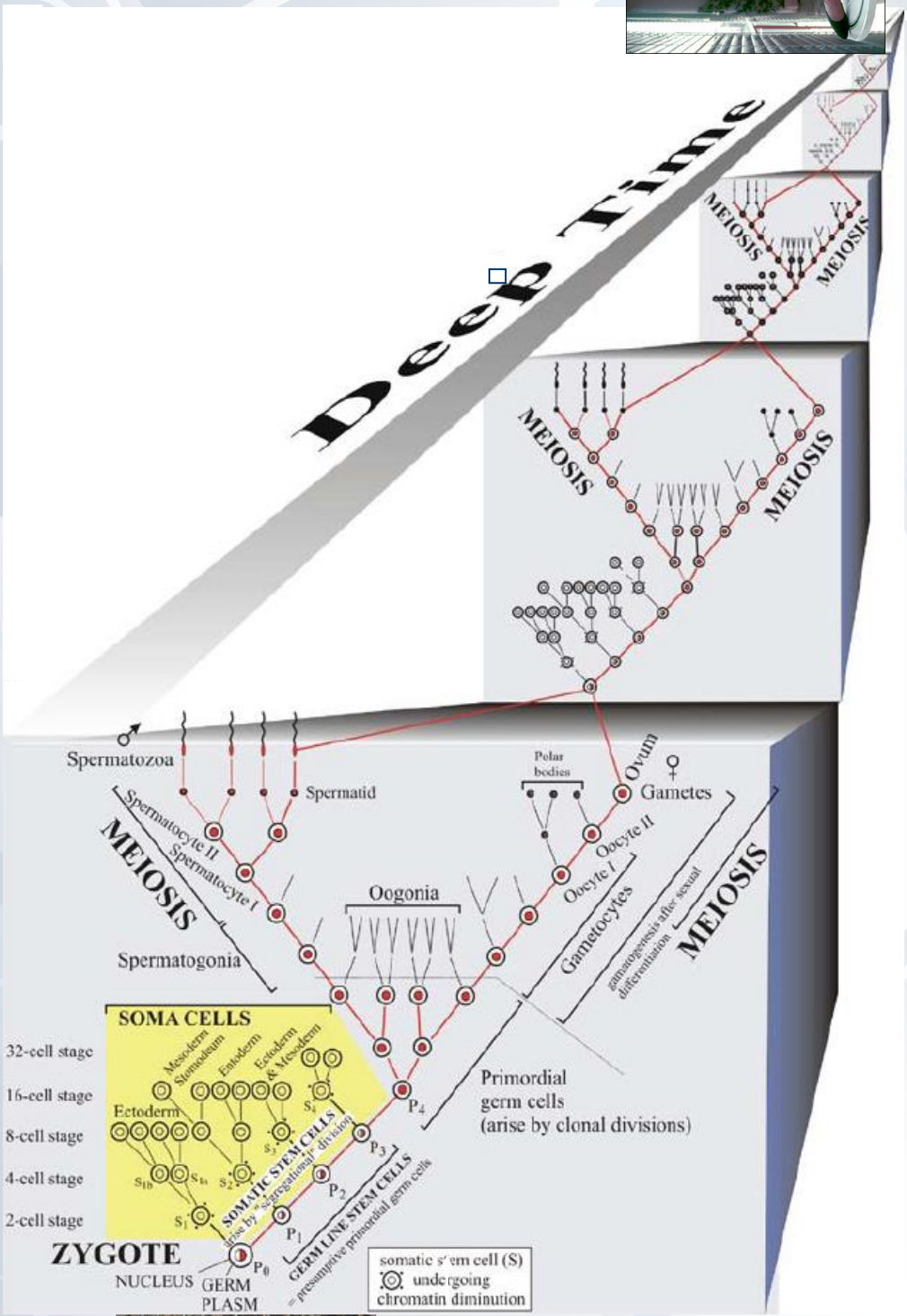
Beyond the codes of DNA: epigenetics as the facsimile of genesis

The differences that make a difference in the logical structures of mammalian genomes

Richard v. Sternberg

Biologic Institute


Deep Time
MEIOSIS
MEIOSIS
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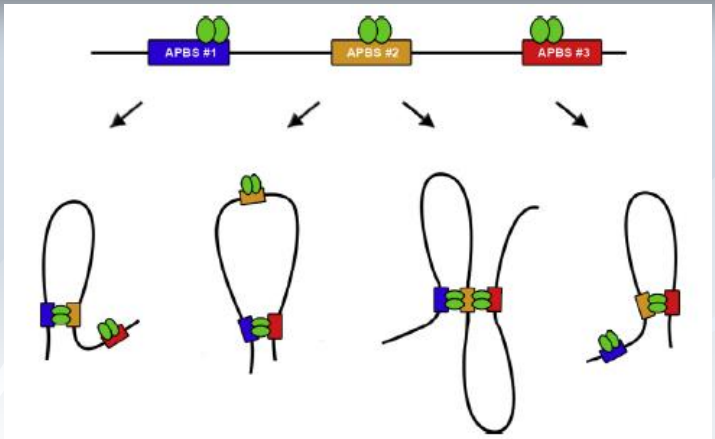
MEIOSIS
Spermatozoa
Spermatid
Spermatocyte II
Spermatocyte I
MEIOSIS
Spermatogonia
Oogonia
Polar bodies
Ovum
♀
Gametes
Oocyte II
Oocyte I
Gametocytes
gamatogenesis after sexual differentiation
MEIOSIS
SOMA CELLS
32-cell stage
16-cell stage
8-cell stage
4-cell stage
2-cell stage
Mesoderm Stomodeum
Ectoderm
Ectoderm & Mesoderm
Ectoderm
SOMATIC STEM CELLS
arise by "segregational" division
Primordial germ cells
(arise by clonal divisions)
GERM LINE STEM CELLS
= presumptive primordial germ cells
ZYGOTE
NUCLEUS
GERM PLASM
somatic s' em cell (S)
undergoing chromatin diminution

On transitional forms:

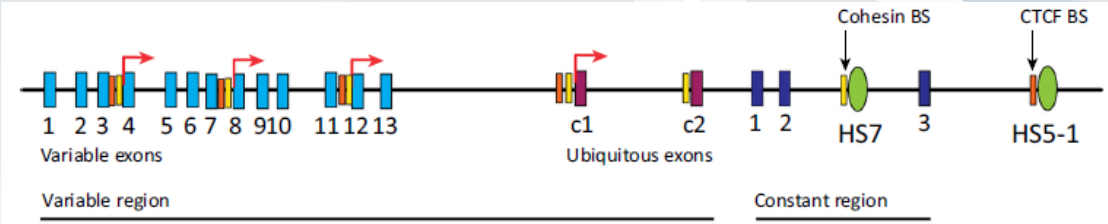
'[D]irect transition between different "types" is only possible if the transitional forms have all the characters that the ancestral and the derived types have and are thus compatible with the factorization of both types. Transitional forms thus have to go over a "complexity hump" where they have more quasi-independent characters than either the ancestral as well as the derived type. The only logical, but biologically unlikely, alternative is a "hopeful monster" that transforms in a single step from the ancestral type to the derived type.'

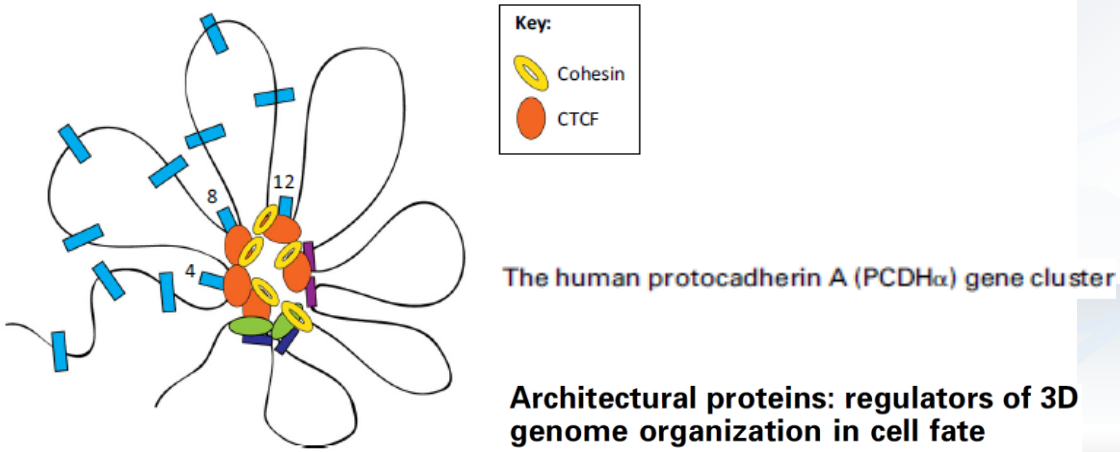


Architectural proteins, transcription, and the three-dimensional organization of the genome

http://dx.doi.org/10.1016/j.febslet.2015.05.025

Caelin Cubeñas-Potts, Victor G. Corces *





The human protocadherin A (PCDHα) gene cluster

Architectural proteins: regulators of 3D genome organization in cell fate

Elena Gómez-Díaz and Victor G. Corces

Trends in Cell Biology, November 2014, Vol. 24, No. 11

Let us recall that chromatin folding allows different circuits to be formed…

Gene folders/ALUs are in turn arranged into "superfolders."

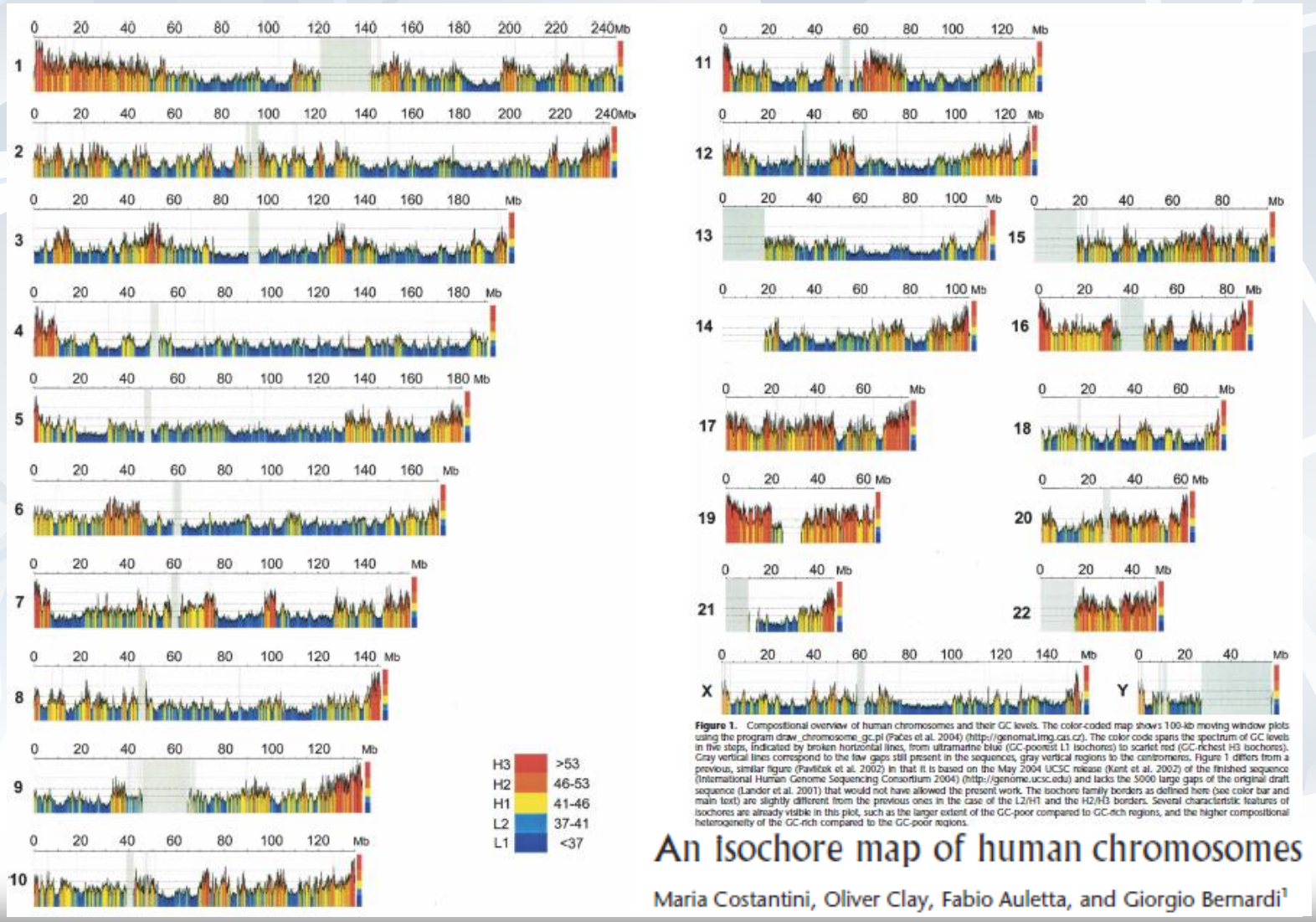


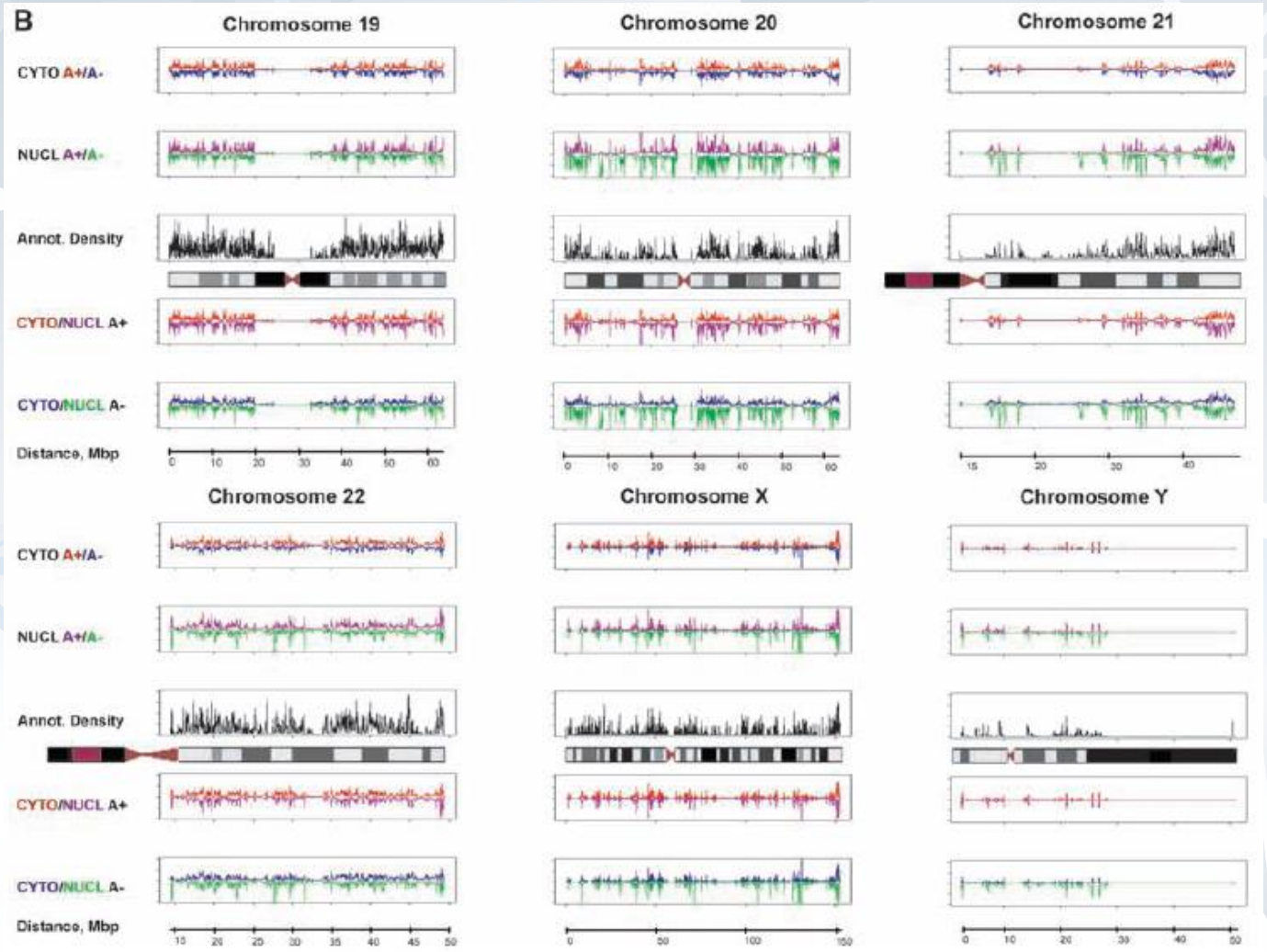
Figure 1. Compositional overview of human chromosomes and their GC levels. The color-coded map shows 100-kb moving window plots using the program draw_chromosome_gc.pl (Pačes et al. 2004) (http://genomat.lmg.cas.cz). The color code spans the spectrum of GC levels in five steps, indicated by broken horizontal lines, from ultramarine blue (GC-poorest L1 isochores) to scarlet red (GC-richest H3 isochores). Gray vertical lines correspond to the few gaps still present in the sequences, gray vertical regions to the centromeres. Figure 1 differs from a previous, similar figure (Pavlíček et al. 2002) in that it is based on the May 2004 UCSC release (Kent et al. 2002) of the finished sequence (International Human Genome Sequencing Consortium 2004) (http://genome.ucsc.edu) and lacks the 5000 large gaps of the original draft sequence (Lander et al. 2001) that would not have allowed the present work. The isochore family borders as defined here (see color bar and main text) are slightly different from the previous ones in the case of the L2/H1 and the H2/H3 borders. Several characteristic features of isochores are already visible in this plot, such as the larger extent of the GC-poor compared to GC-rich regions, and the higher compositional heterogeneity of the GC-rich compared to the GC-poor regions.

