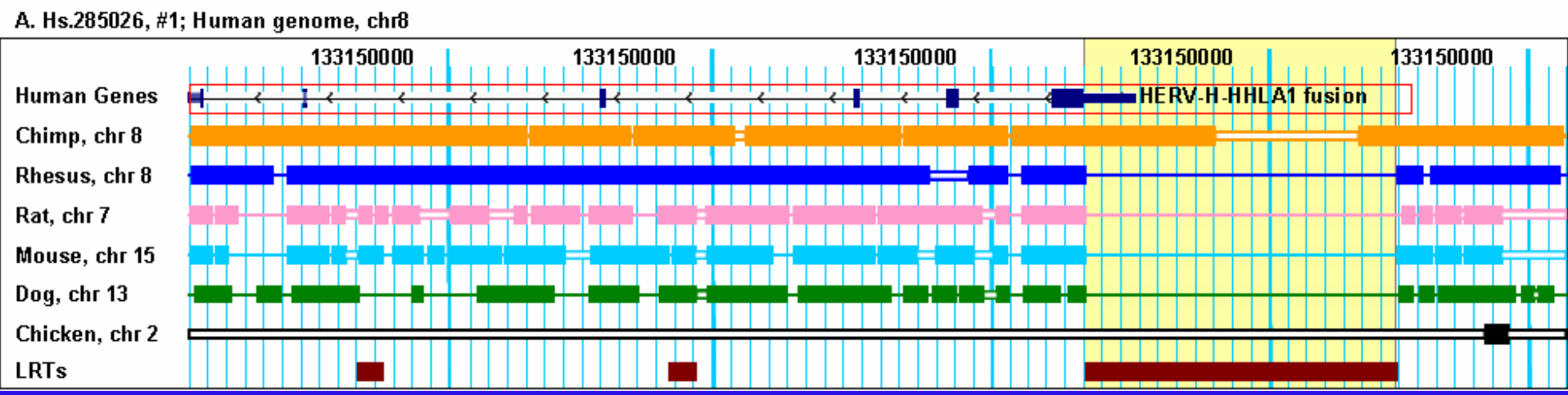
Phylogeny trees of tumor-related sequences in primates



Phylogenetic trees were constructed with neighbor-joining method using pairwise deletion and tested with 1000 bootstrap replicates

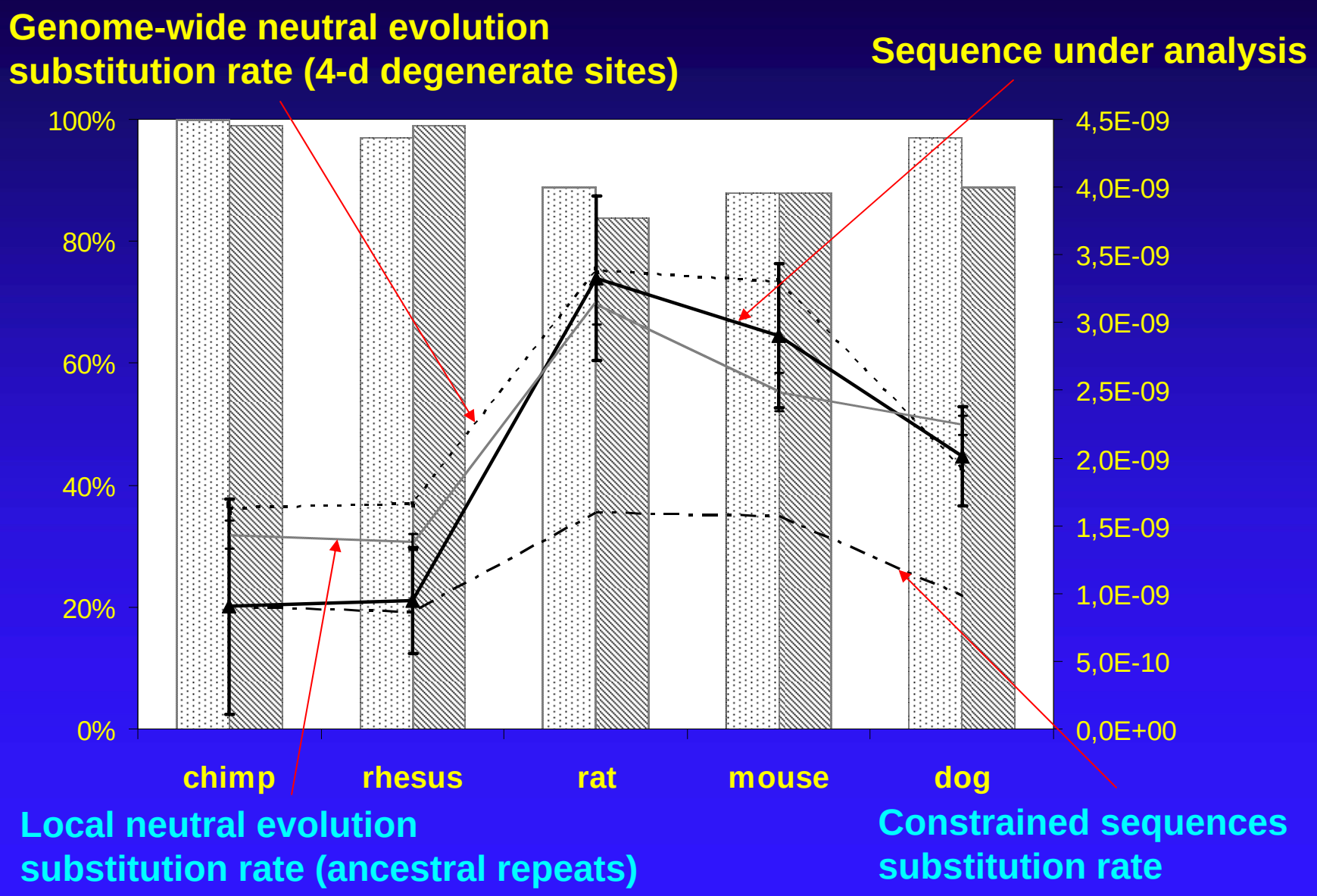
Hs.285026 – HHLA1

Chained alignments of Human Genome (May 2004) with *T. rubripes*, *D. rerio*, *G. gallus*, *C. familiaris*, *M. musculus*, *R. norvegicus*, *M. mulatta* and *P. troglodytes*



Insertion of HERV-H LTR created ORF in humans (Samusik et al., 2009; the result similar to that of Knowles and McLisaught, 2009)

Hs.202247 – Orthopedia Homolog conservation analysis



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Nine *in silico* tumor-specific clusters experimentally confirmed as tumor-specific

↓

Eight tumor-specific, (relatively) evolutionarily new sequences

(TSEEN sequences **- t**umor **s**pecifically **e**xpressed, **e**volutionarily **n**ew **s**equences)

Summary of comparative genomics analysis: Orthology

	Protein-Coding	Long Spliced	Short Non-spliced
Stand-Alone	Hs.285026 (HHLA1) Hs.46320 (SPRR1A) Hs.389457 (T)	Hs.150166 Hs.633957	Hs.426704 (rRNA repeating unit)
Intron-Mapped		Hs.202247 (OTP) Hs.128594 (CACNA2D3)	Hs.133107 (PVT1)

Specific for human

Specific for monkeys or apes

Specific for mammals

Neutral evolution vs conservatism

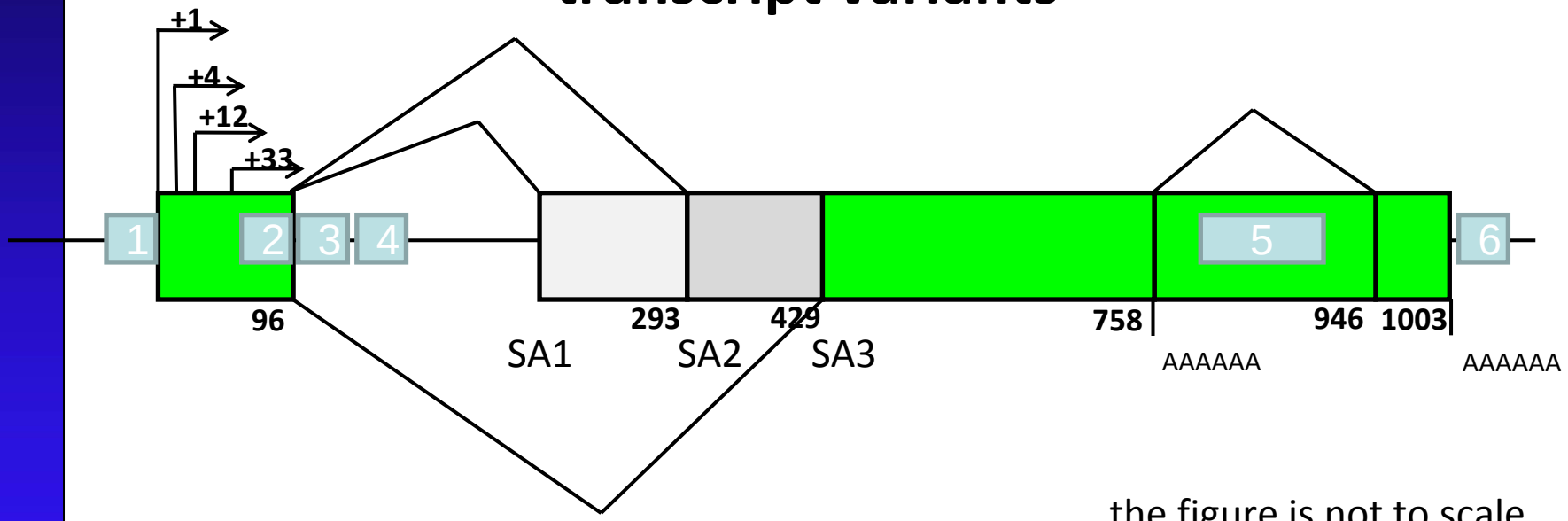
	Protein-Coding	Long Spliced	Short Non-spliced
Stand-Alone	Hs.285026 (HHLA1) Hs.46320 (SPRR1A) Hs.389457 (T)	Hs.150166 Hs.633957	Hs.426704
Intron-Mapped		Hs.202247 (OTP) Hs.128594 (CACNA2D3)	Hs.133107 (PVT1)