An Isochore map of human chromosomes

Maria Costantini, Oliver Clay, Fabio Auletta, and Giorgio Bernardi[1]

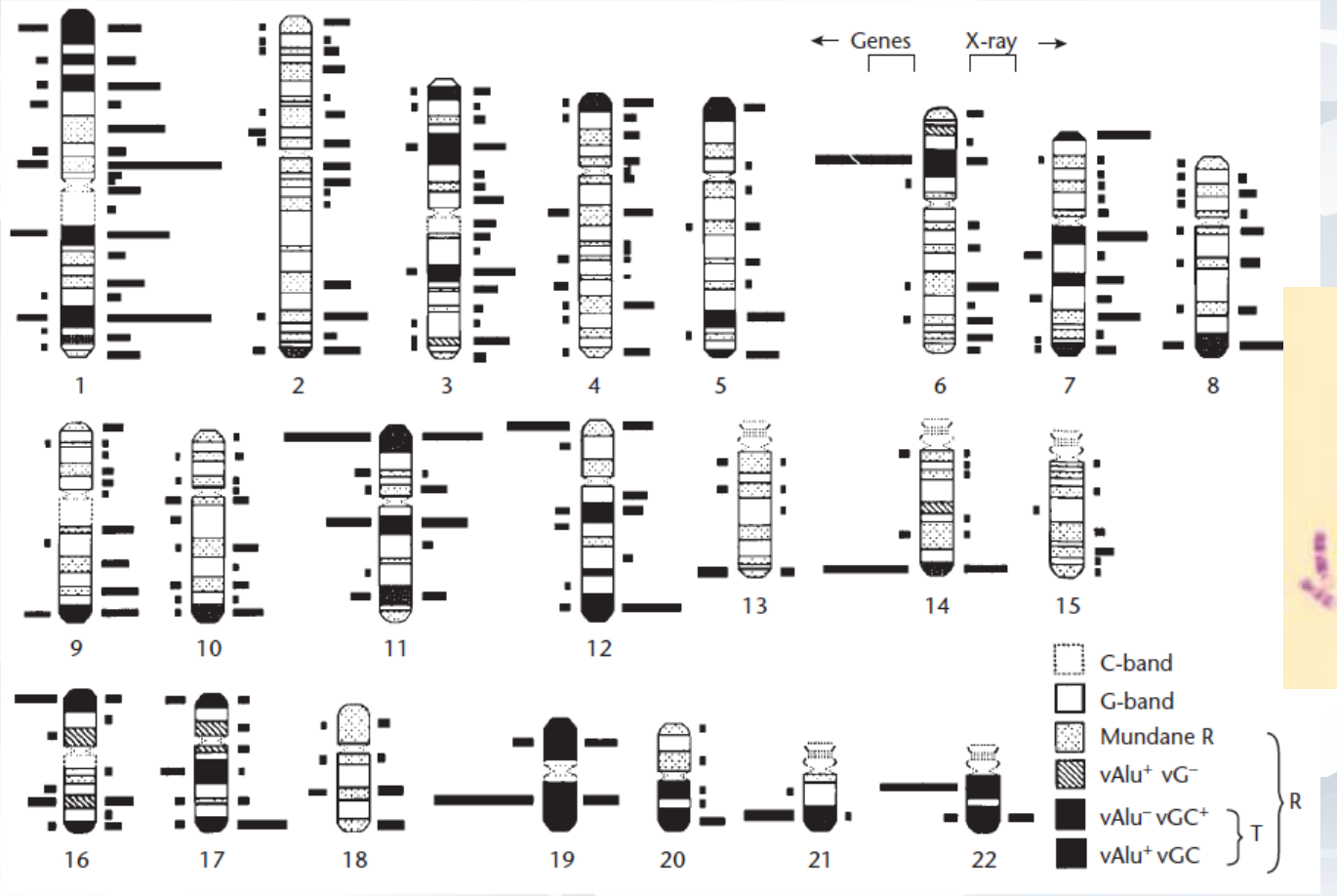
Genome Research 16:536–541 ©2006

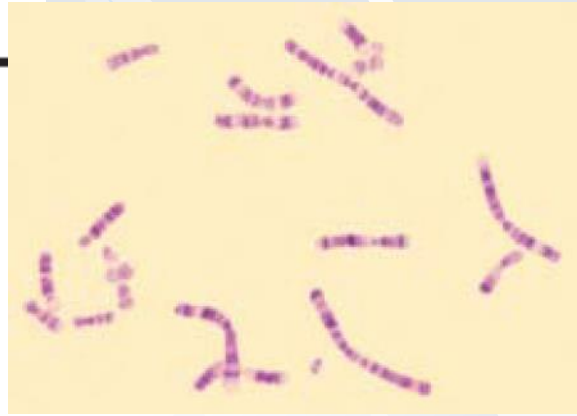
Different “superfolders” encode different classes of RNA outputs.



Transcriptional Maps of 10 Human Chromosomes at 5-Nucleotide Resolution
Jill Cheng, *et al.*
Science **308**, 1149 (2005);

And chromosome "superfolders" are in turn ordered into banding patterns.



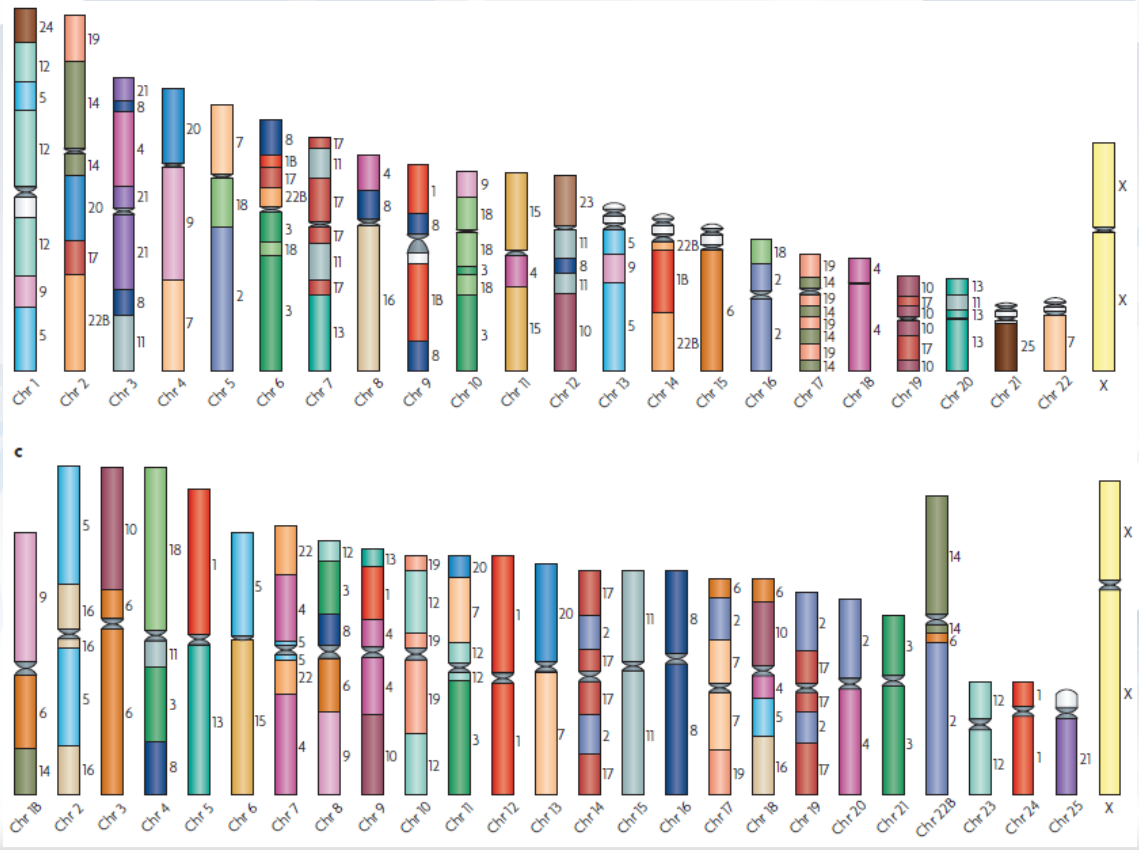


Chromosomal Bands and Sequence Features

ENCYCLOPEDIA OF LIFE SCIENCES © 2005,

Gerald P. Holmquist, *City of Hope, Duarte, California, USA*

Now, most chromosome bands ("megafolders") are conserved across mammals, but their ordering can be different.

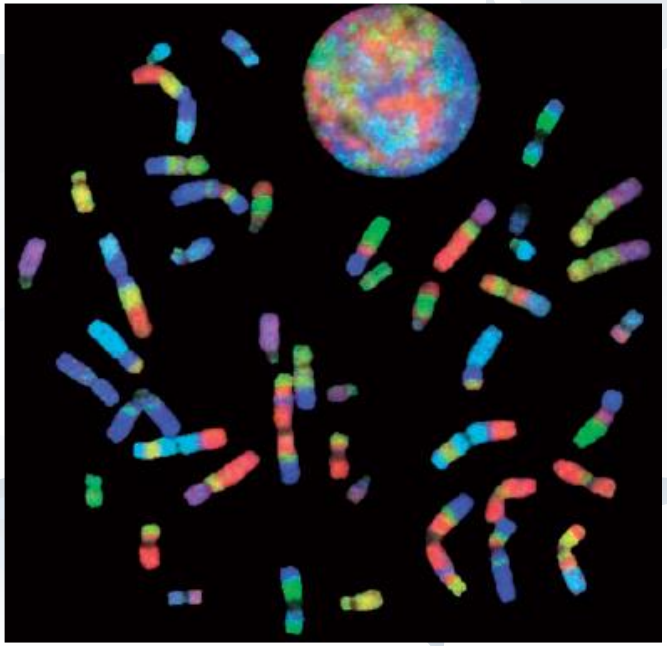


The number, types, and ordering of *protein-coding* genes is much the same across mammals.

Mammalian karyotype evolution

Malcolm A. Ferguson-Smith and Vladimir Trifonov*‡*

Abstract | The chromosome complements (karyotypes) of animals display a great diversity in number and morphology. Against this background, the genomes of all species are remarkably conserved, not only in transcribed sequences, but also in some chromosome-specific non-coding sequences and in gene order. A close examination with chromosome painting shows that this conservation can be resolved into small numbers of large chromosomal segments. Rearrangement of these segments into different combinations explains much of the observed diversity in species karyotypes.



Aardvark and Human Chromosomes

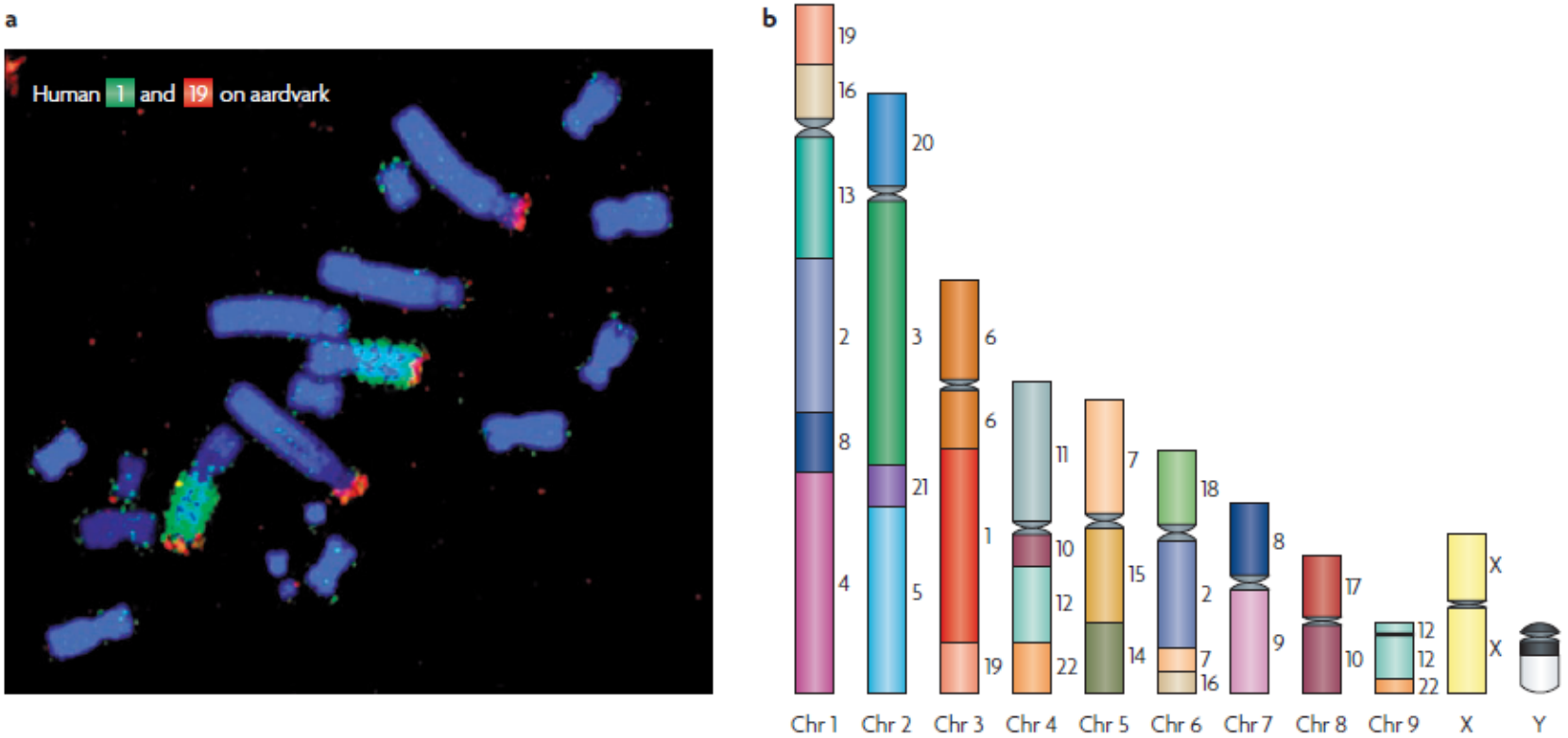


Figure 2 | **Mapping human homologies on aardvark chromosomes. a** | Paint probes that are specific for human chromosomes 1 and 19 hybridize to aardvark chromosomes 1p and 3q. **b** | A complete map of the human homologies on aardvark chromosomes. Image in part **a** courtesy of F. Yang, The Wellcome Trust Sanger Institute, Cambridge, UK.

Dolphin and Human Chromosomes

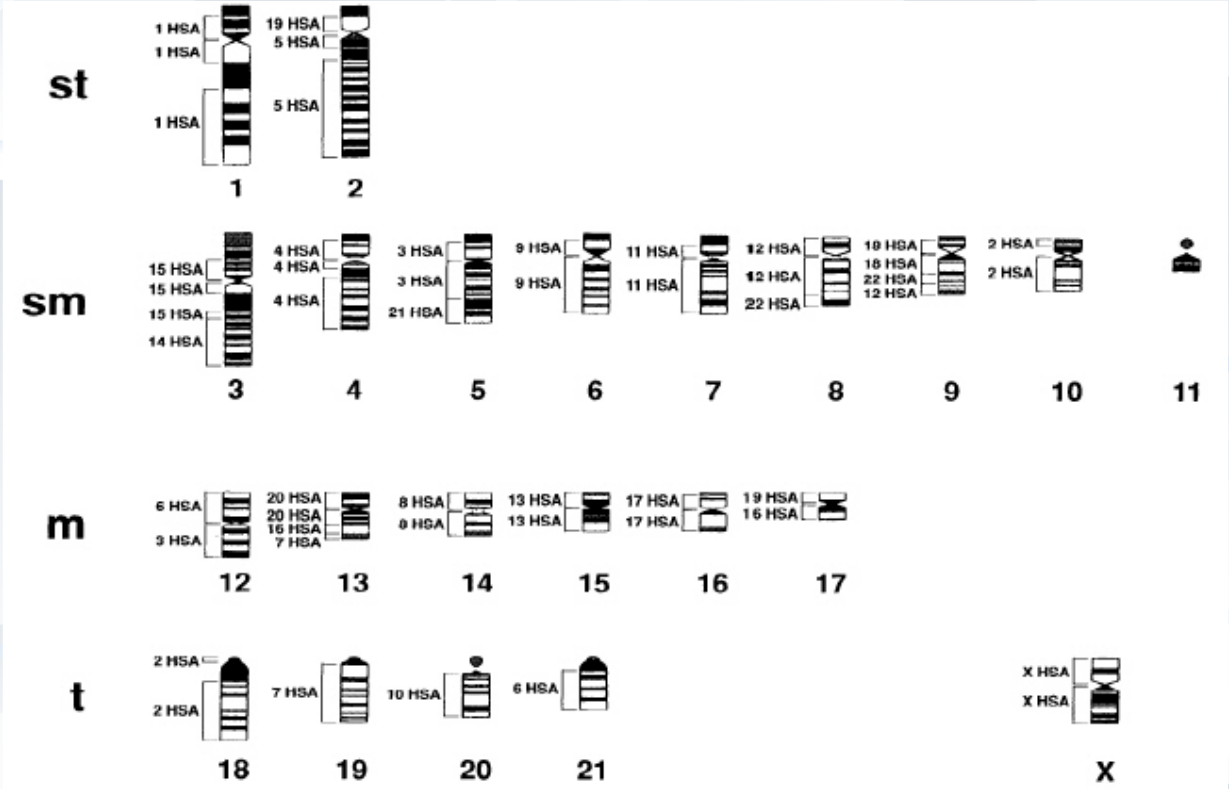


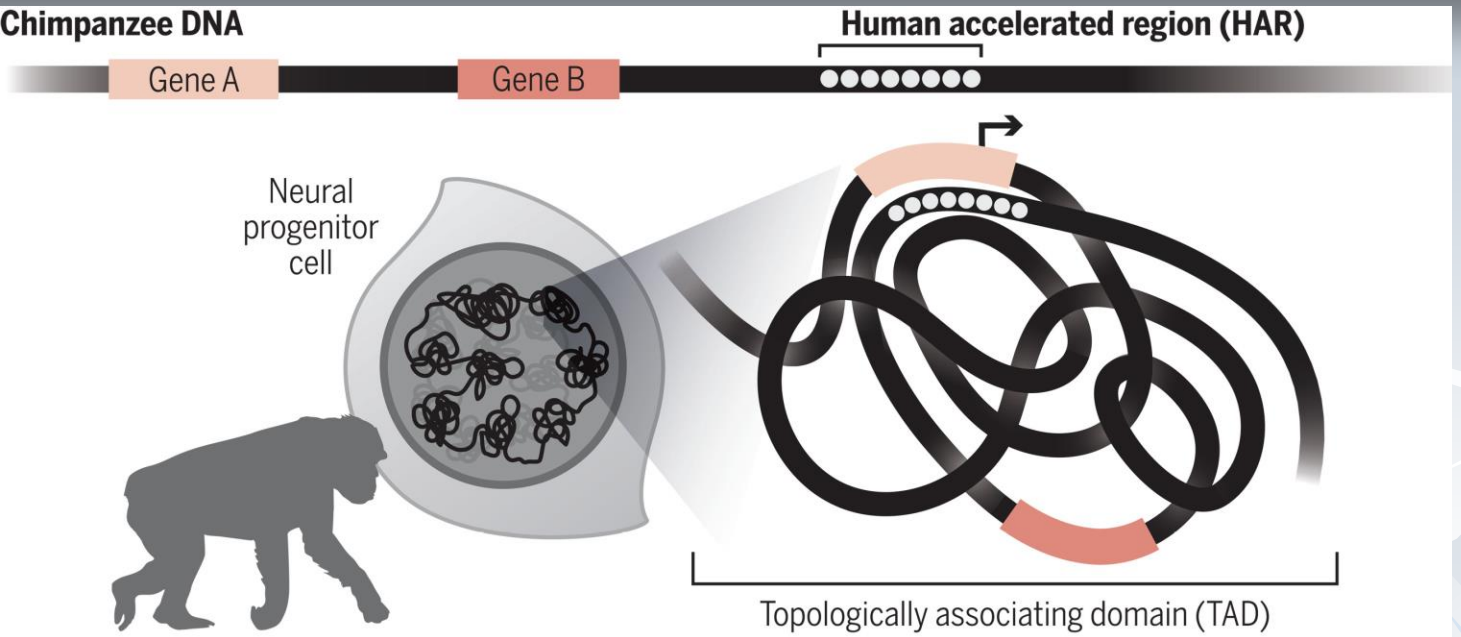
Fig. 2. Ideogram of the GBG-banded *Tursiops truncatus* karyotype showing homologies detected between *T. truncatus* and human (HSA) chromosomes. Bracketed regions of dolphin chromosomes indicate segments of homology with human paints. The limits of conserved segments shown in this figure are based on visual examination of the ZOO-FISH painting results.

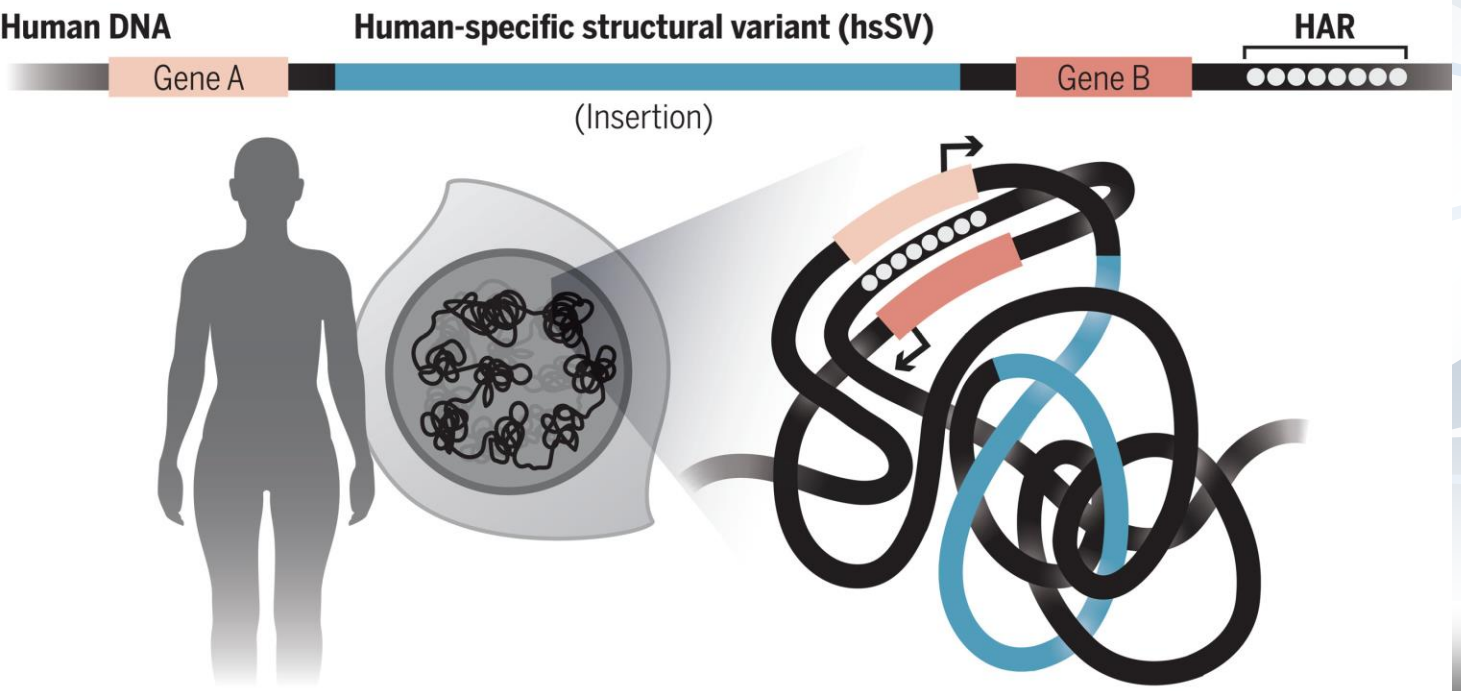
Bielec, P. E., Gallagher, D. S., Womack, J. E., and Busbee, D. L.. *Homologies Between Human and Dolphin Chromosomes Detected by Chromosome Painting.* Cytogenetics & Cell Genetics. 1998: 81 (1): 18-25.

"…the dolphin genome and the human genome are basically the same. It's just that there are a few chromosomal rearrangements that have changed the way the genetic material is put together."

Dr. D. L. Busbee

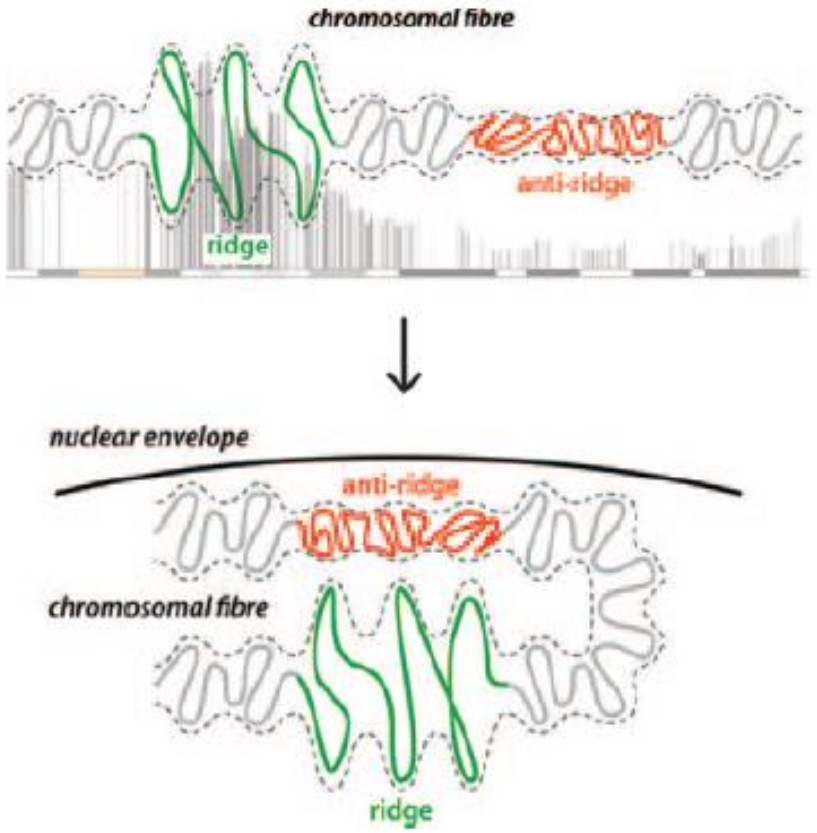
The significance of this that the DNA data content for our protein "parts list" is largely shared with all mammals (and vertebrates in general).





Which brings us to genetics in 3D and 4D

Co-expressed loci are clustered together along in the nucleus, sometimes to “create” genes



The Three-Dimensional Structure of Human Interphase Chromosomes Is Related to the Transcriptome Map[▽]

Sandra Goetze,[1]† Julio Mateos-Langerak,[1]† Hinco J. Gierman,[2] Wim de Leeuw,[3] Osdilly Giromus,[1] Mireille H. G. Indemans,[2] Jan Koster,[2] Vladan Ondrej,[4] Rogier Versteeg,[2] and Roel van Driel[1]*

MOLECULAR AND CELLULAR BIOLOGY, June 2007, p. 4475–4487

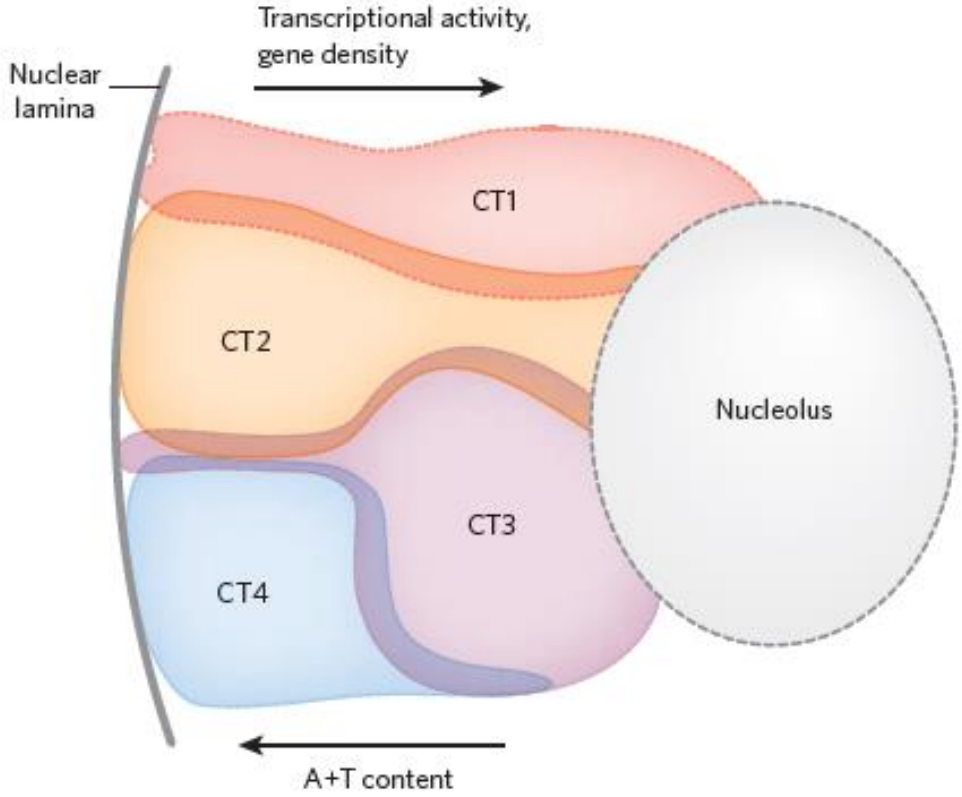


Figure 3 | Radial organization of chromosome territories within the nucleus regulates opportunities for chromatin crosstalk. The relative positions of chromosomes in an interphase nucleus depend on the proportion of genes and the A+T content. The opportunities for chromatin crosstalk between

Chromosome crosstalk in three dimensions

Anita Göndör[1] & Rolf Ohlsson[1]

NATURE|Vol 461|10 September 2009|

And these are in turn organized into "topologically-associating domains" that are cell-specific.

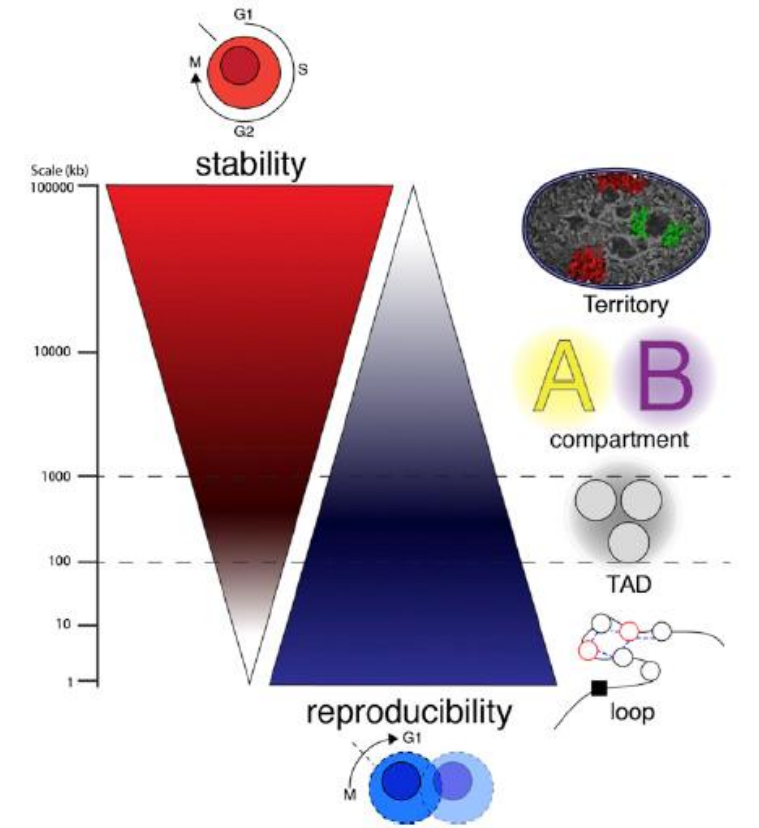


Figure 3. The Stability and Reproducibility of Chromosomal Interactions

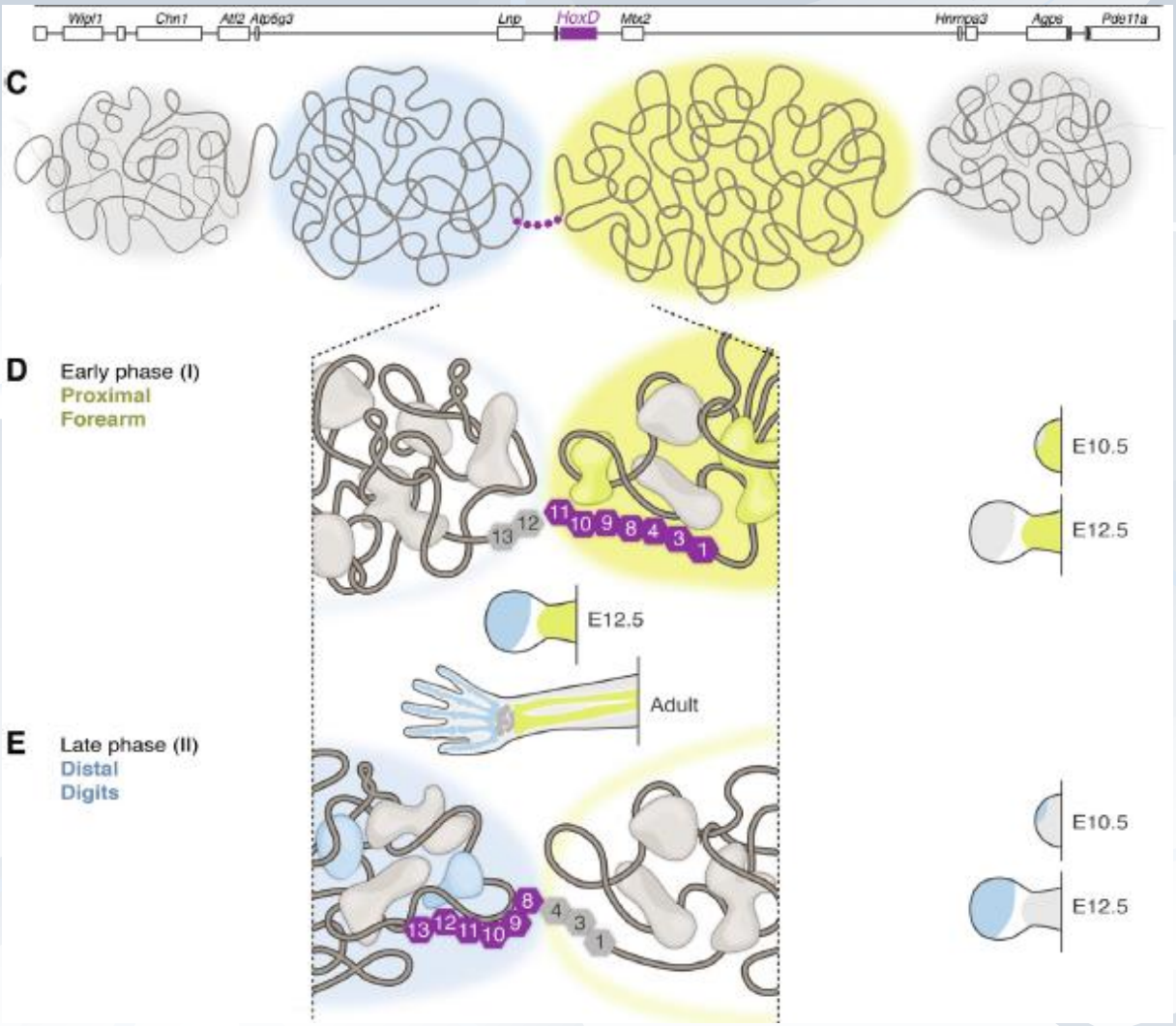
Chromosomal territories and compartments are very stable within one cell cycle of a given cell, but they are unlikely to be reproduced from one cell cycle to the next. Conversely, interactions between loops (within TADs) will be unstable and variable within each cell cycle, but this "instability" is reproducible from one cell cycle to the next. At the junction between stability and reproducibility, TADs confine looping, while maintaining the possibility of compartmentalization.