Constrained sequence

Neutrally evolving sequence

Locus Hs.633957coding for tumor-specific miRNA

Scheme of the locus Hs.633957 with its identified regulatory and structural elements and the possible transcript variants

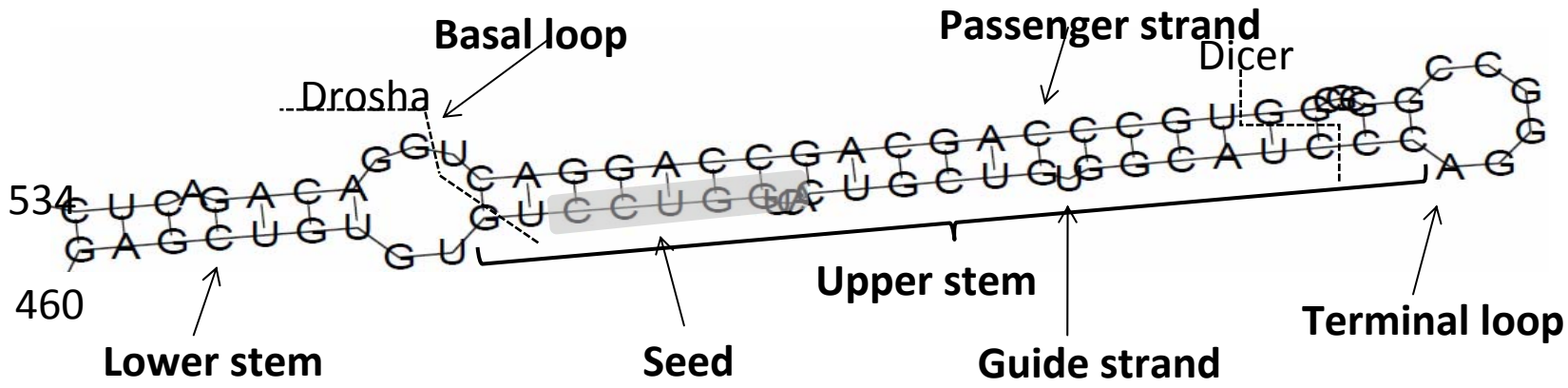


the figure is not to scale

1. GC-box
2. TFBS for MEF2A
3. TFBS for GATA
4. TFBS for c-Myc/Max
5. miRNA
6. AluJo

The major splice variant is shown in green

The Potential pre-miRNA Hairpin Encoded by Hs.633957 RNA



Northern hybridization of RNA from different tumor cell lines with anti-miRNA probe

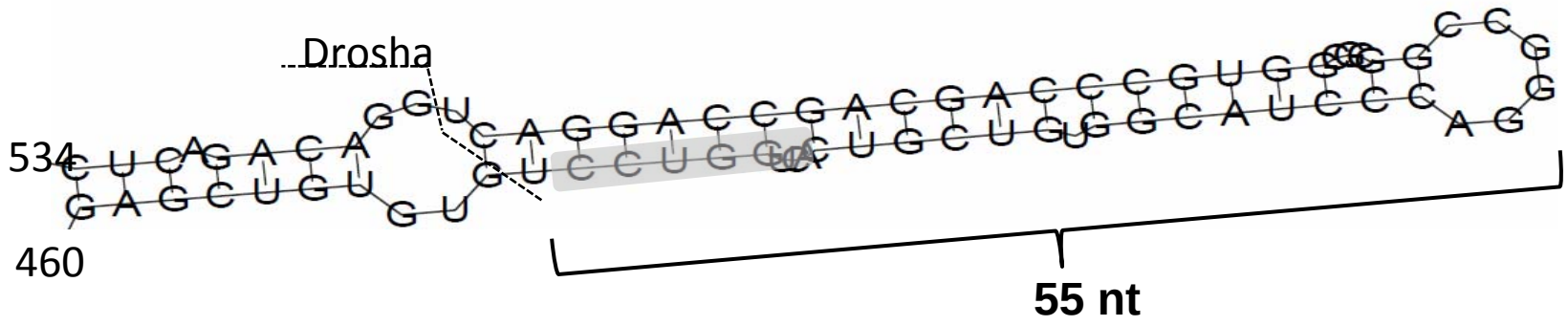
293 H9 Panc PC

rRNA, tRNA

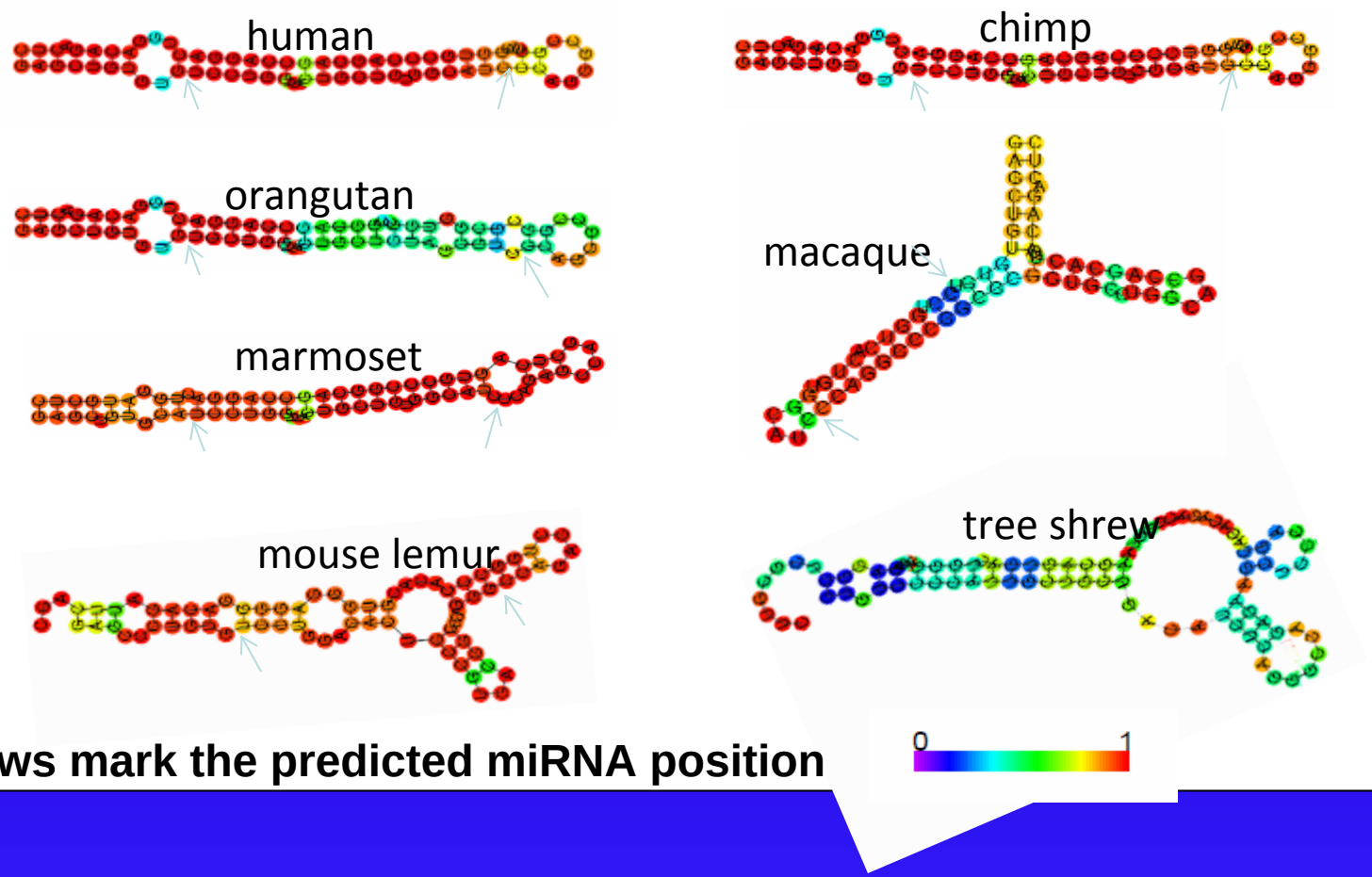
55 nt pre-miRNA

34 nt

The 55 nt fragment may be the product of Drosha cleavage



The Secondary Structures of Potential pre-miRNA Hs.633957 and Its Orthologs



Arrows mark the predicted miRNA position

Interaction of Potential miRNA Hs.633957 and Its Orthologs With the Target Sites in DPYS (dihydropyrimidinase) mRNA

```
                          ....|....| ....|....| ....|....
                              5          15         25
Human miRNA            5' tcctggtcAc tgctgtggc atc...... 3'
Human DPYS             3' aggaccagGg acgacaccg tag...... 5'

Chimp miRNA            5' tcctggtcAc tgctgtggc atc...... 3'
Chimp DPYS             3' aggaccagGg acgacaccg tag...... 5'

Orangutan miRNA        5' tcctggtcAc tgctgtAgc Gtc...... 3'
Orangutan DPYS         3' aggaccagGg acgacaCcg Tag...... 5'

Macaque miRNA          5' tcctggtc~~ ~actgtggc atc...... 3'
Macaque DPYS           3' aggaccagGG Gtgacaccg tag...... 5'

Marmoset miRNA         5' tcctggtcAc Tgctgtggc atc...... 3'
Marmoset DPYS          3' aggaccagGg Ccgacaccg tag...... 5'

Lemur miRNA            5' tccTGgAcAc TgcCGtgAc GgcCcagGG 3'
Lemur DPYS             3' aggCTcAgGg Gcg~~ac~g AcgCgtcAG 5'
```