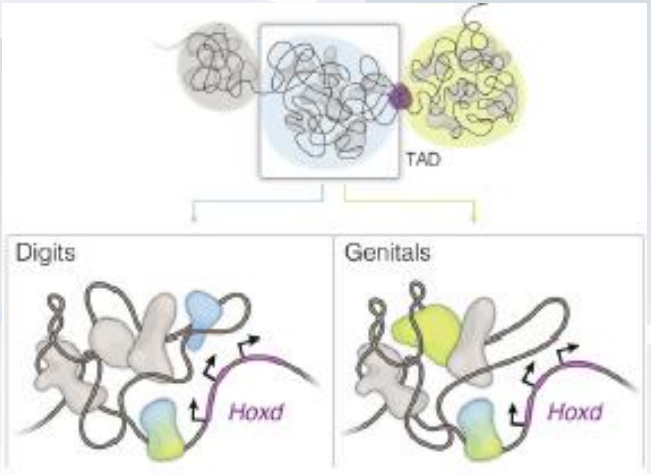
The Hierarchy of the 3D Genome

Johan H. Gibcus[1] and Job Dekker[1,*]

Molecular Cell *49*, March 7, 2013

A regulatory switch between two adjacent TADs underlies the bimodal regulation occurring at the *HoxD* locus during limb development.

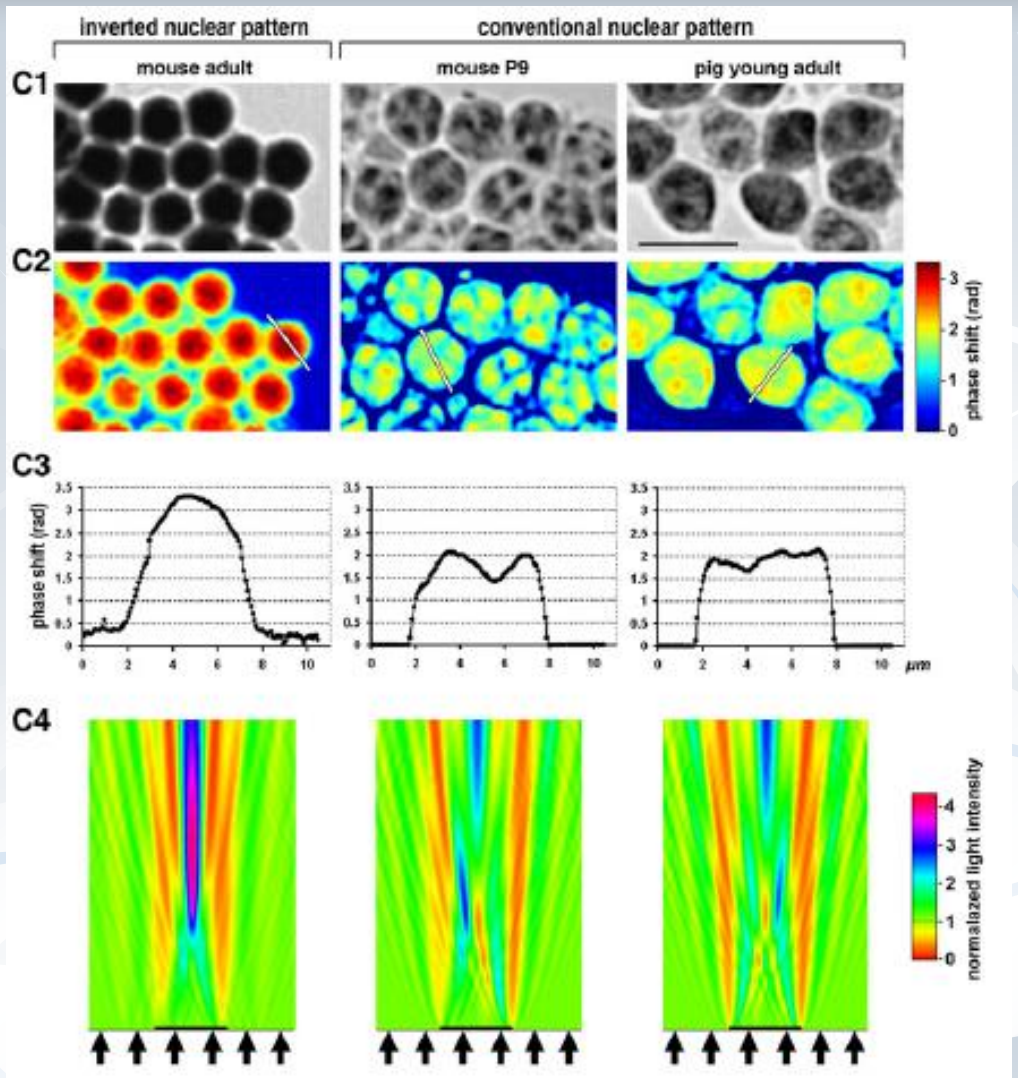




Structure, function and evolution of topologically associating domains (TADs) at *HOX* loci

Nicolas Lonfat [a,1], Denis Duboule [a,b,*]

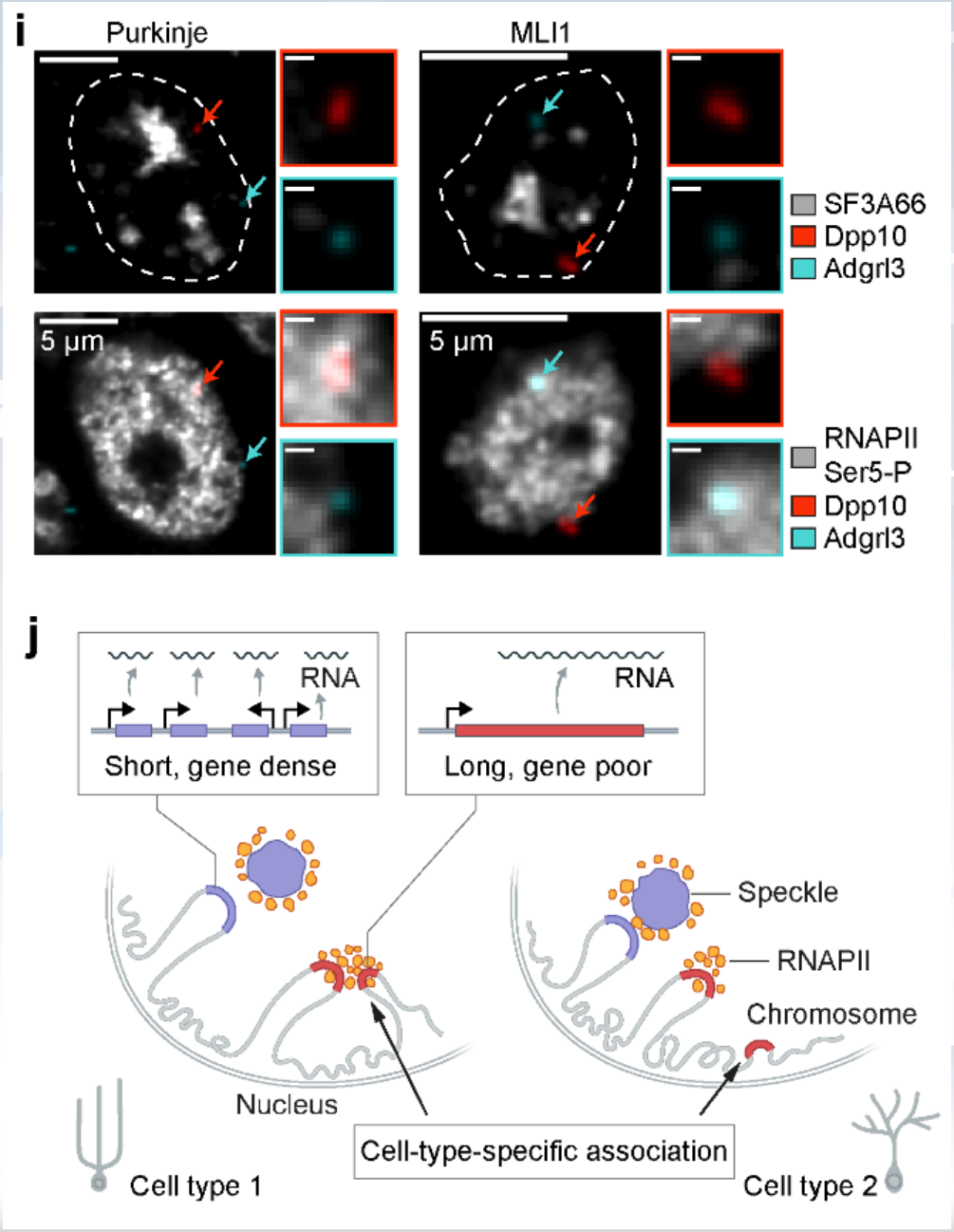
http://dx.doi.org/10.1016/j.febslet.2015.04.024



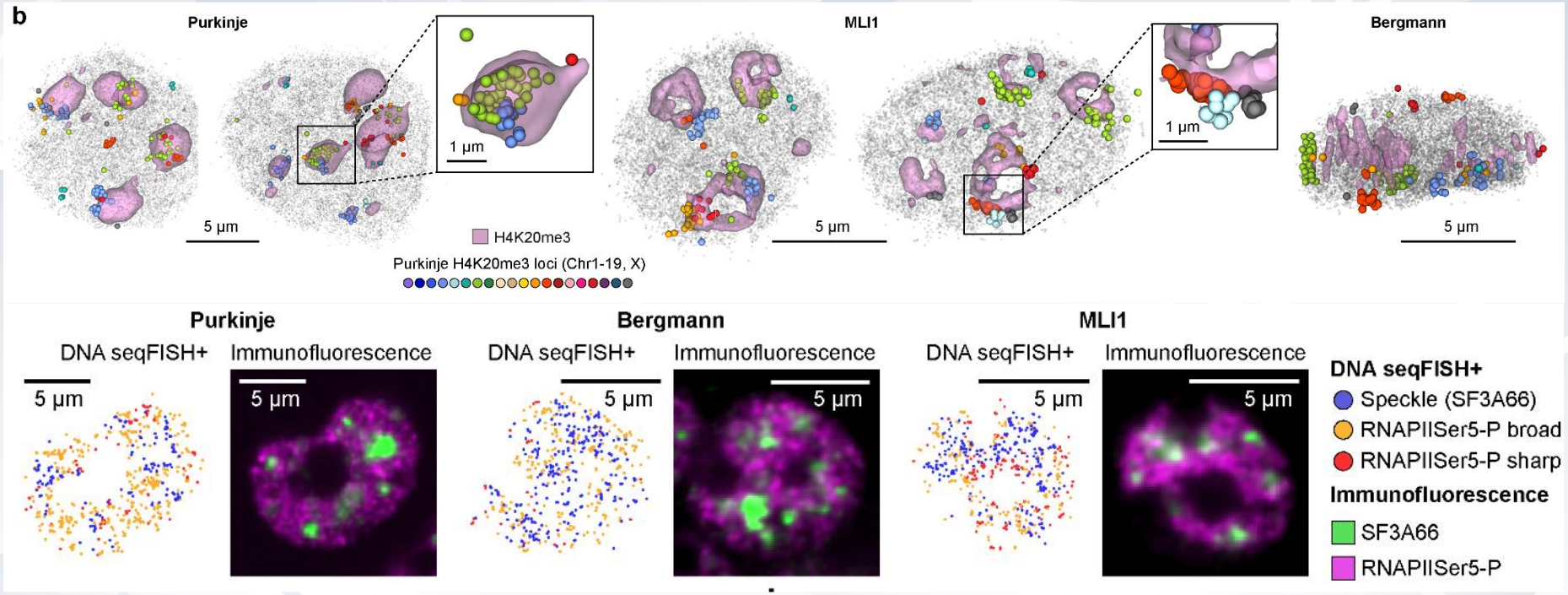
Nuclear Architecture of Rod Photoreceptor Cells Adapts to Vision in Mammalian Evolution

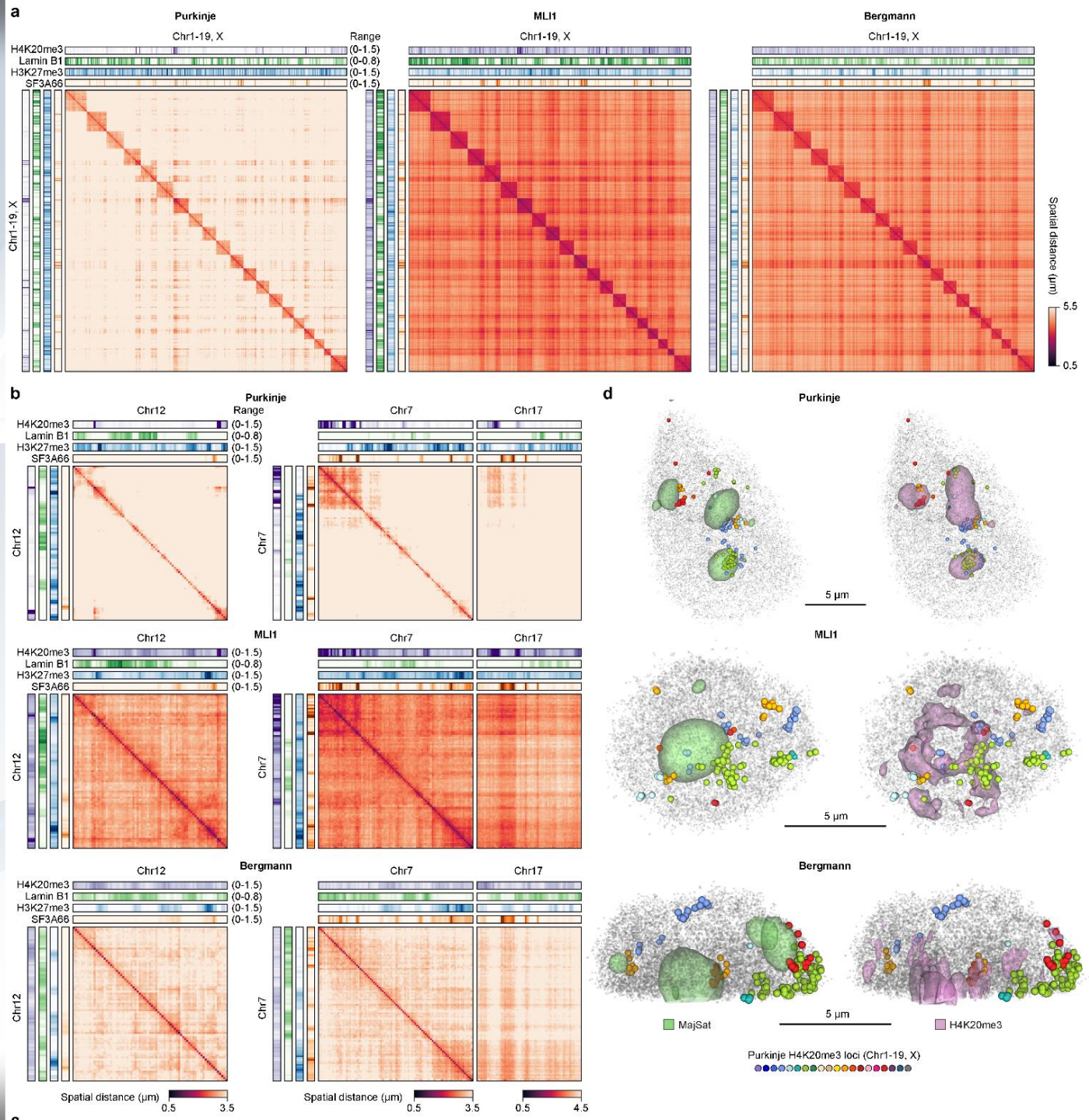
Irina Solovei,[1] Moritz Kreysing,[2] Christian Lanctôt,[1,5] Süleyman Kösem,[1] Leo Peichl,[3] Thomas Cremer,[1,4] Jochen Guck,[2,*] and Boris Joffe[1,*]

Cell *137*, 356–368, April 17, 2009



Brain-specific genes have dynamic 3D shapes


b
Purkinje
MLI1
Bergmann
5 µm
1 µm
H4K20me3
Purkinje H4K20me3 loci (Chr1-19, X)
Purkinje
Bergmann
MLI1
DNA seqFISH+
Immunofluorescence
DNA seqFISH+
Speckle (SF3A66)
RNAPIISer5-P broad
RNAPIISer5-P sharp
Immunofluorescence
SF3A66
RNAPIISer5-P