Evolutionarily novel gene coding for miRNA

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↓ CDD

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Nine tumor-specific clusters experimentally confirmed as tumor-specific

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Hs.633957 – TSEEN miRNA gene

(TSEEN gene **- t**umor **s**pecifically **e**xpressed, **e**volutionarily **n**ew gene)

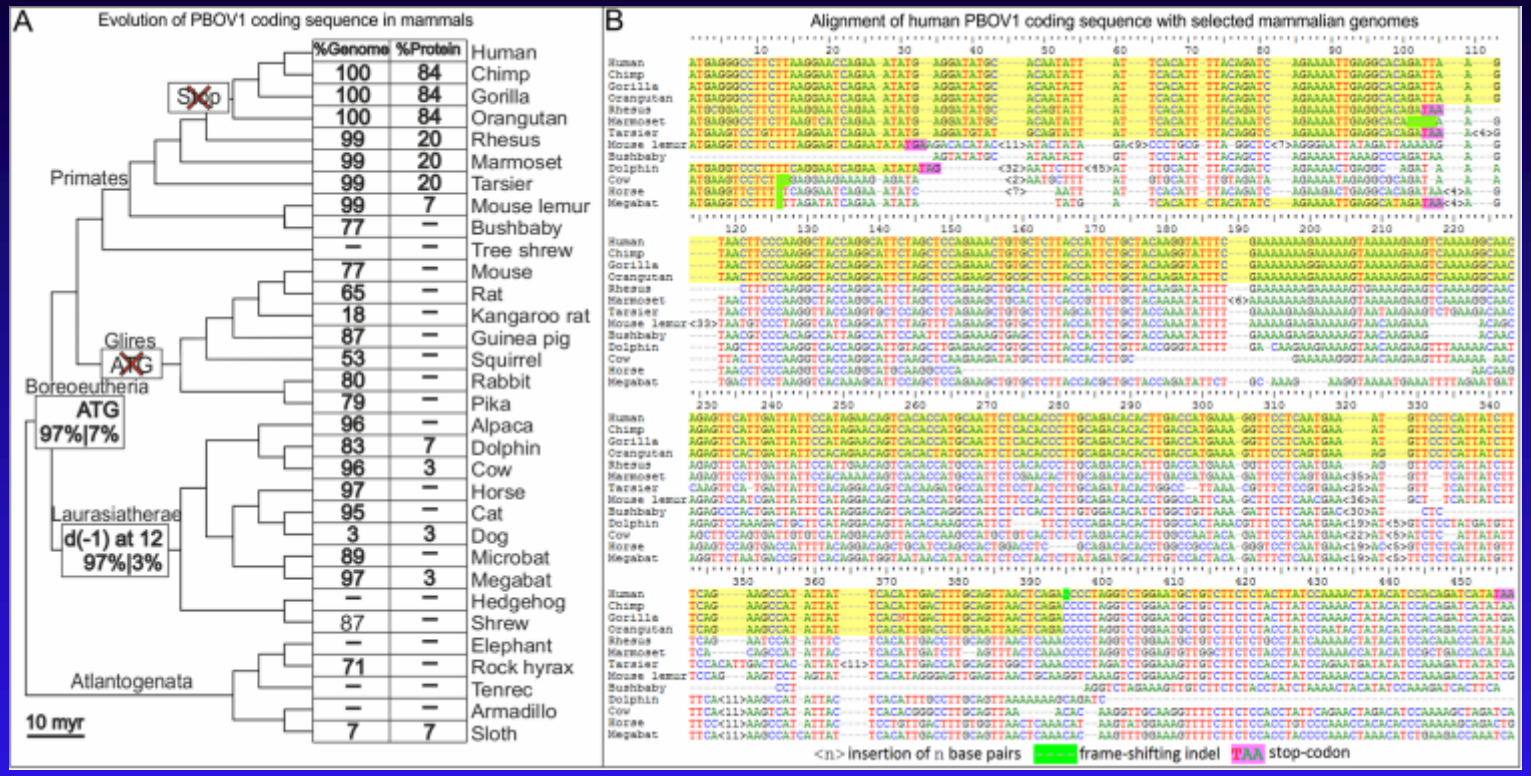
TSEEN gene of long non-coding RNA (Hs.202247)

Hs.202247

The second approach: tumor-specificity of established novel genes

PBVO1: a human orphan gene (Clamp et al., 2007)

PBOV1 is a protein coding gene that originated de novo in primate evolution

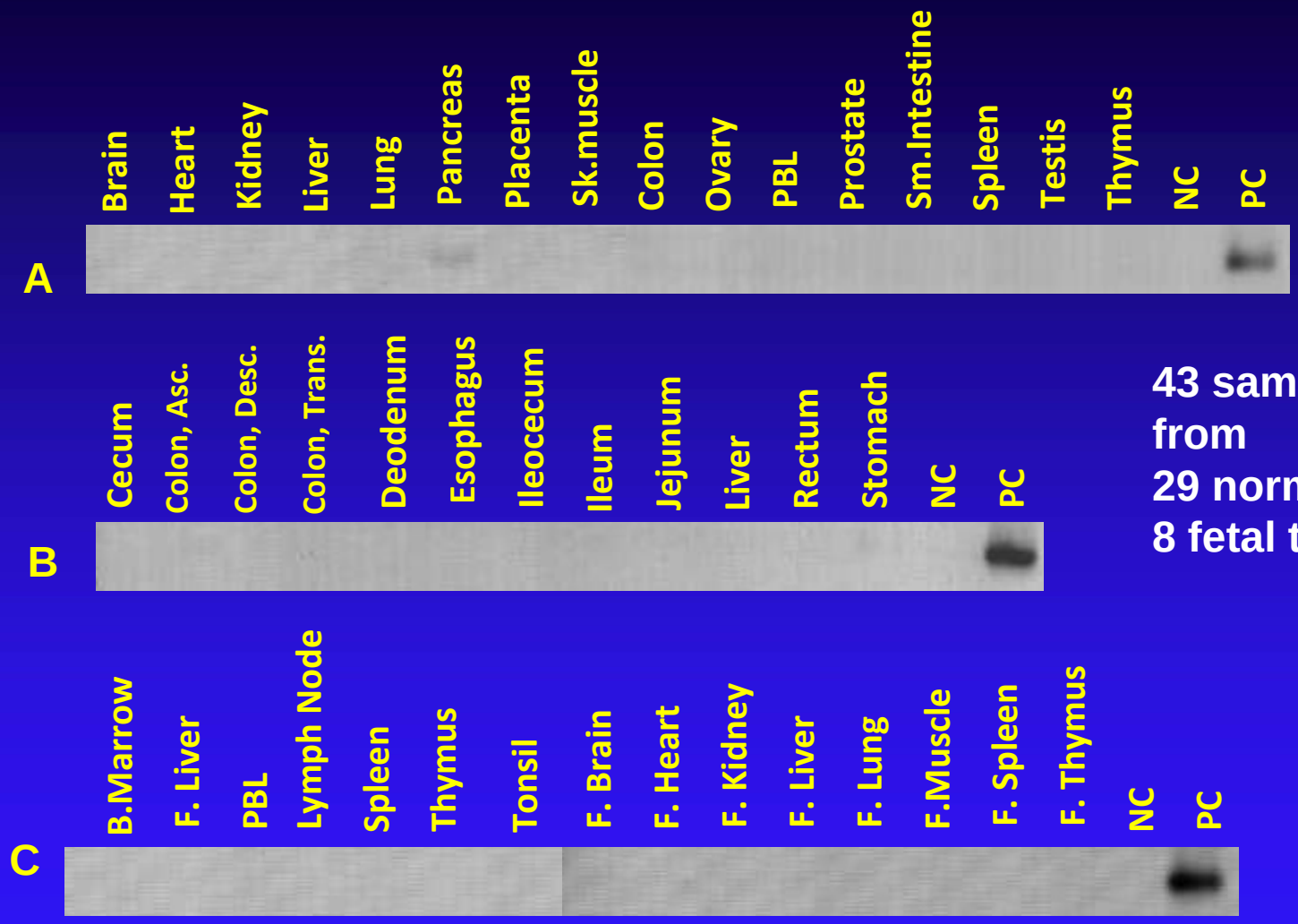


Single-exon gene, ORF encodes a 137-aa protein
C-terminal 16% of sequence is human-specific
Over 80% of protein sequence is absent from Rhesus and more distant species
Start-codon doesn't exist in the majority of non-primate species
Protein-coding sequence is not conserved, Ka/Ks ~ 1.0
Unusually high codon usage bias of 0.21 (p=0.004 over a random sequence)

PBVO1 protein lacks known functional features

- Protein existence is confirmed by Western blot and MS/MS identifications
- Protein lacks any annotated or predicted domains
- Over 60% of protein is predicted to be disordered (IPSSP software)

PBOV1: Expression in normal tissues



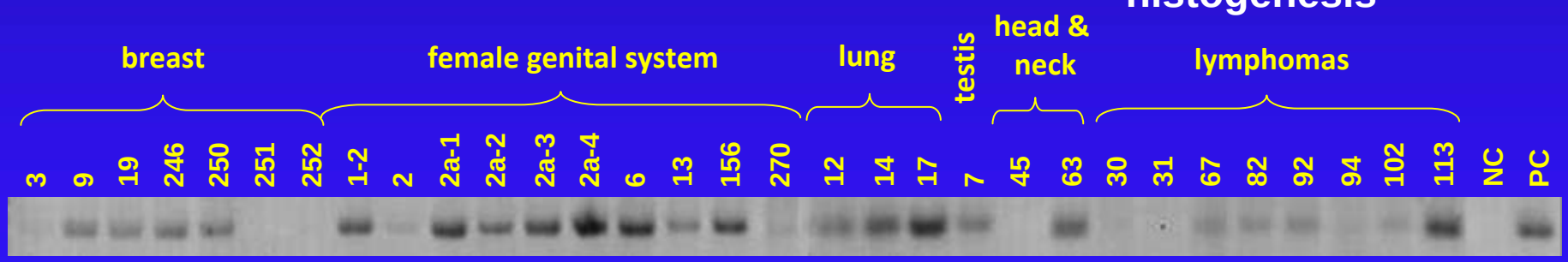
43 samples
from
29 normal tissues
8 fetal tissues

A- Human MTC Panel 1, Human MTC Panel 2(Clontech, USA)
B-Human Digestive System MTC Panel(Clontech, USA)
C-Human Immune System MTC Panel, Human Fetal MTC Panel(Clontech, USA)

PBOV1: Expression in tumor tissues

BioChain tumor panel

63 samples from 28 tumors of different histogenesis



BMC tumor panel

Novel Human Genes

(Clamp et al., 2007, Knowles and McLysaght, 2009)

DCD, FAM9, HTN1, IL32, LACRT, OCLM, PRH2, C1orf61, CCLU1, DNAH10OS, DP6

Genes expressed in tumors and in normal tissues

FAM9, HTN1, IL32, LACRT, OCLM, PRH2, C1orf61, DNAH10OS

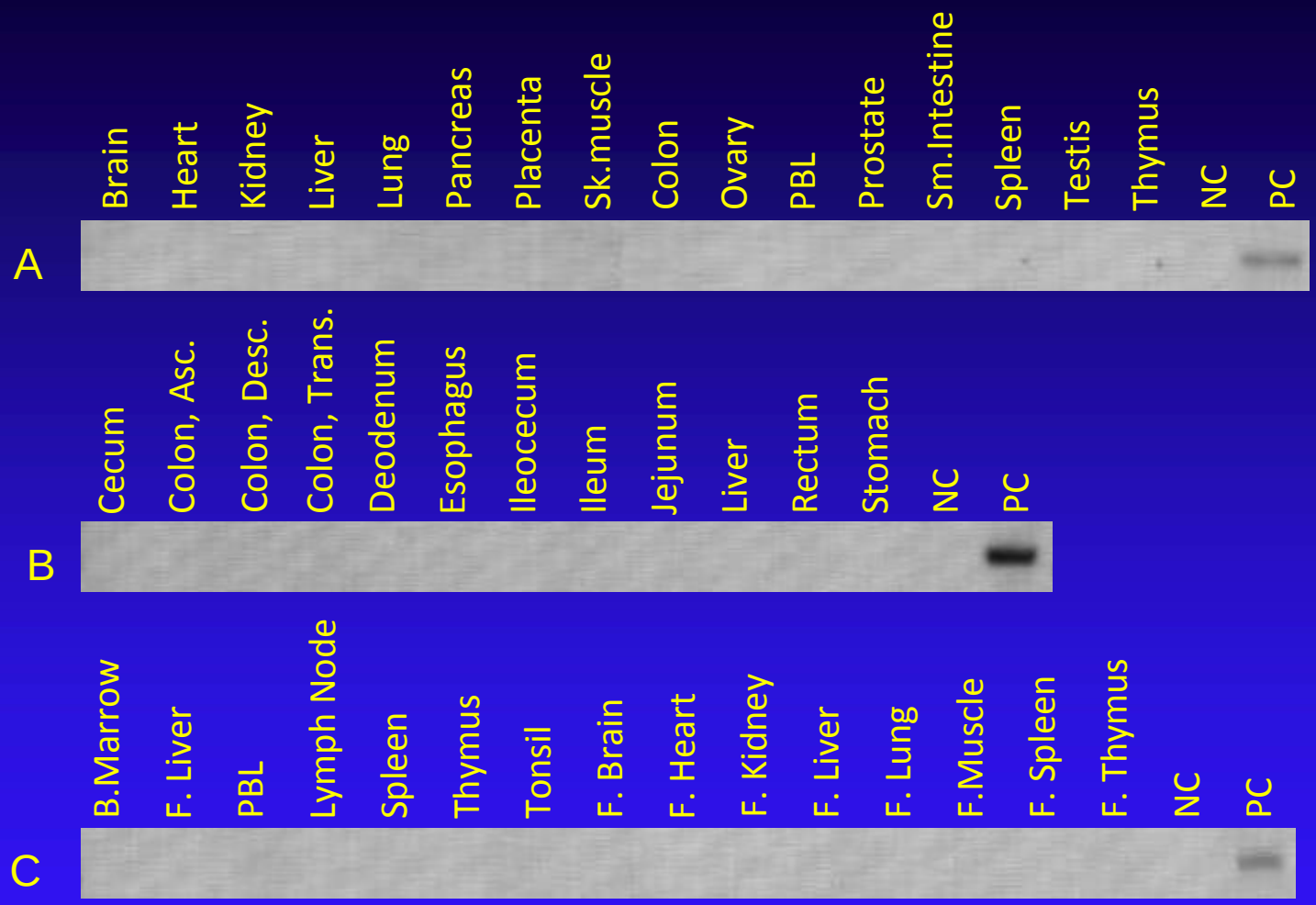
Genes expressed in tumors only

CCLU1, DCD, DP_6

CLLU1

Knowles D. G. and McLysaght A. Recent de novo origin of human protein-coding genes [Genome Res. - 2009. - Vol. 19. - pp. 1752-1759.

CLLU1: Expression in normal tissues



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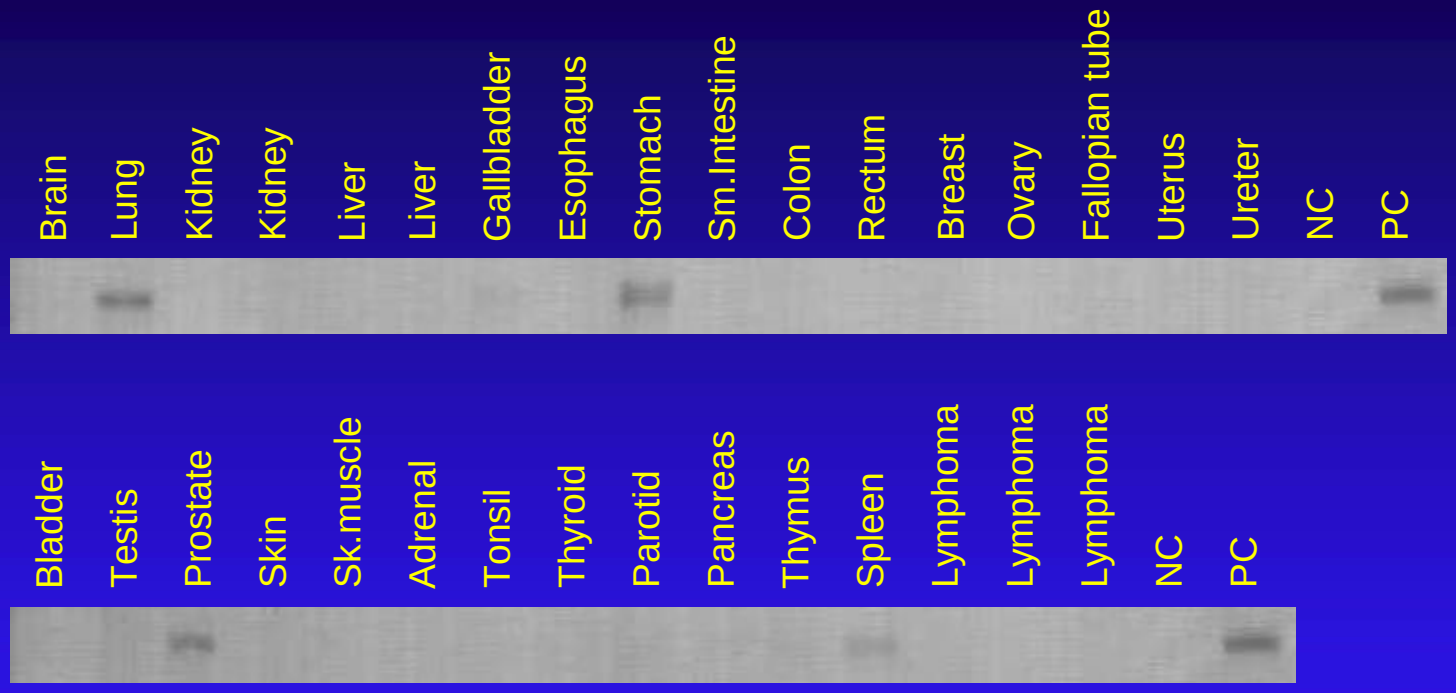
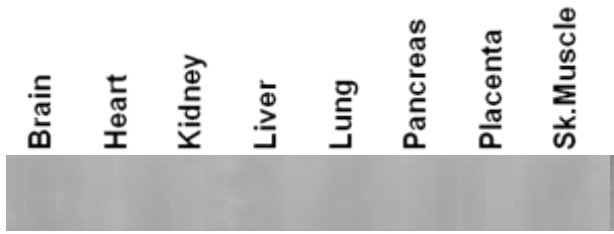
CLLU1: Expression in tumor tissues



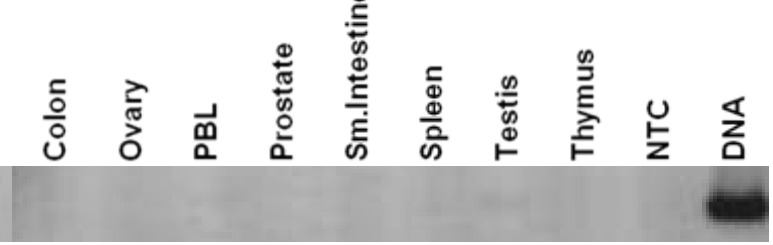
BioChain Institute tumor panel (USA)