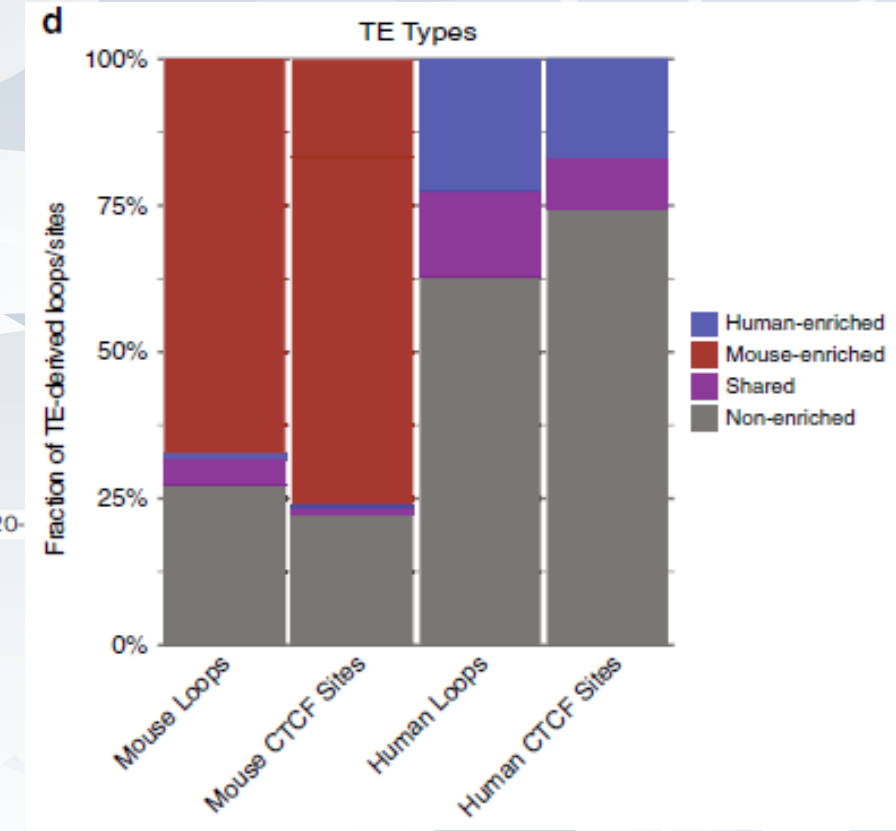


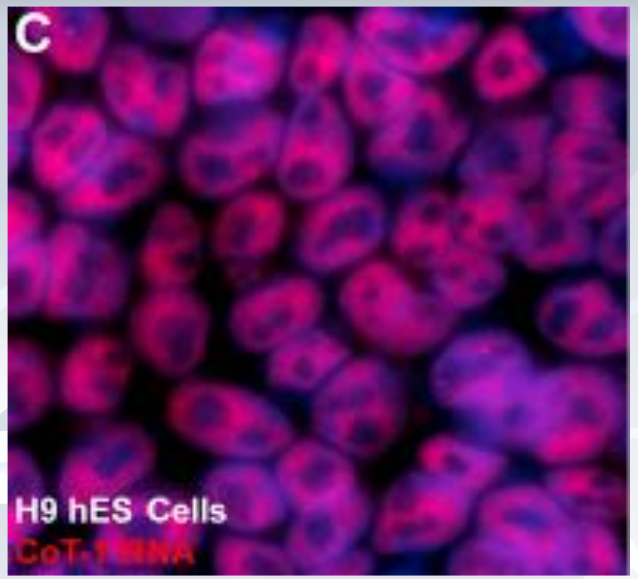
From 1D to 3D genomic states

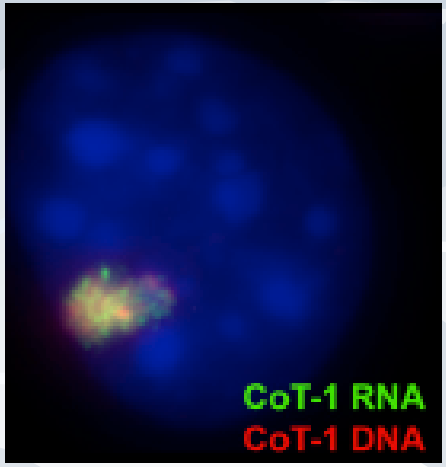
Transposable elements contribute to cell and species-specific chromatin looping and gene regulation in mammalian genomes

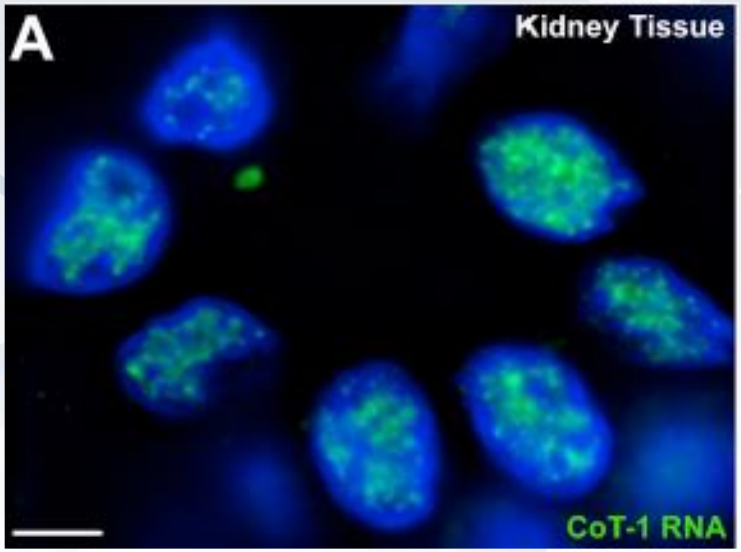
Adam G. Diehl [1], Ningxin Ouyang[1] & Alan P. Boyle [1,2]✉

NATURE COMMUNICATIONS | (2020)11:1796 | https://doi.org/10.1038/s41467-020-15520-









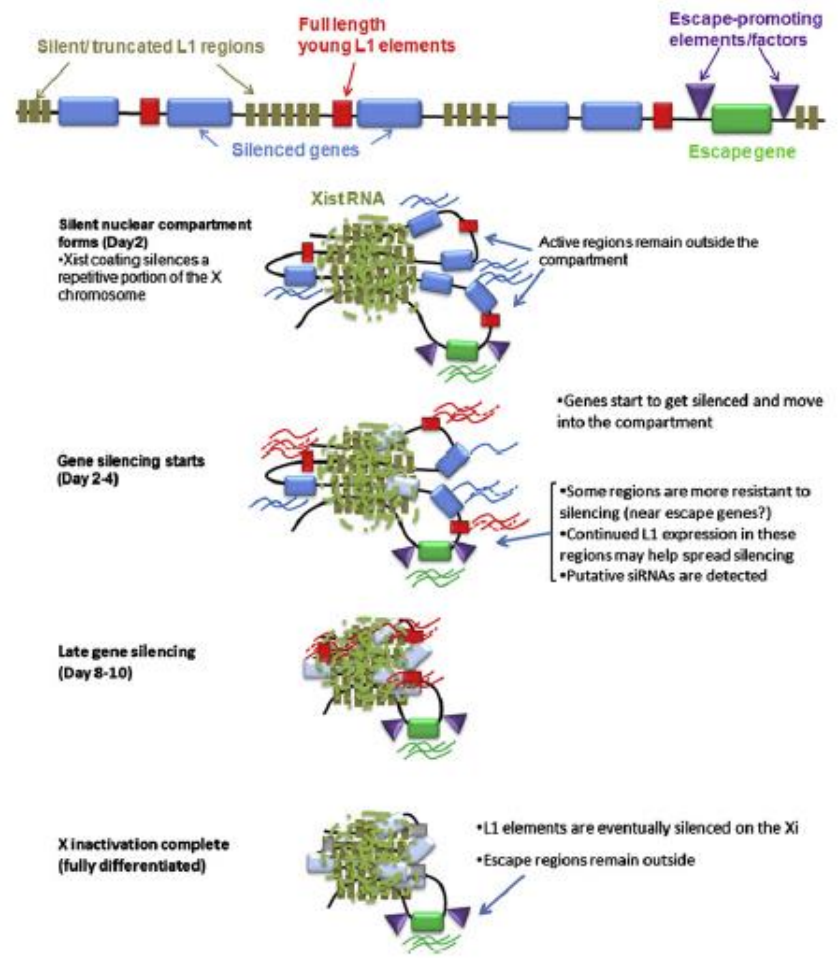
L1-repeat RNAs are known to form CoT-1 coats around chromosomes in nuclei, which are organizational. Most chromatin RNA is of this class, which is resynthesized with each cell division.

Stable C_0T-1 Repeat RNA Is Abundant and Is Associated with Euchromatic Interphase Chromosomes

Cell *156*, 907–919, February 27, 2014

Lisa L. Hall,[1,3] Dawn M. Carone,[1,3] Alvin V. Gomez,[1,4] Heather J. Kolpa,[1] Meg Byron,[1] Nitish Mehta,[1] Frank O. Fackelmayer,[2] and Jeanne B. Lawrence[1,*]

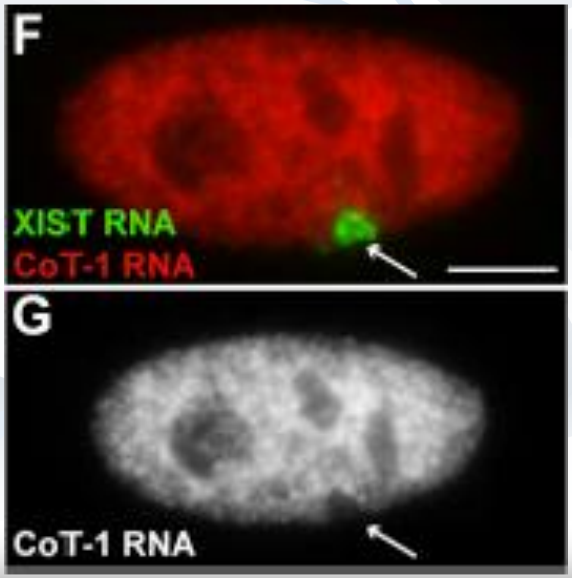
L1 elements also participate in barring access to large parts of an X chromosome.



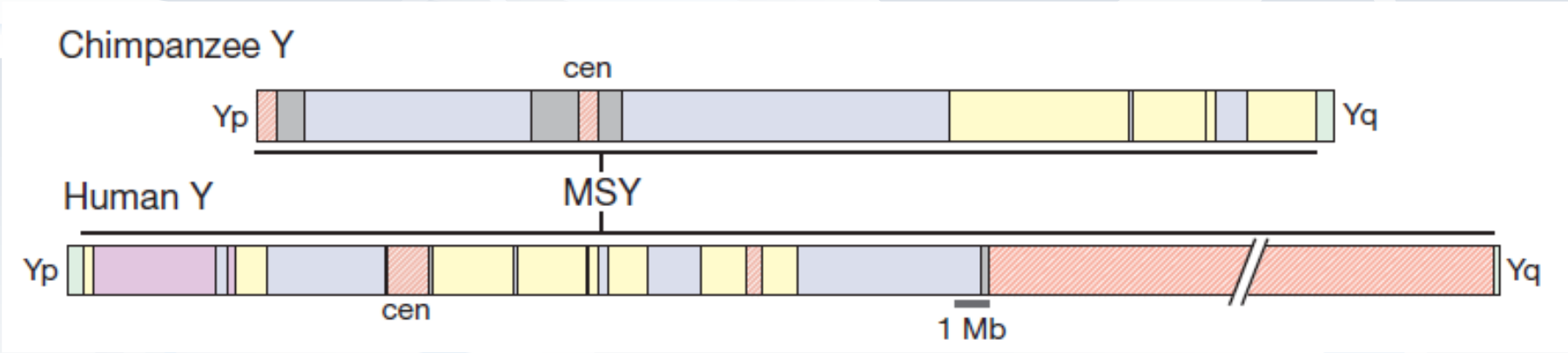
LINE-1 Activity in Facultative Heterochromatin Formation during X Chromosome Inactivation

Jennifer C. Chow,[1,2,3] Constance Ciaudo,[1,2,3,4] Melissa J. Fazzari,[5] Nathan Mise,[6,7] Nicolas Servant,[1,8,9] Jacob L. Glass,[5] Matthew Attreed,[5] Philip Avner,[6] Anton Wutz,[10] Emmanuel Barillot,[1,8,9] John M. Greally,[5] Olivier Voinnet,[4] and Edith Heard[1,2,3,*]

Cell *141*, 956–969, June 11, 2010



The chimp and human Y chromosomes are almost entirely species-specific.



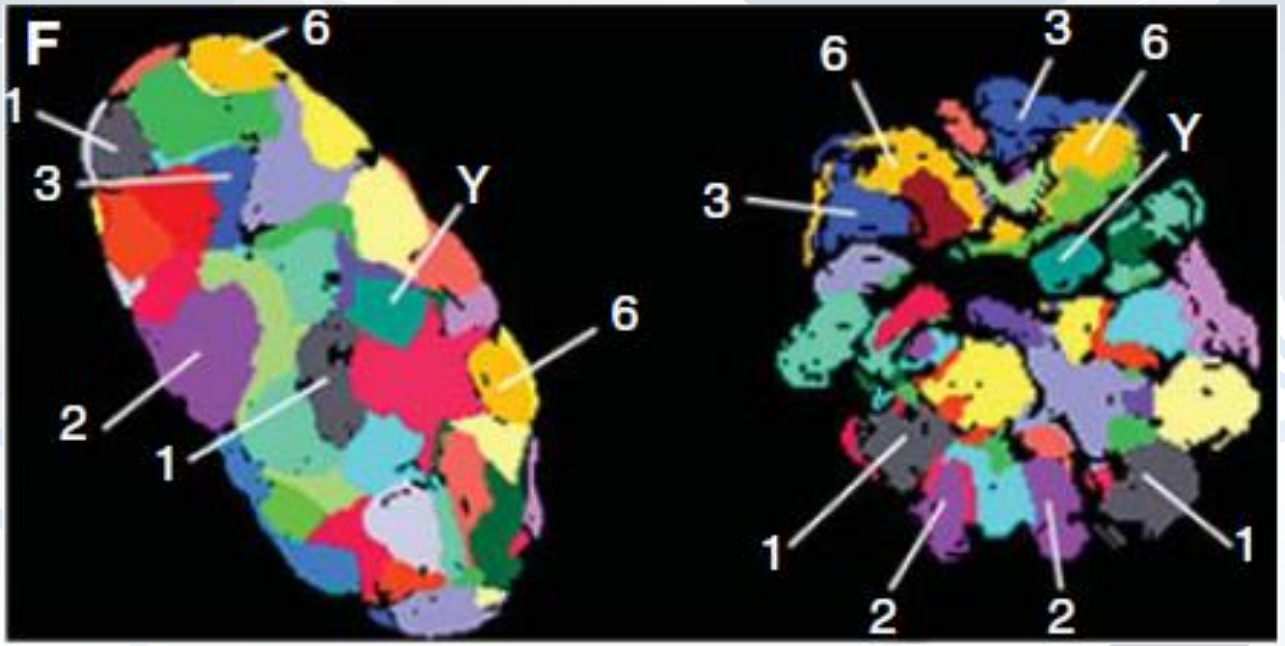
Human Y chromosomal sequences makes up two percent of a man's DNA…every man is 2% less a chimp than a woman is by Darwinian reckoning!

Chimpanzee and human Y chromosomes are remarkably divergent in structure and gene content

Jennifer F. Hughes[1], Helen Skaletsky[1], Tatyana Pyntikova[1], Tina A. Graves[2], Saskia K. M. van Daalen[3], Patrick J. Minx[2], Robert S. Fulton[2], Sean D. McGrath[2], Devin P. Locke[2], Cynthia Friedman[4], Barbara J. Trask[4], Elaine R. Mardis[2], Wesley C. Warren[2], Sjoerd Repping[3], Steve Rozen[1], Richard K. Wilson[2] & David C. Page[1]

Vol 463|28 January 2010|doi:10.1038/nature08700

Moreover, the Y chromosome is can be critical in this context.



Chromosome Territories

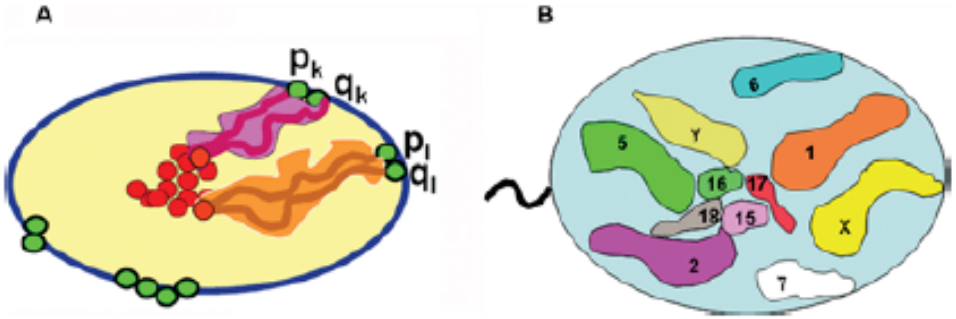
Cold Spring Harb Perspect Biol 2010;2:a003889

Thomas Cremer[1,2] and Marion Cremer[1]

Indeed, the Y chromosome is essential for sperm formation, and sperm transmit a chromosome-order code to the egg.

Figure 1 | Model of genome architecture (**A**) and intranuclear positioning of chromosomes (**B**) in human sperm

In (**A**), selected chromosome territories, telomeres (green circles) and centromeres (red circles) are shown. (**B**) Schematic representation of the preferred positioning for 11 human chromosomes based on longitude/radial localization and inter-chromosomal distances.



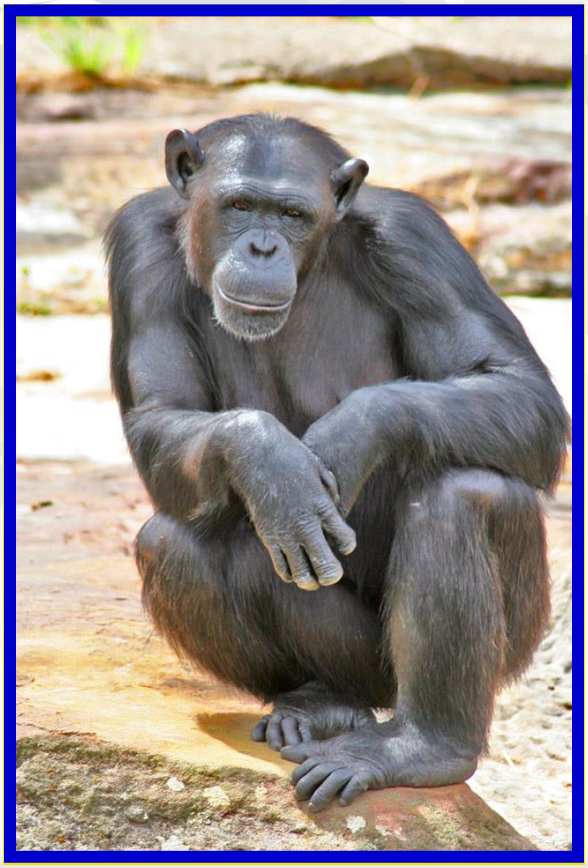
The Y also forms a nuclear compartment for various RNAs and proteins.