Probe DP_6

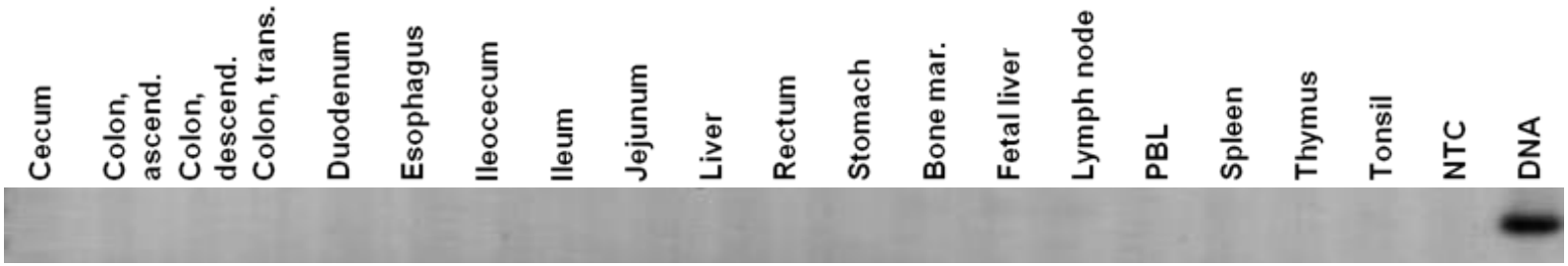
MTC1



MTC2

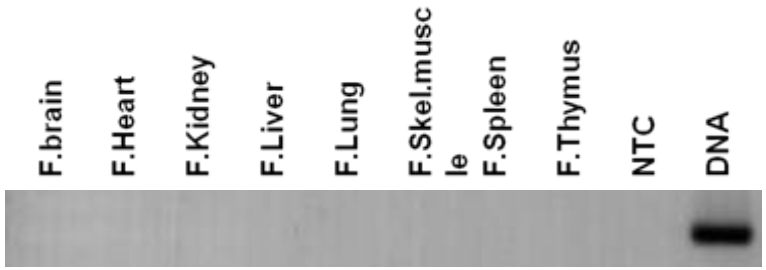


Digestive MTC Panel

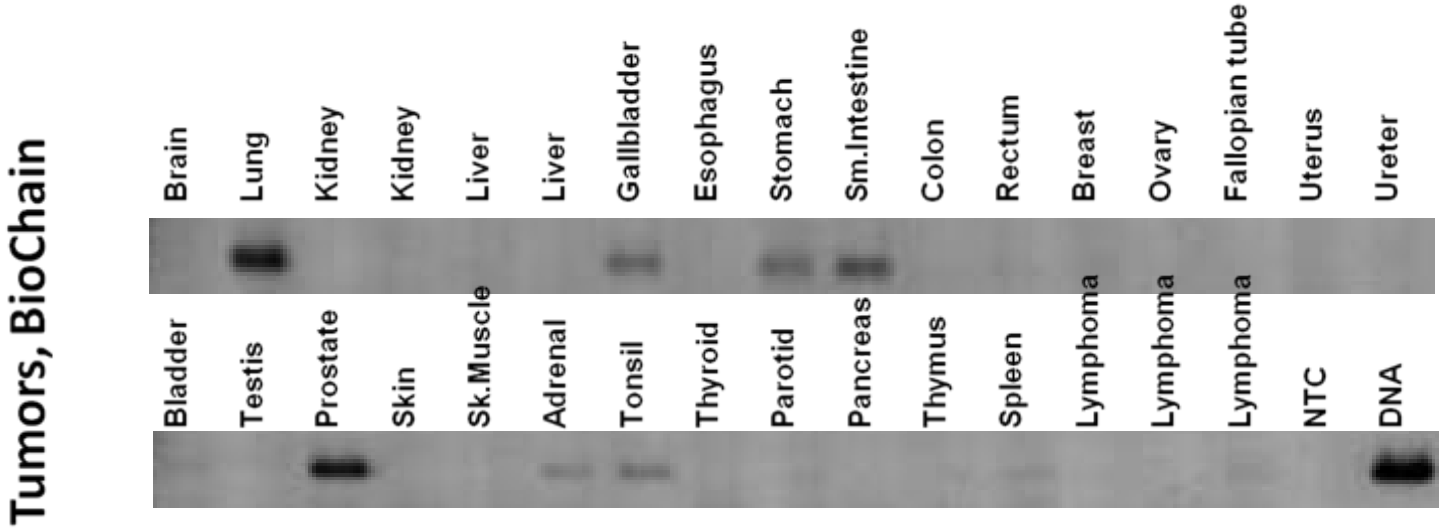


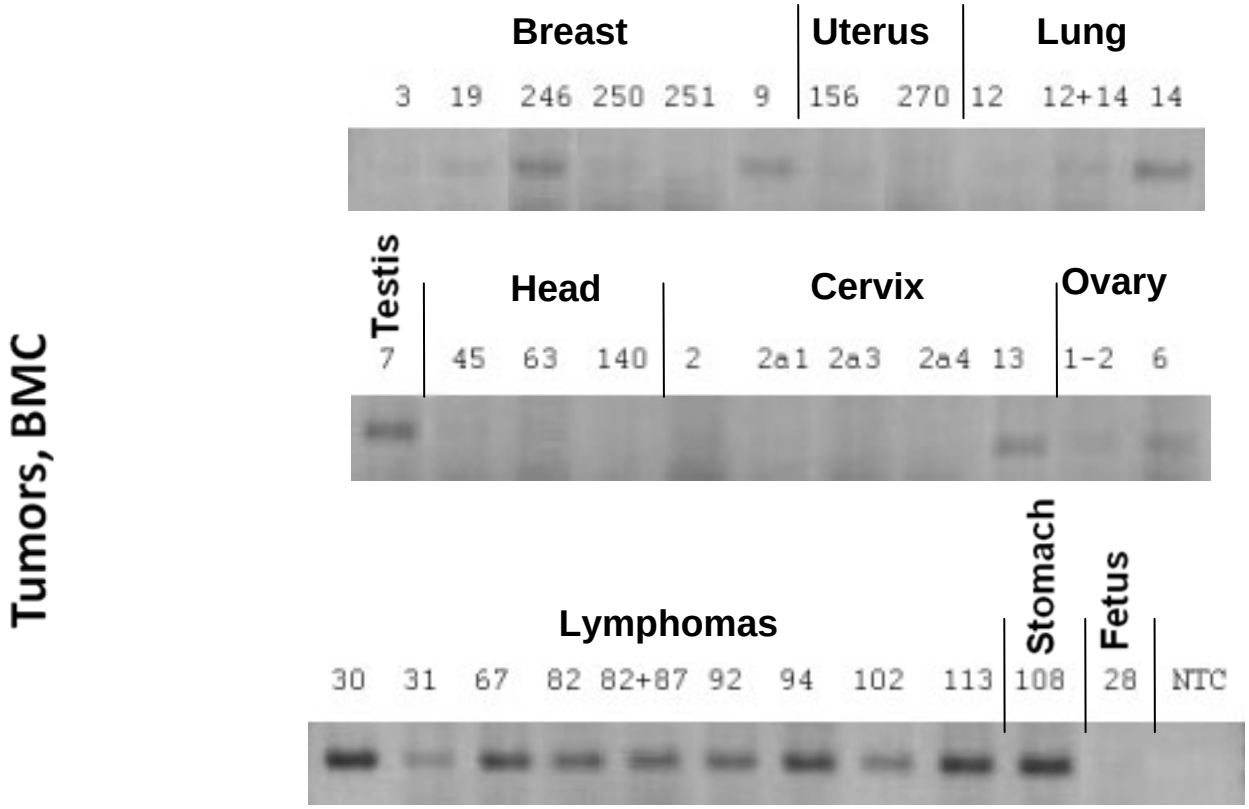
Immune MTC Panel

Fetal MTC Panel



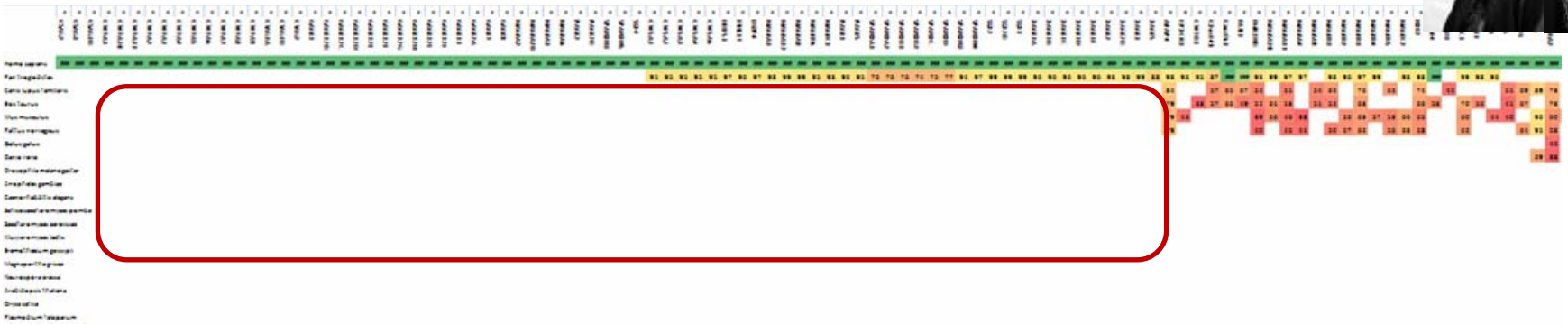
Probe DP_6


Tumors, BioChain
Brain
Lung
Kidney
Kidney
Liver
Liver
Gallbladder
Esophagus
Stomach
Sm.Intestine
Colon
Rectum
Breast
Ovary
Fallopian tube
Uterus
Ureter
Bladder
Testis
Prostate
Skin
Sk.Muscle
Adrenal
Tonsil
Thyroid
Parotid
Pancreas
Thymus
Spleen
Lymphoma
Lymphoma
Lymphoma
NTC
DNA


Tumors, BMC
Breast
Uterus
Lung
3
19
246
250
251
9
156
270
12
12+14
14
Testis
Head
Cervix
Ovary
7
45
63
140
2
2a1
2a3
2a4
13
1-2
6
Lymphomas
Stomach
Fetus
30
31
67
82
82+87
92
94
102
113
108
28
NTC

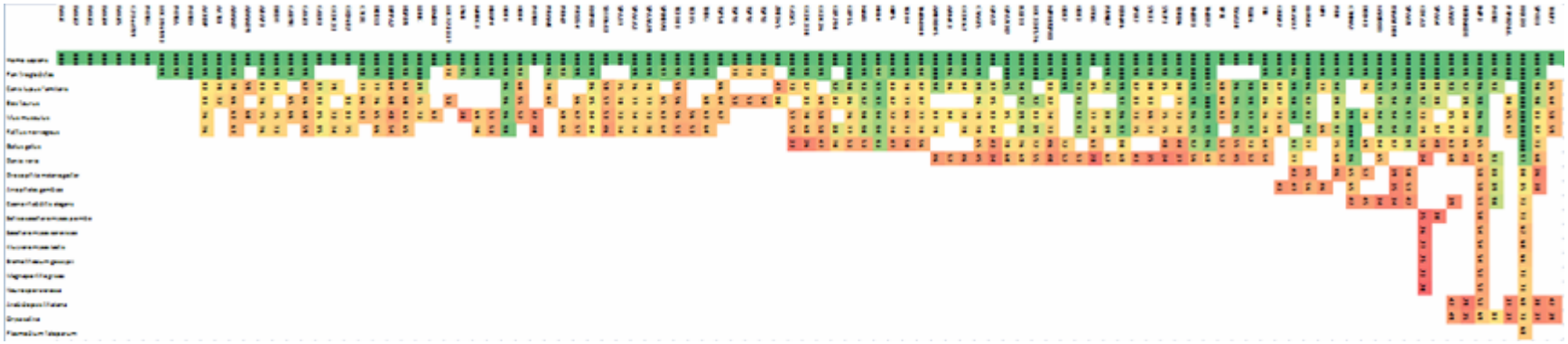
Distribution of CT genes among different genomes (NCBI: HomoloGene release 65)

Human CT genes on X chromosome



max min

All other Human CT genes



Control genes myosins and keratins

Algorithm:

UCSC Genome Browser, University of California Santa Cruz
Tool: BLAT

Results:

Gene family	CSAG	CT47	CTAG	GAGE	MAGEA	MAGEB	MAGEC	PAGE	SPANX	SSX	CT45	XAGE
Human gene number	2	12	3	16	13	7	2	7	11	14	6	9
Pan troglodytes gene number	1	2	1	(3)	4(5)	7	1	6	4	8	4	3
Pongo abelii gene number	1	4(1)	1	(1)	6(2)	7	1	5	4	8	3	3
Gorilla gorilla gene number	1	3(2)	2	(1)	6(2)	7	1	6	5	8	4	3(1)
Canis lupus gene number	0	0	0	0	0	0	0	0	0	0	0	0
Mus musculus	0	0	0	0	0	0	0	0	0	1	0	0
Danio rerio gene number	0	0	0	0	0	0	0	0	0	0	0	0
* dN/dS (average for family)	0,5	na	0,61	2,3	0,93	1,09	1,2	2,4	1,5	2,05	na	1,5

() - pseudogenes

*** Rapid evolution of cancer/testis genes on the X chromosome**// Brian J Stevenson // Ludwig Institute for Cancer Research and Swiss Institute of Bioinformatics, CH-1015 Lausanne, Switzerland // BMC Genomics // 23 may 2007*

Processed pseudogenes expressed in tumors (from Zhang et al., 2003)

Table 5. Examples of Human Processed Pseudogenes With Medical Implications

Protein name	Gene name	No. of pseudogenes	Medical implications	MIM no.[a]
Cyclohilin A, peptidyl-prolyl *cis–trans* isomerase A, (P05092)	PPIa, CYPA	63	Affects survival rates in human transplants, binds gag protein of HIV-1	123840
Glyceraldehyde 3-phosphate dehydrogenase (P04406)	GAPD	52	Overexpressed in lung cancer cells	138400
Nucleophosmin (P06748)	NPM1, NPM	34	More abundant in tumor cells than in normal resting cells	164040
Nef attachable protein (Q9P2Y3)		32	Attachable to human immunodeficiency virus type 1 Nef protein	
Prohibitin (P35232)	PHB	20	Possible tumor suppressor gene	176705
Hsc70-interacting protein, Hip (P50502)	ST13,HIP, SNC6	14	Suppression of tumorigenicity 13 (colon carcinoma)	606796
SET protein, HLA-DR associated protein II, PHAPII (Q01105)	SET	13	Myeloid leukemia associated, involved in human renal development and Wilms' tumor	600960
FSHD (Q14333)	FSHD	13	Facioscapulohumeral muscular dystrophy	606009
B lymphocyte activation-related protein BC-2048 (Q96PM7)		12	B-lymphocyte activation-related	
Translationally controlled tumor protein, TCTP, p23 (P13693)	TPT1	12	Tumor protein translationally controlled, histamine-releasing factor	600763
Melanoma antigen (Q9UMX8)		10	Melanoma antigen recognized by HLA-A1-restricted T-cells	
Retinoic acid receptor responder protein 2 (Q99969)	RARRES2, TIG2	10	Retinoic acid receptor responder protein 2 (tazarotene induced)	601973
Teratocarcinoma-derived growth factor 1, CRGF (P13385)	TDGF1, CRIPTO	6	Required for proper laterality development in humans, role in midline and forebrain development	187395
Small EDRK-rich factor 2, gastric cancer-related protein (Q9BZH7)	SERF2, FAM2C	6	Candidate gene for spinal muscular atrophy, gastric cancer-related	605054
Cytokeratin 19, CK 19 (P08727)	KRT19	4	Used as marker to detect micrometastatic tumor cells	148020

[a]Entry in the OMIM database: Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim/).

Conclusions

1. Taken together, these results obtained by complementary approaches support the hypothesis of expression of evolutionarily novel genes, originated in DNA of germ cells, in tumors. This may be a new biological phenomenon analogous to the phenomenon of tumor-embryonic antigens.

2. A set of several novel genes may be expressed in a tumor. Novel genes are expressed in a broad spectrum of tumors suggesting the possibility of universal tumor markers.

Collaborators and co-authors

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George Mason University, Fairfax

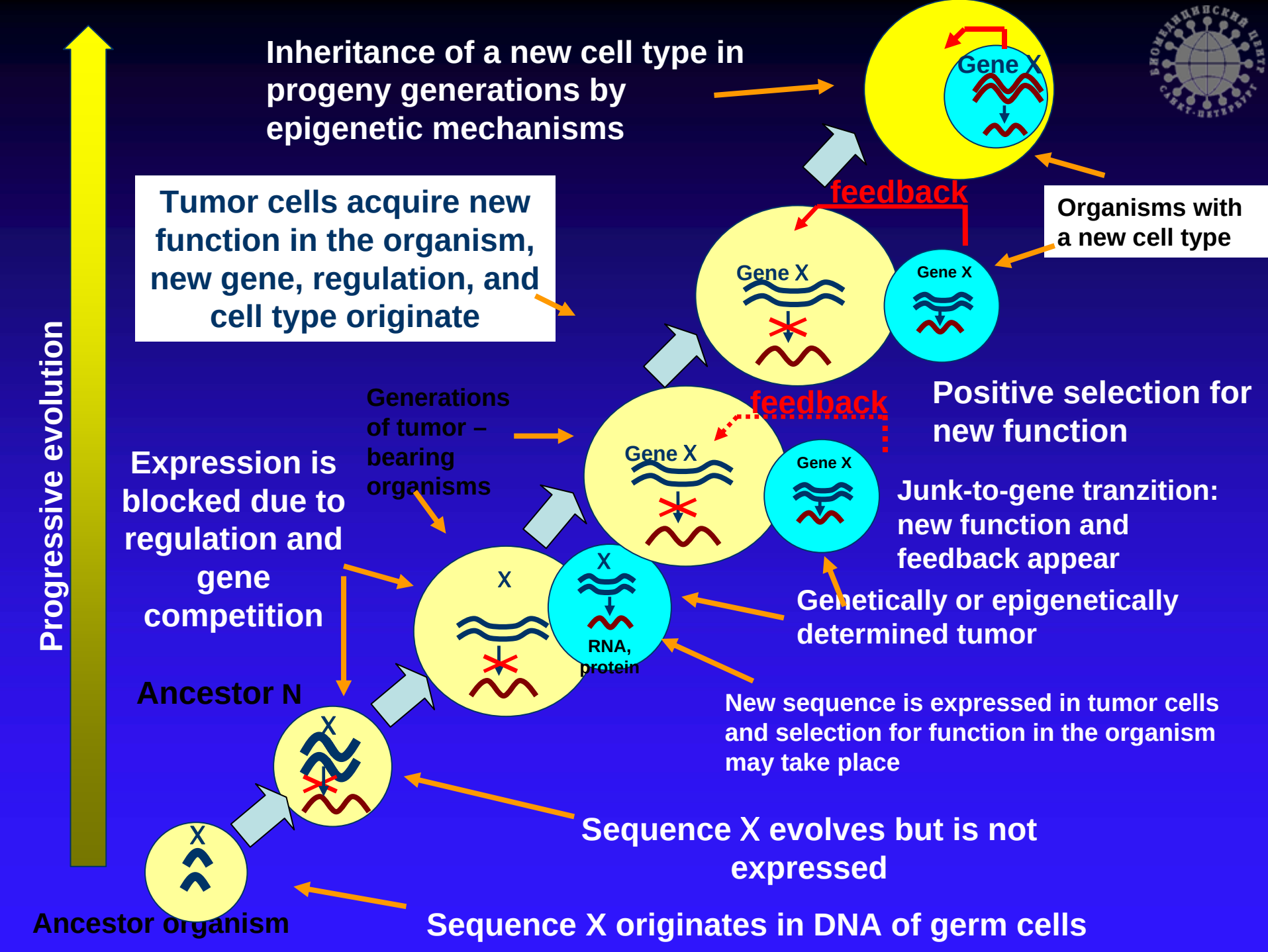
A.Baranova

The hypothesis of the possible evolutionary role of tumors in the origin of new cell types by means of expression of evolutionarily new genes in tumors.