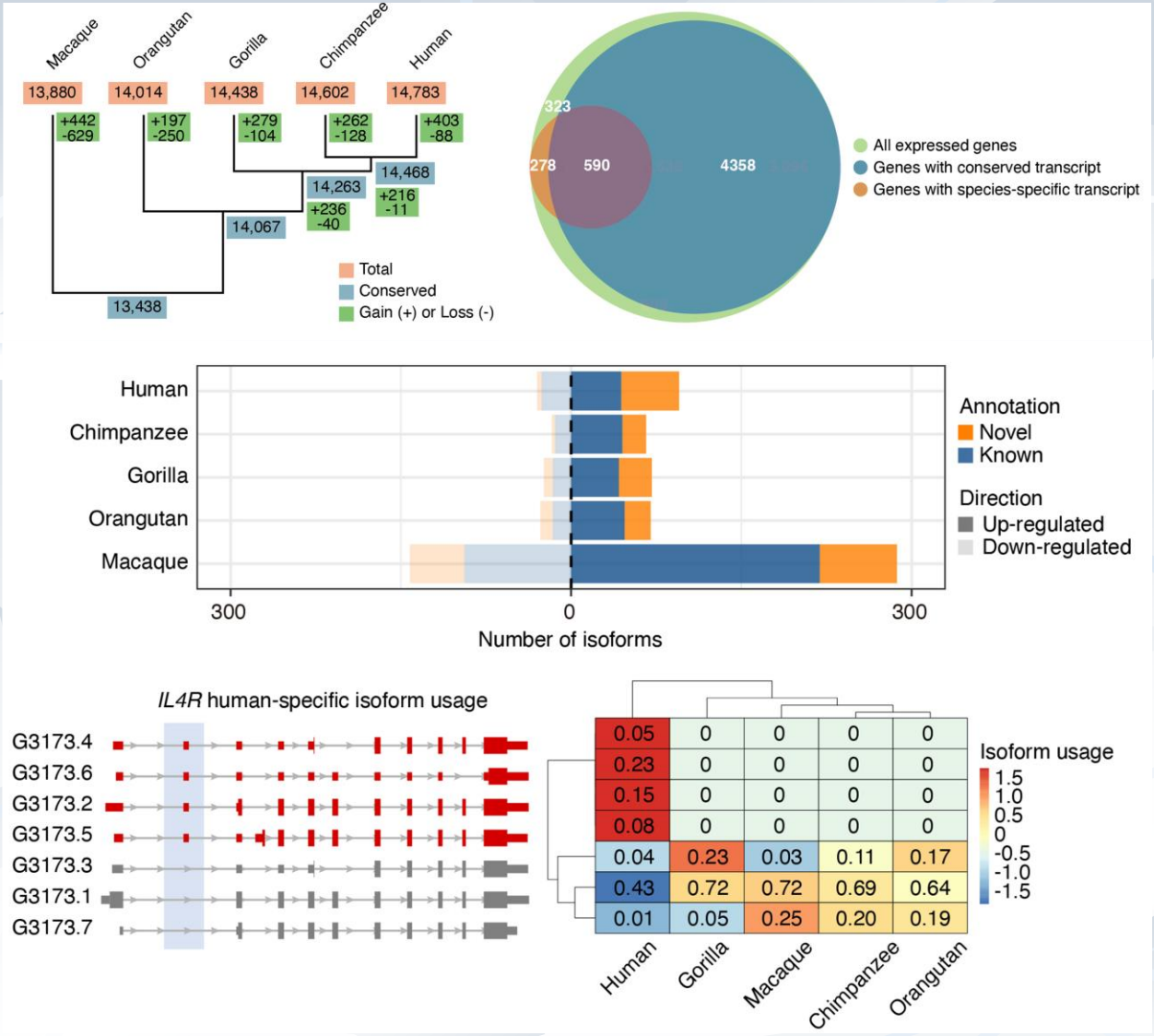
Organization of chromosomes in spermatozoa: an additional layer of epigenetic information?

A. Zalensky[1] and I. Zalenskaya
The Jones Institute for Reproductive Medicine, Eastern Virginia Medical School, Norfolk, VA 23518, U.S.A.

Biochemical Society Transactions (2007) Volume 35, part 3

But perhaps the main reason we are not chimps is that we process our DNA-encrypted data in different ways.

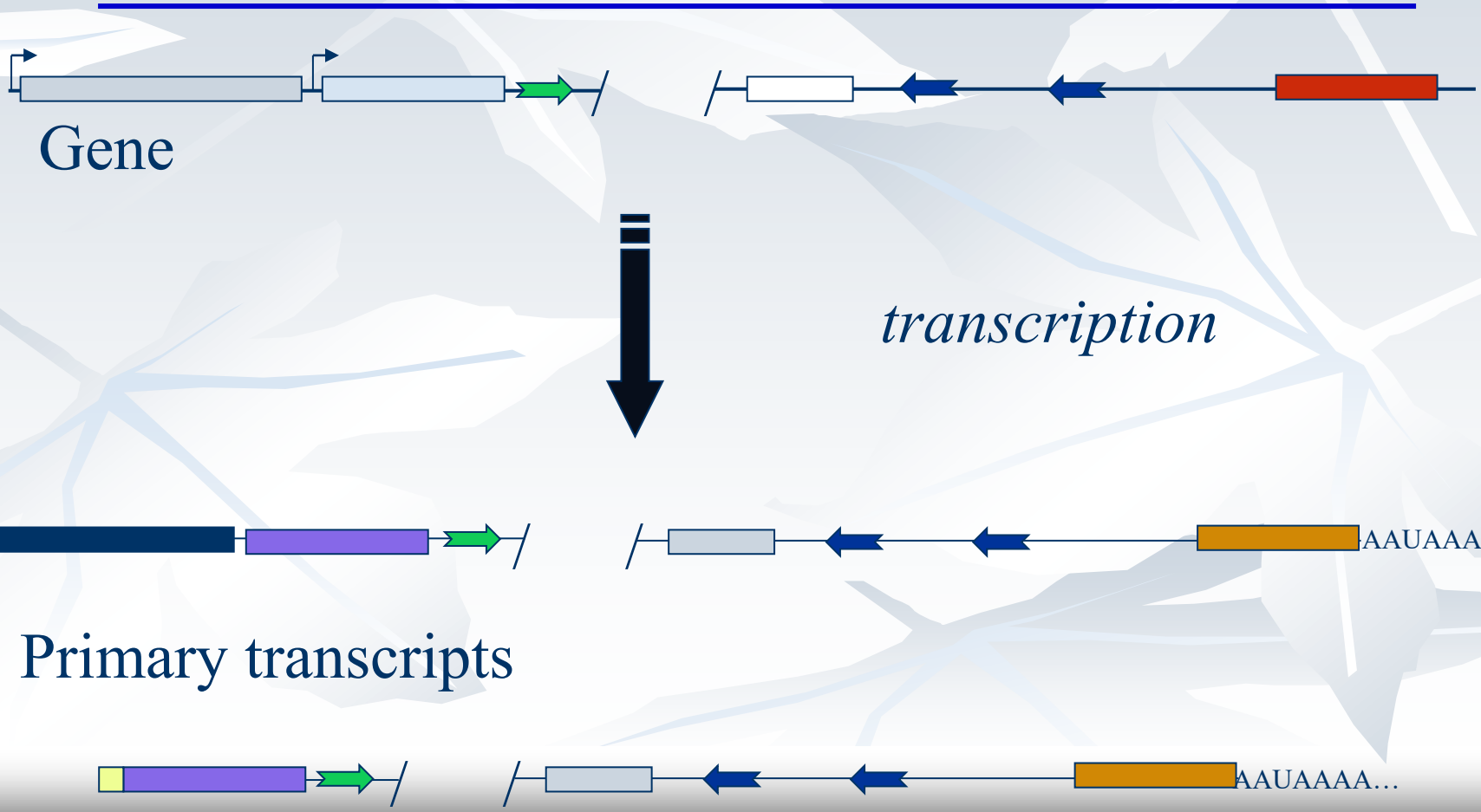




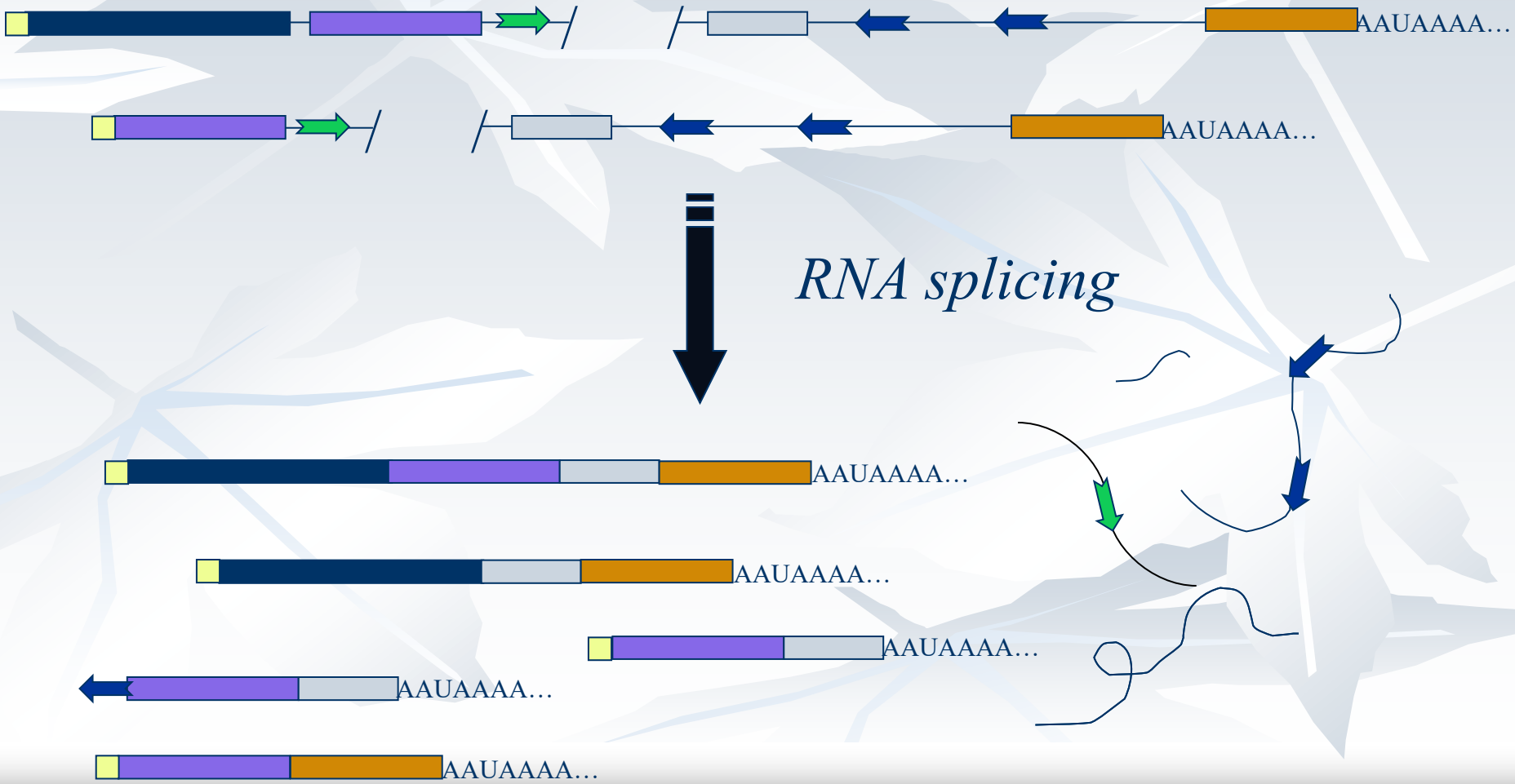
Recall that how genes are "transcribed" or used by our cells is human-specific in thousands of instances.

Ferrández-Peral L, Zhan X, Alvarez-Estape M, et al. 2022. Transcriptome innovations in primates revealed by single-molecule long-read sequencing. *Genome Res*. 32: 1448-1462.

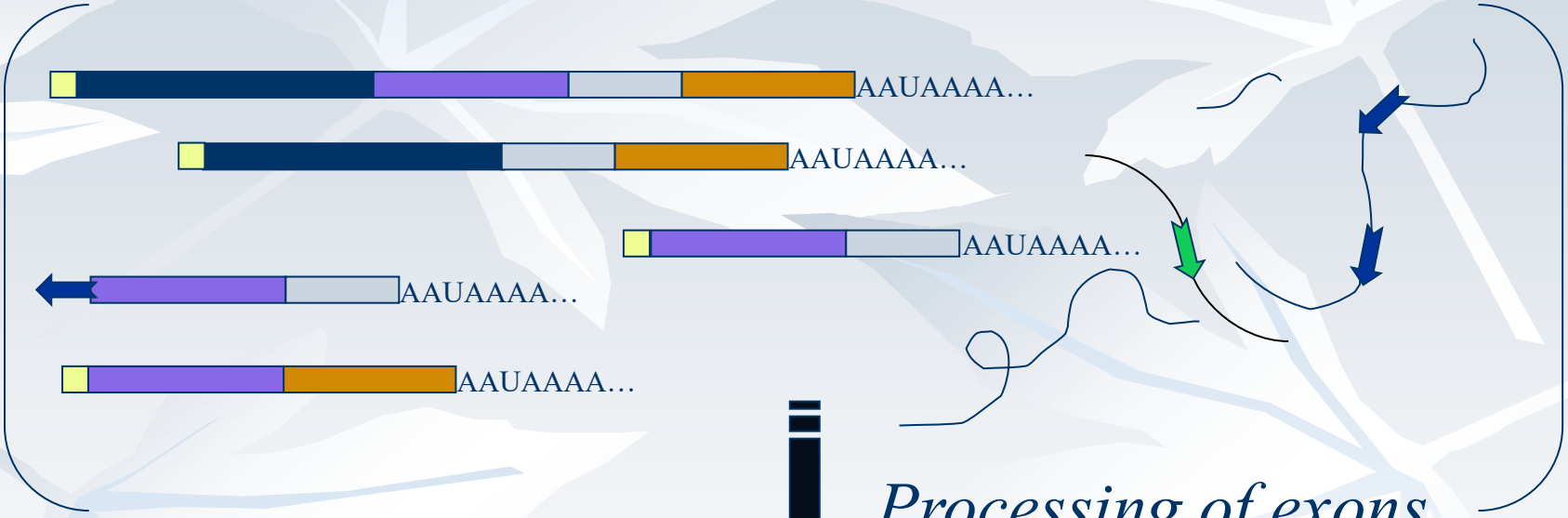
Here a key piece of evidence is that some genes can potentially encode many different transcripts (over 1,000,000 in one case!)



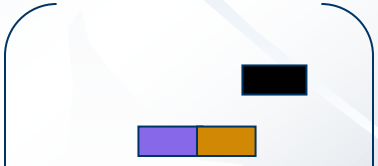
And the splicing of RNAs generates yet more gene products



In addition, it was soon realized that the ‘junk’ sections of RNAs are processed into a host of functional sequences



Processing of exons and introns



ncRNAs
(various roles)

snoRNAs
(RNA editing)

microRNAs
(regulatory)

It is known that cellular pathways literally rewrite genetic scripts to make new transcripts and proteins, a widespread phenomenon called “RNA editing”

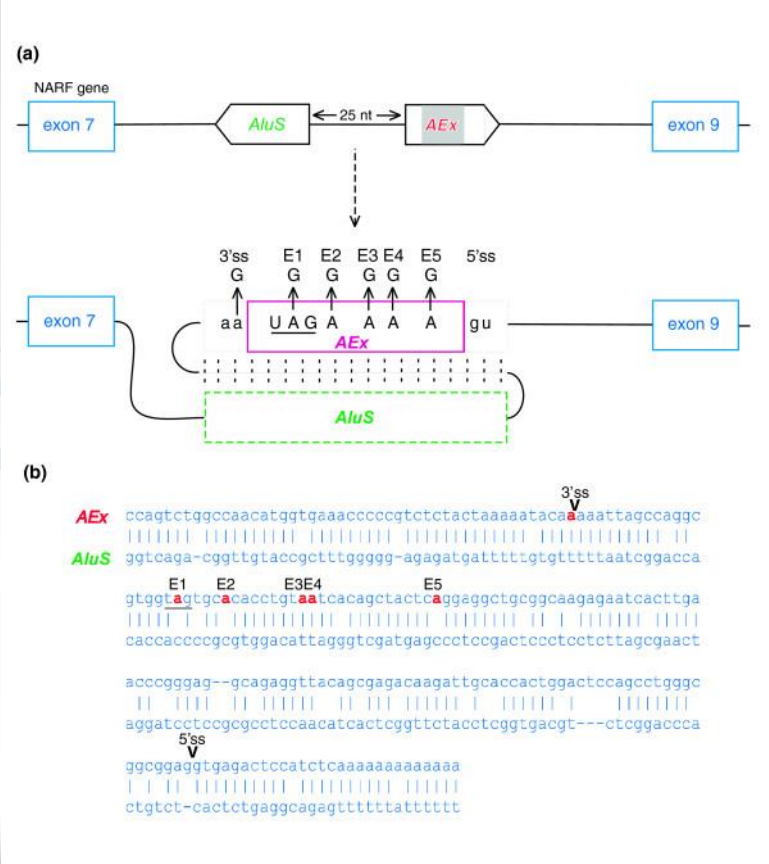


Fig. 1, Lev-Maor, G. et al., 2007. RNA-editing-mediated exon evolution. Genome Biology 8(2): R29.

Human RNAs containing *Alu*s are rewritten in brain cells. There are ~5 editing sites per element.