Genetically or epigenetically predetermined tumors may play evolutionary role by providing conditions (space and resources) for expression of newly evolving genes. Tumors may be considered as proving ground, or reservoir, for expression of evolutionarily new genes which may lead to the origin of new cell types.

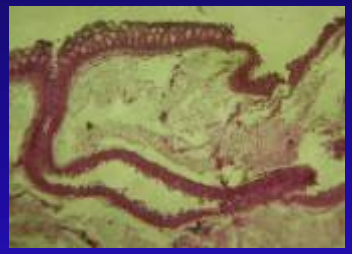
Kozlov A.P. J. theor. Biol. (1979) 81, 1-17

Kozlov A.P. Medical Hypotheses (2010) 74, 177-185

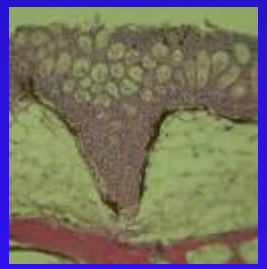

Progressive evolution
Inheritance of a new cell type in progeny generations by epigenetic mechanisms
Tumor cells acquire new function in the organism, new gene, regulation, and cell type originate
Gene X
feedback
Organisms with a new cell type
Gene X
Gene X
Positive selection for new function
Generations of tumor – bearing organisms
feedback
Gene X
Gene X
Junk-to-gene tranzition: new function and feedback appear
Expression is blocked due to regulation and gene competition
X
X
RNA, protein
Genetically or epigenetically determined tumor
Ancestor N
X
New sequence is expressed in tumor cells and selection for function in the organism may take place
Sequence X evolves but is not expressed
X
Ancestor organism
Sequence X originates in DNA of germ cells

The hood of Carassius auratus var. oranda is benign tumor

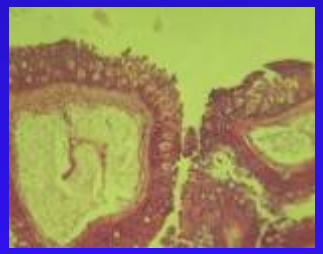
Skin Epithelium Papillomatous Neoplasms With Downgrowths



Papillomas With Deep Downgrowths



Exophytic Papillomas and Papillomatous Neoplasms



This result means that the benign tumor was artificially selected for in this variety of fish during several hundred years (Kozlov et al., 2012)

Examples of pathologies and pathogens which may have adaptive and/or evolutionary importance

- Viruses may play an evolutionary role by transducing genes between different groups of organisms (Anderson, 1970; Reanney, 1974; Zdanov, Tikchonenko, 1974).
- Sickle cell trait provides some protection against Plasmodium falciparum, the parasite responsible for the most severe form of malaria (Allison, 1961; Livingstone, 19
- Mutational process

Example of tumor which have played role in evolution: Rhizobia – legumes symbiosis

Nitrogen-fixing root nodules of legumes symbiotically associated with Rhizobia are examples of a situation in which tumor acquires function in the organism.

Difference between tumors induced by *Agrobacterium and Rhizobium*

Kingdom – *Bacteria*
Type – *Proteobacteria*
Class – *Alphaproteobacteria*
Subclass – *Rhizobiales*
Family – *Rhizobiaceae*

Genus ***Agrobacterium***

Genus ***Rhizobium***

Gall: proliferation of plant tissue similar to cancer growth

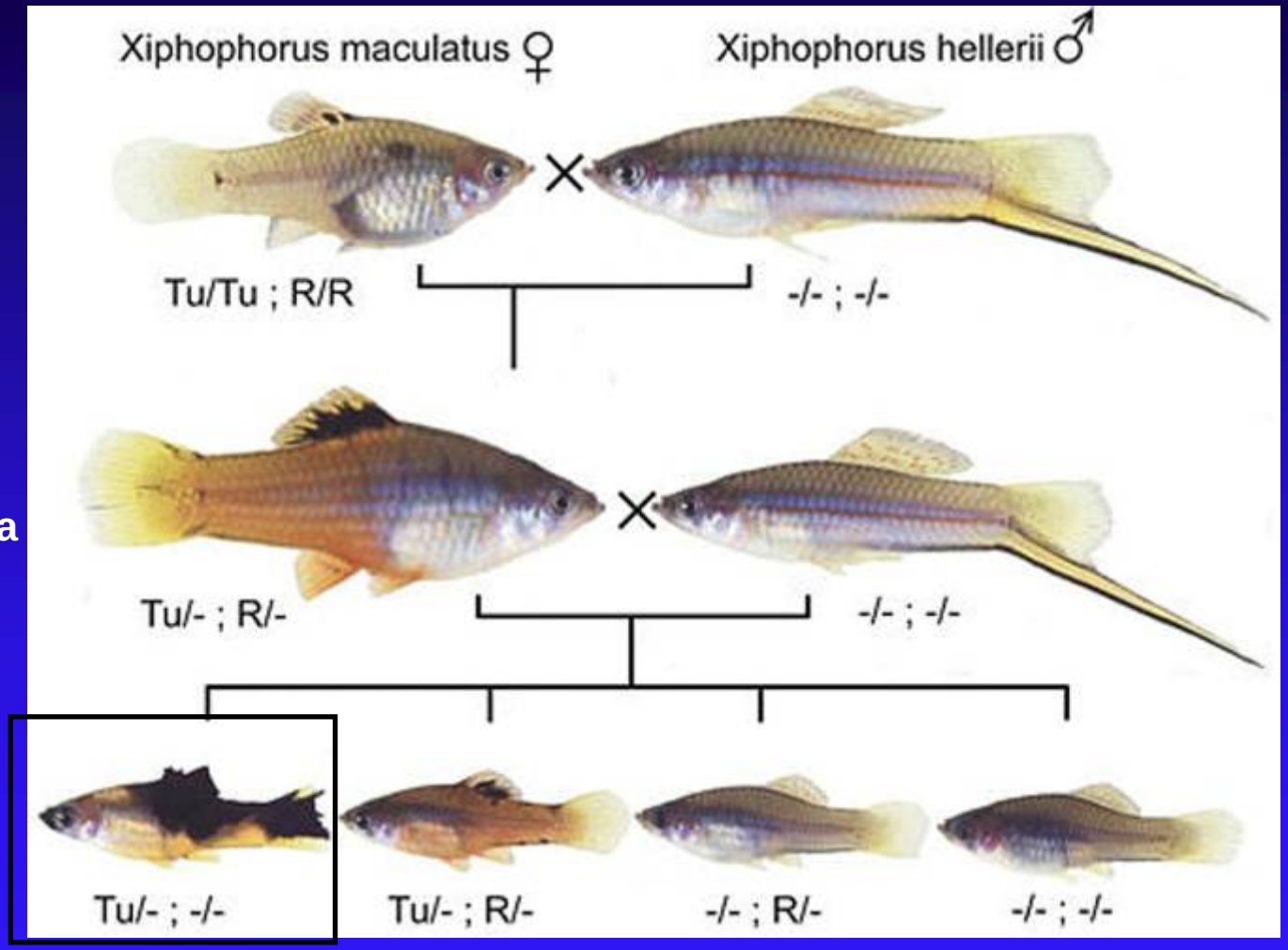
Nitrogen-fixing nodules on leguminous plant roots

Example of tumor which have played role in evolution: melanoma in Xiphophorus fishes

Macromelanophores – a novel cell type present in genus Xiphophorus. These macromelanophores are controlled by two genes, Tu gene and tumor suppressor R gene. Malignant tumor formation is promoted in back-cross progeny fishes with tumor suppressor deficient genotype.

We assume that in the course of evolution the reverse could happen. The origin of tumor suppressor gene could differentiate melanomas to generate new cell type of functional camouflage-related melanocytes and stabilize the population of fishes previously highly predisposed to cancer.

Model of Genetically Determined Xyphophorus Melanoma



benign melanoma

Fatal malignant melanoma

benign melanoma

Papillomatosis and Appearance of Macrovilli in the Rodent Stomach

Vorontsov, 2003

The cardiac portion of the stomach in several rodent genera is lined with macrovilli developed from the growth of corneal epithelium. Microvilli favor development of symbiotic flora and are called symbiovilli.

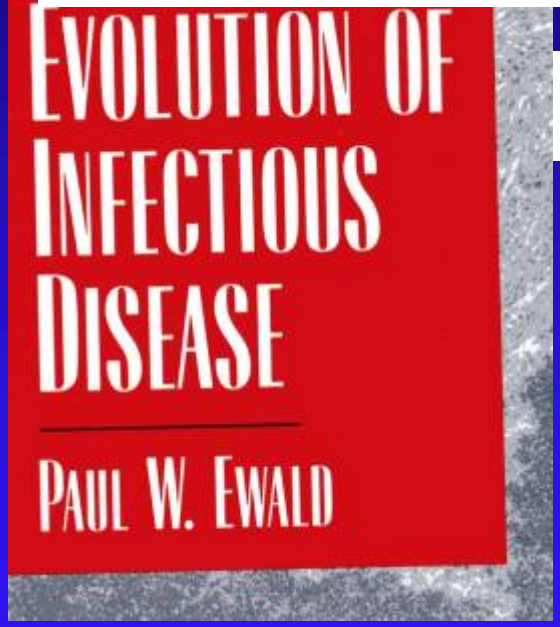
Cases of hereditary malignant neoplasm giving rise to formation of multiple macrovilli in the cardiac portion of the stomach have been found in the vole Microtus abbreviatus.

It was assumed that the early stages of papillomatosis, by creating favorable conditions for symbiotic microflora, became advantageous and were selected.

Evolutionary approach to health and disease

Darwinian medicine

The integration of evolutionary biology with the health sciences brings to an overlapping discipline, termed Darwinian medicine, which takes an evolutionary approach to the entire spectrum of issues related to health and disease. For example, senescence is considered as a consequence of selection for traits that are beneficial during the early and middle years of life–span. Williams, G.C. and Nesse, R.M. 1991.The Dawn of Darwinian medicine. Q.Rev.Biol. 66, 1-22.



Evolutionary epidemiology

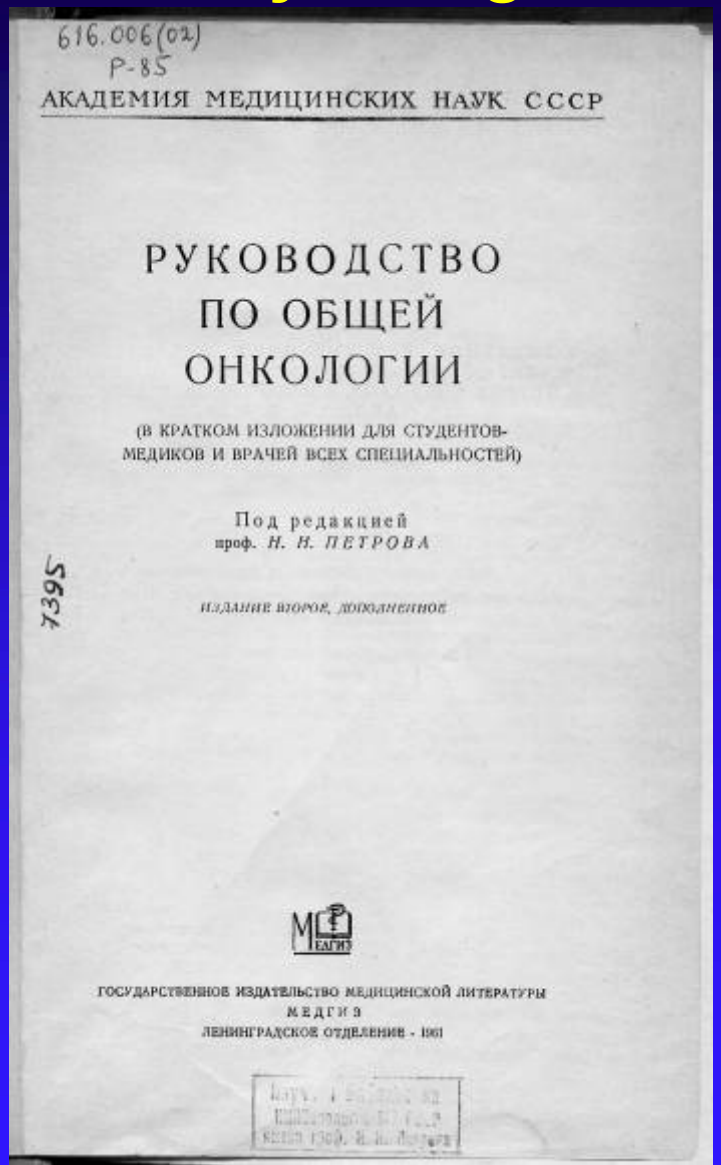
Evolutionary epidemiology broadens the scale of inquiry still further to assess
how the characteristics that traditional epidemiology has identified to be important – lethality, illness, transmission rates, prevalences of infection – change over time as hosts and parasites evolve in response to each other and to outside environments

Evolutionary oncology

We were looking for the evolutionary role of tumors (Kozlov, 1976, 1979, 1983, 1987, 1988, 1996, 2008).

Genetically or epigenetically predetermined tumors at the early stages of progression, or benign tumors, or some tumor-like processes which provide multicellular organisms with extra cell masses are considered as potentially evolutionarily meaningful, not malignant tumors at the late stages of progression

General oncology considers tumors as a broad biological phenomenon, which includes not only malignant tumors



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АКАДЕМИЯ МЕДИЦИНСКИХ НАУК СССР

РУКОВОДСТВО
ПО ОБЩЕЙ
ОНКОЛОГИИ

(В КРАТКОМ ИЗЛОЖЕНИИ ДЛЯ СТУДЕНТОВ-
МЕДИКОВ И ВРАЧЕЙ ВСЕХ СПЕЦИАЛЬНОСТЕЙ)

Под редакцией
проф. Н. Н. ПЕТРОВА

7395

издание второе, дополненное

ГОСУДАРСТВЕННОЕ ИЗДАТЕЛЬСТВО МЕДИЦИНСКОЙ ЛИТЕРАТУРЫ
МЕДГИЗ
ЛЕНИНГРАДСКОЕ ОТДЕЛЕНИЕ - 1961

Textbook on General Oncology
Prof.N.N.Petrov, ed. 1961
Leningrad,
Academy of Medical Sciences of the USSR

Comparative oncology discovered tumors in virtually all multicellular organisms

Comparative oncology suggests that tumors in lower vertebrates (e.g.fishes) have lower malignancy potential comparing with mammalian tumors

Widespread occurrence of tumors and tumor-like processes in multicellular organisms suggests that tumors might play some role (or several roles) in the evolution of species.

Features of tumors which could be used in evolution:

- **Gene activation in tumor cells**
- **The ability of tumor cells to differentiate with concomitant loss of malignancy.**

PBOV1 expression features and possible functional role

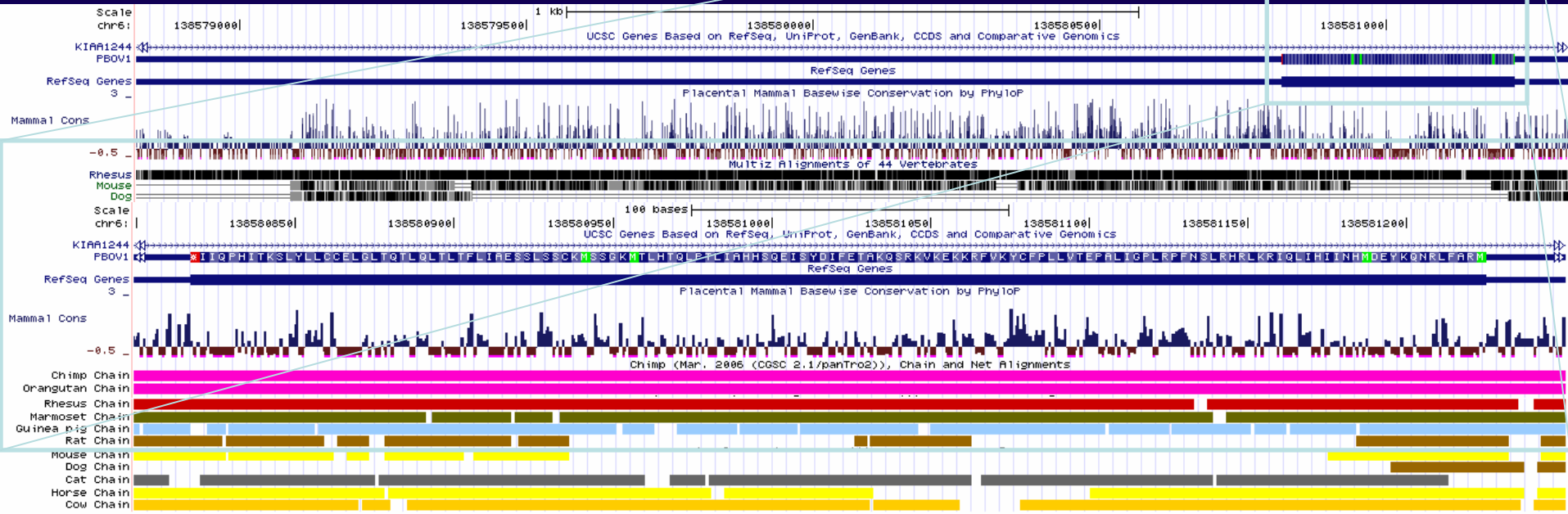
PBOV1 expression in tumors is partially explained by genomic features

1. The promoter sequence of PBOV1 gene is enriched in MYC-N binding sites (MYC-N is overexpressed in brain and lung cancers),
2. PBOV1 gene is situated in an intron of BIG3 gene (a member of the estrogen signalling pathway that is overexpressed in breast cancer and possibly other hormone-dependent tumors)

Hypothetical function of PBOV1

- One non-synonymous SNP in PBOV1 is associated with increased breast cancer risk
- Possibly a novel type of tumor suppressor, which is activated in the course of cancer progression and may trigger an immune response.

PBOV1 is a protein coding gene that originated de novo in primate evolution



- Single-exon gene, ORF encodes a 137-aa protein
- C-terminal 12% of sequence is human-specific
- Over 72% of protein sequence is absent from Rhesus and more distant species
- Start-codon doesn't exist in the majority of non-primate species
- Protein-coding sequence is not conserved, Ka/Ks ~ 1.0
- Unusually high codon usage bias of 0.21 (p=0.004 over a random sequence)