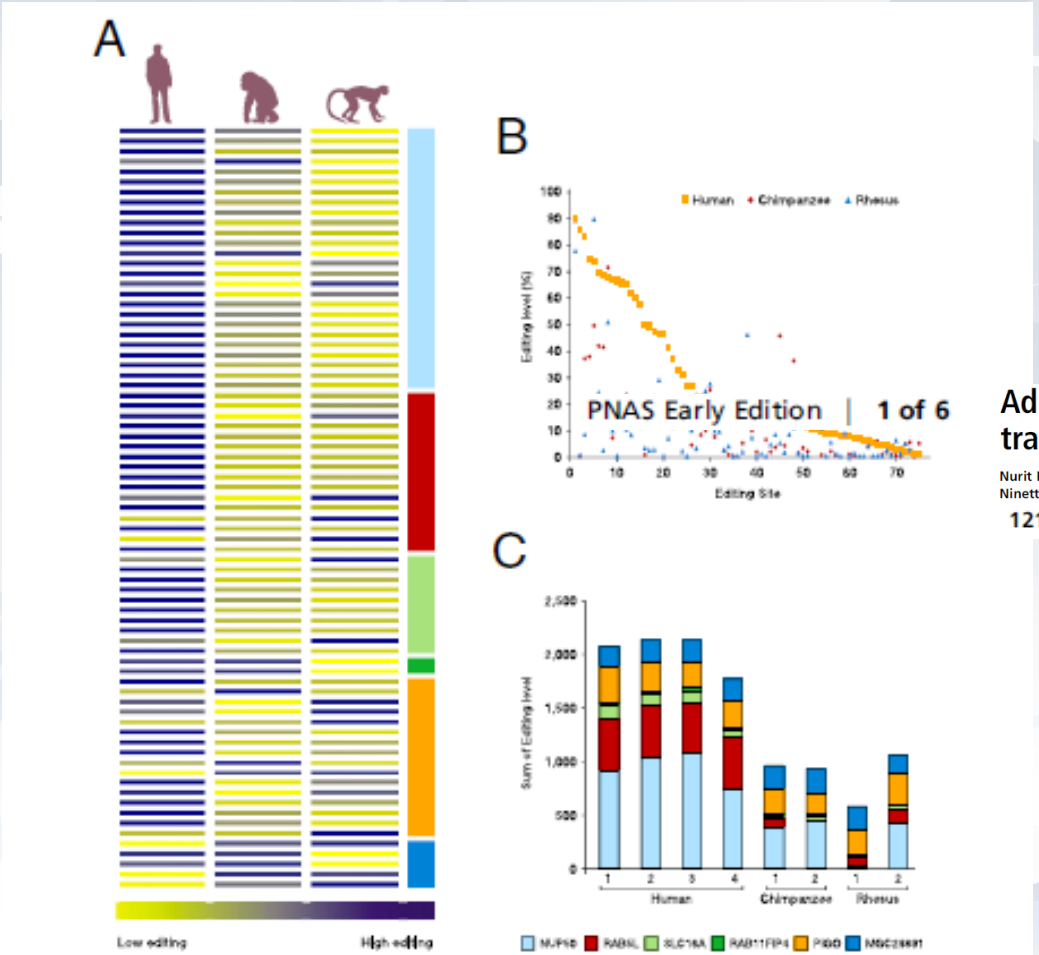


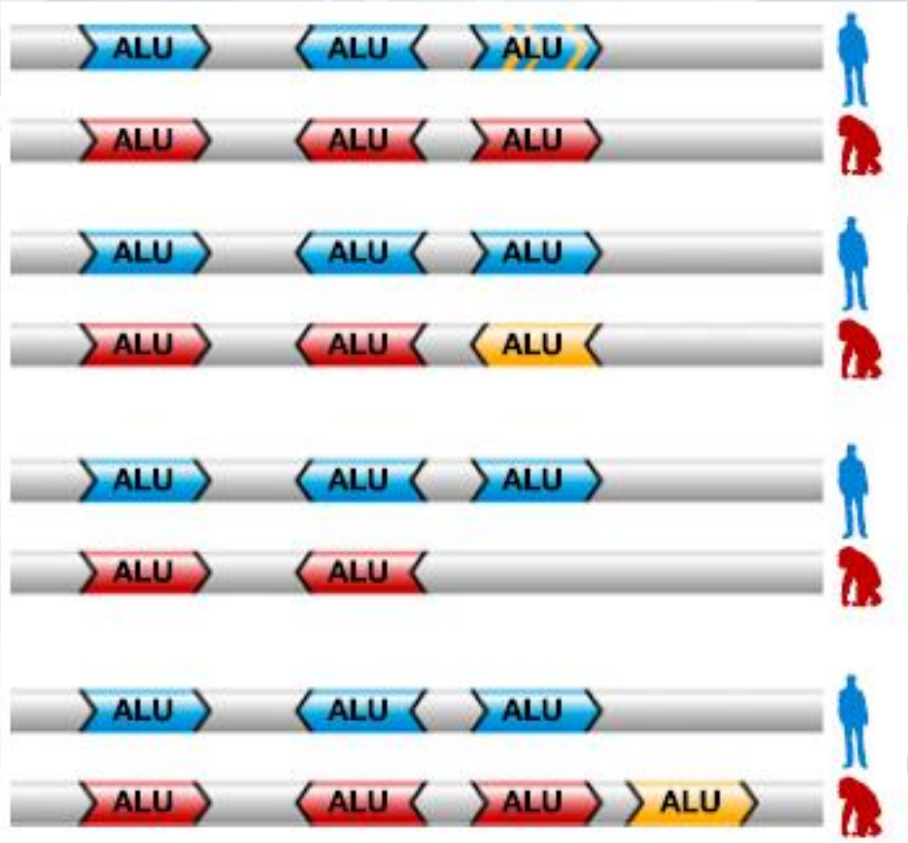
Fig. 1. Higher editing level in human vs. nonhuman primates. (*A*) Editing levels of 75 sites in six transcripts originating from cerebellum tissues of four humans, two chimpanzees, and two rhesus monkeys were quantified after

Adenosine-to-inosine RNA editing shapes transcriptome diversity in primates

Nurit Paz-Yaacov[a,b], Erez Y. Levanon[c], Eviatar Nevo[d,1], Yaron Kinar[e], Alon Harmelin[f], Jasmine Jacob-Hirsch[a], Ninette Amariglio[a], Eli Eisenberg[g], and Gideon Rechavi[a,b,1]

12174–12179 | PNAS | July 6, 2010 | vol. 107 | no. 27

This species-specific difference is correlated with patterns of *Alu* distribution.



Adenosine-to-inosine RNA editing shapes transcriptome diversity in primates

Nurit Paz-Yaacov[a,b], Erez Y. Levanon[c], Eviatar Nevo[d,1], Yaron Kinar[e], Alon Harmelin[f], Jasmine Jacob-Hirsch[a], Ninette Amariglio[a], Eli Eisenberg[g], and Gideon Rechavi[a,b,1]

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And with the fact that a substantial number of human-specific *Alus* are located in brain-specific data files.

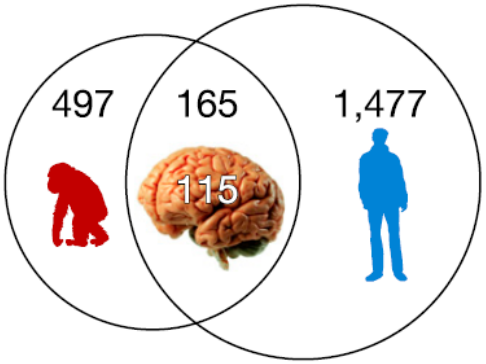

Fig. 3. Analysis of newly inserted *Alus*. Number of common human and chimpanzee genes showing new (independent) *Alu* element insertions. Among the 165 shared genes representing new independent *Alu* insertions in the human and chimpanzee, 115 are neurological function and neurological disease-associated genes.

Adenosine-to-inosine RNA editing shapes transcriptome diversity in primates

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12174–12179 | PNAS | July 6, 2010 | vol. 107 | no. 27

Evolutionary and ontogenetic changes in RNA editing in human, chimpanzee, and macaque brains

RNA 2013 19: 1693-1702

ZHONGSHAN LI,[1,5] HINDRIKE BAMMANN,[1,2,5] MINGSHUANG LI,[3] HONGYU LIANG,[3] ZHENG YAN,[1,4] YI-PING PHOEBE CHEN,[4] MIN ZHAO,[3,6] and PHILIPP KHAITOVICH[1,2,6]

A biochemical landscape of A-to-I RNA editing in the human brain transcriptome

Genome Res. 2014 24: 522-534

Masayuki Sakurai,[1,4] Hiroki Ueda,[1,4] Takanori Yano,[1] Shunpei Okada,[1] Hideki Terajima,[1] Toutai Mitsuyama,[2] Atsushi Toyoda,[3] Asao Fujiyama,[3] Hitomi Kawabata,[1] and Tsutomu Suzuki[1,5]

Indeed, ribosomal and transfer RNAs must be highly edited in order to become functional in all known taxa

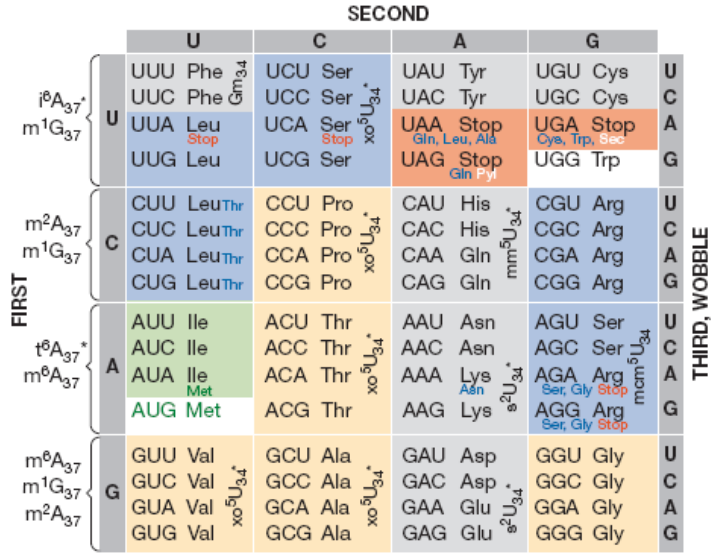


Fig 1 | Universal genetic code. The 64 codes are associated with the transfer RNA (tRNA) modifications that are important for decoding and/or translocation. Twofold degenerate amino-acid codes are highlighted in grey and fourfold degenerate codes are highlighted in tan. Amino acids with six codons are highlighted in blue. The threefold degenerate codons of Ile are highlighted in green, whereas the single codons of Met and Trp are highlighted in white. The three stop codons are highlighted in orange. Non-canonical codon use by some organisms and the mitochondrion is shown by using a small font for the amino acids (blue) or translational stop codons (red). The modified nucleoside abbreviations are defined in the text. Selenocysteine (Sec) and pyrrolysine (Pyl) codons are denoted in white. In the mitochondrion, $tRNA^{Met}$ responds to AUG and AUA, which is not used as an Ile codon (Agris *et al*, 2007; Szymański & Barciszewski, 2007; Björk *et al*, 1987).

Bringing order to translation: the contributions of transfer RNA anticodon-domain modifications

Paul F. Agris

EMBO *reports* VOL 9 | NO 7 | 2008

tRNA's Wobble Decoding of the Genome: 40 Years of Modification

Paul F. Agris*, Franck A. P. Vendeix and William D. Graham

J. Mol. Biol. (2007) 366, 1–13

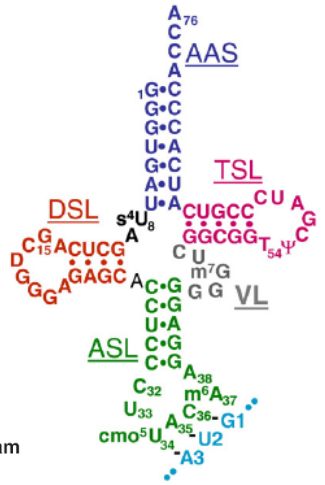


Figure 2. tRNA primary sequence, secondary structure, and codon binding. The sequence and secondary structure of *E. coli* $tRNA^{Val}$. The physical and functional domains of the *E. coli* $tRNA^{Val}_{UAC}$ sequence and secondary structure are the amino acid-accepting stem, AAS (dark blue), the dihydrouridine stem and loop, DSL (red), the anticodon stem and loop, ASL (green), the variable loop, VL (gray), and the thymidine stem and loop, TSL (purple). The modified nucleosides in this tRNA are: s^4U, 4-thiouridine; D, dihydrouridine; cmo^5U, uridine-5-oxyacetic acid; m^6A, N6-methyladenosine; m^7G, 7-methylguanosine; ribothymidine, T; and pseudouridine, Ψ. Because of the wobble nucleoside modification, cmo^5U_{34}, *E. coli* $tRNA^{Val}_{UAC}$ is capable of decoding all of the fourfold degenerate valine codons.[32–34] The tRNA is shown binding the cognate codon for valine, GUA, in light blue.

Clearly, a gene provides the substrate for many types of information that are layered on by the cell. In fact…

- Many RNAs, because of being rearranged and edited, **do not mirror** ***any DNA sequence;***
- The RNA-level codes that are formed are often topological in nature; and
- Many RNA-level codes are sequence-independent.

Although the gene has conventionally been viewed as the fundamental unit of genomic organization, on the basis of ENCODE data it is now compellingly argued that this unit is not the gene but rather the transcript (Washietl et al. 2007; Djebali et al. 2012a). On this view, genes represent a higher-order framework around which individual transcripts coalesce, creating a polyfunctional entity that assumes different forms under different cellular states, guided by differential utilization of regulatory DNA.

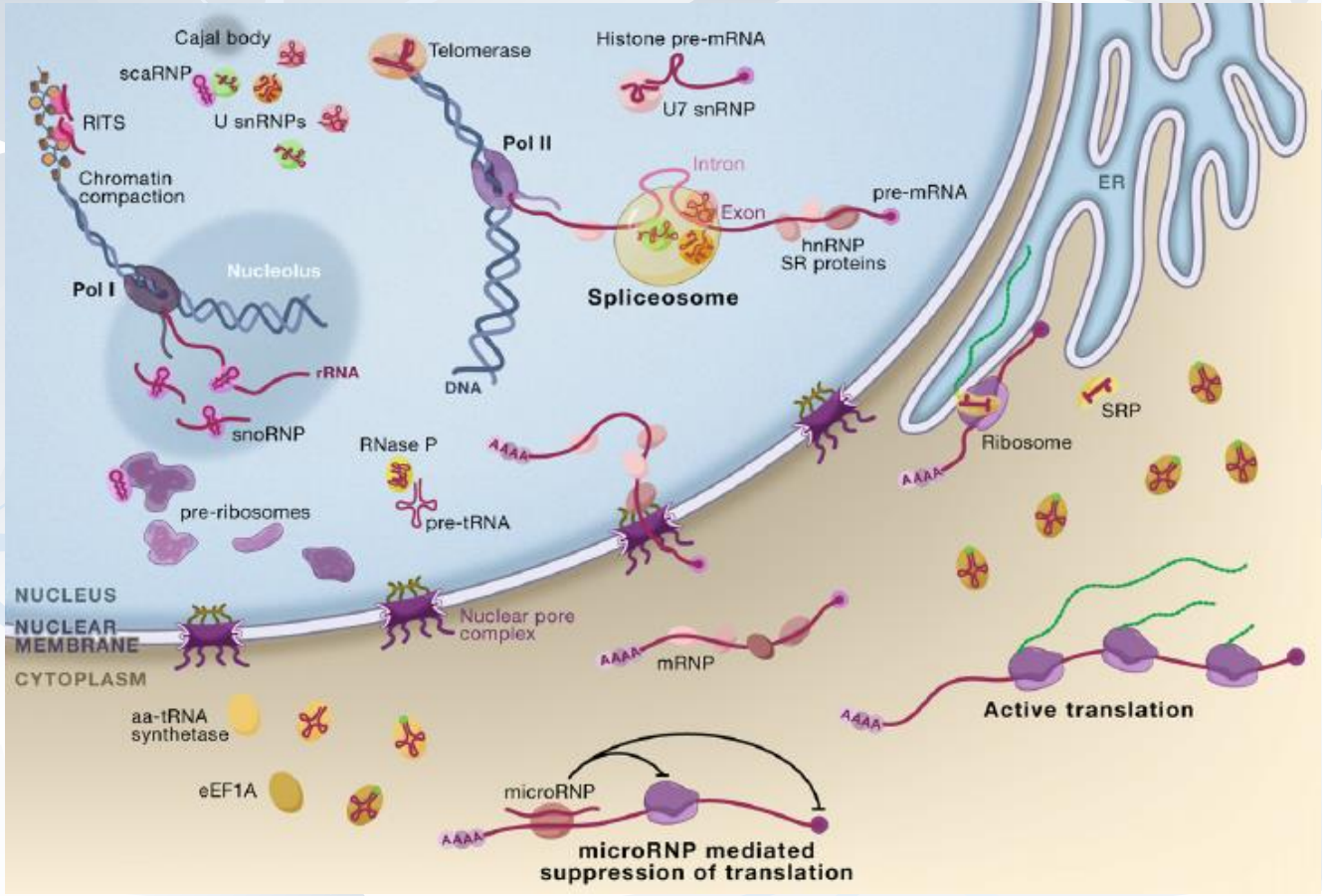
What does our genome encode?

John A. Stamatoyannopoulos

Genome Res. 2012 22: 1602-1611

Consider, say, only the lower-level process whereby transcripts are alternatively spliced to generate RNA and protein specifications

At any one time in a metazoan cell, thousands of RNAs are rewritten by editing, processing, and splicing events:

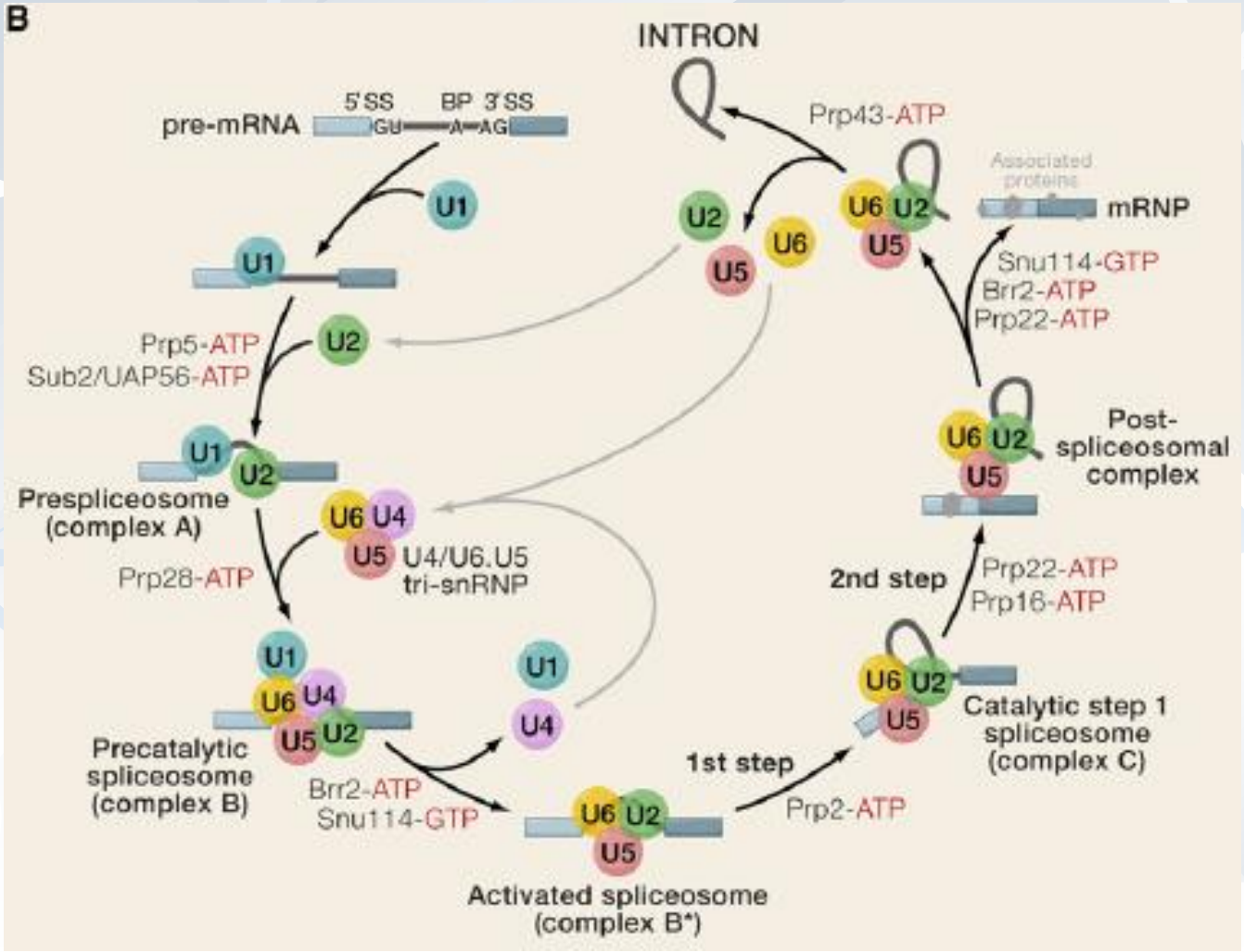


The Spliceosome: Design Principles of a Dynamic RNP Machine

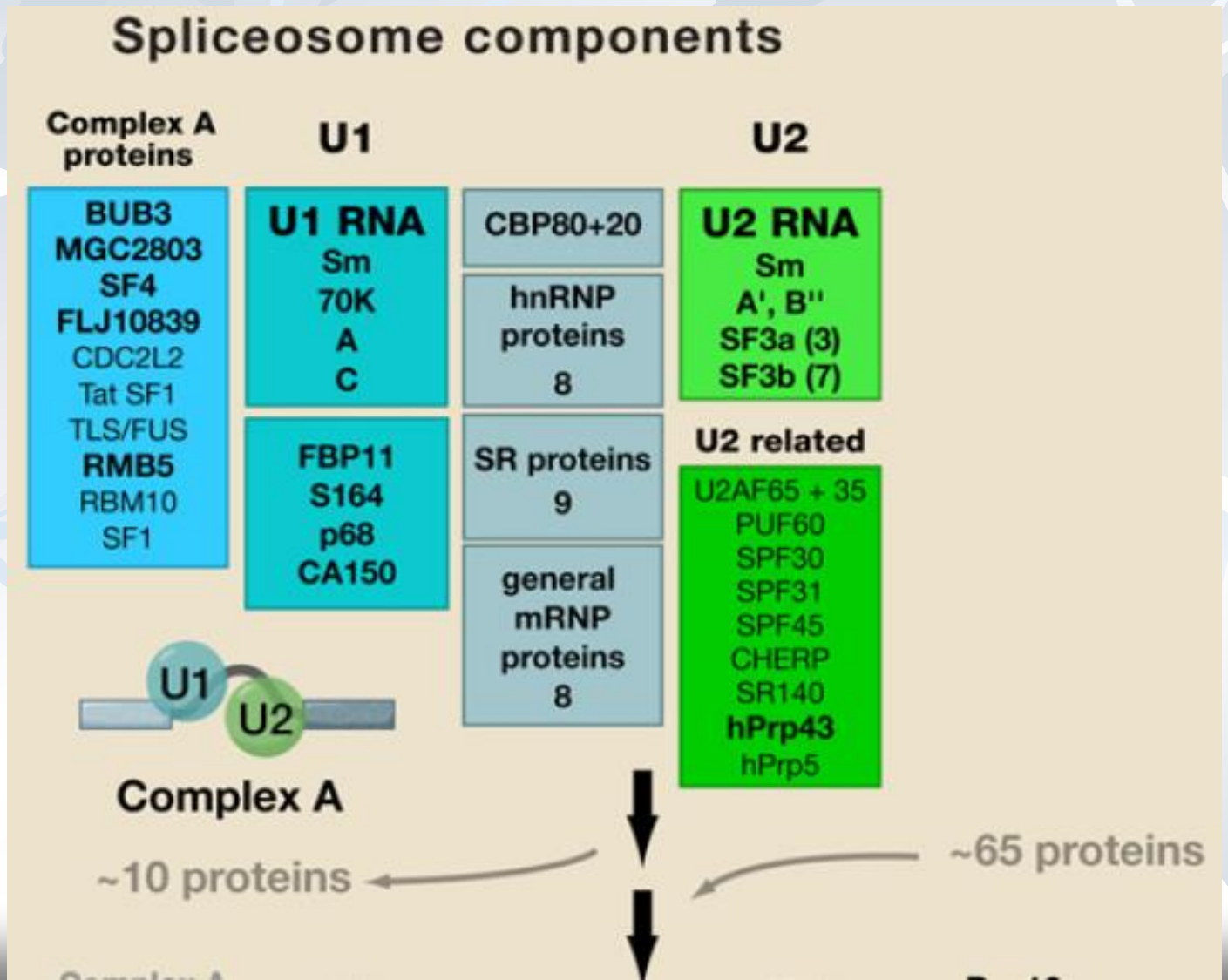
Markus C. Wahl,[2,3,*] Cindy L. Will,[1,*] and Reinhard Lührmann[1,*]

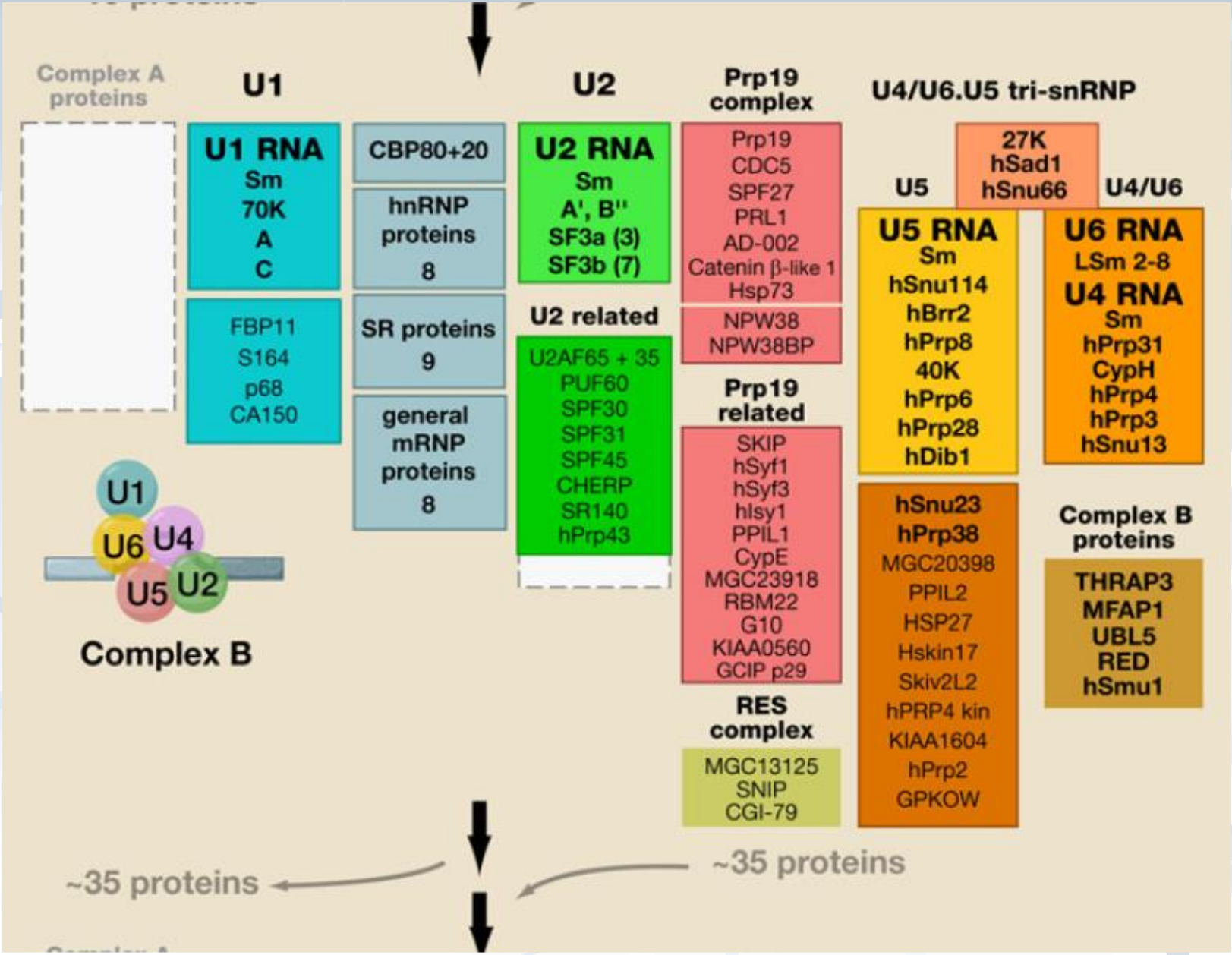
Cell *136*, 701–718, February 20, 2009

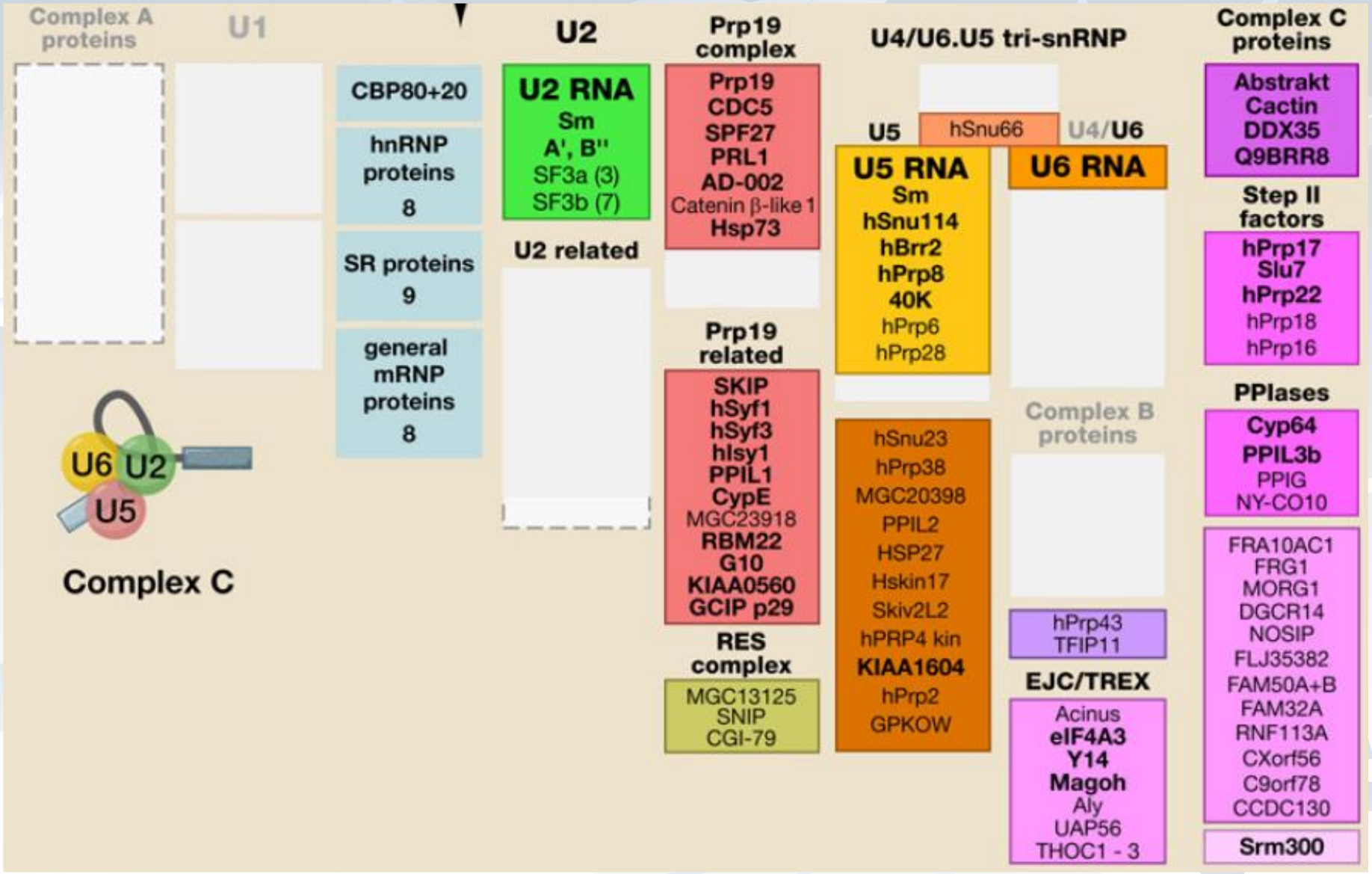
A spliceosome consists of hundreds of proteins and RNAs that are in a constant state of flux:



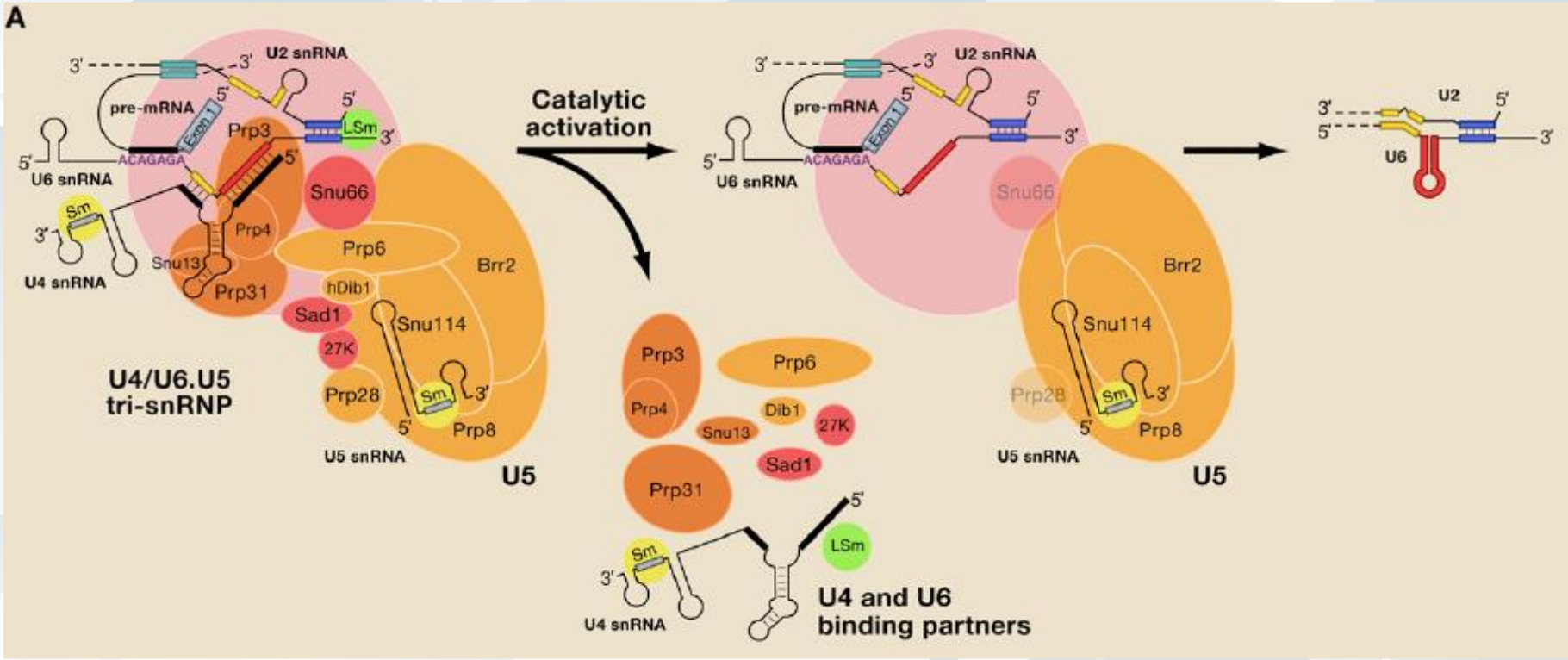
At each stage, some protein/RNA complexes are added while others are removed…



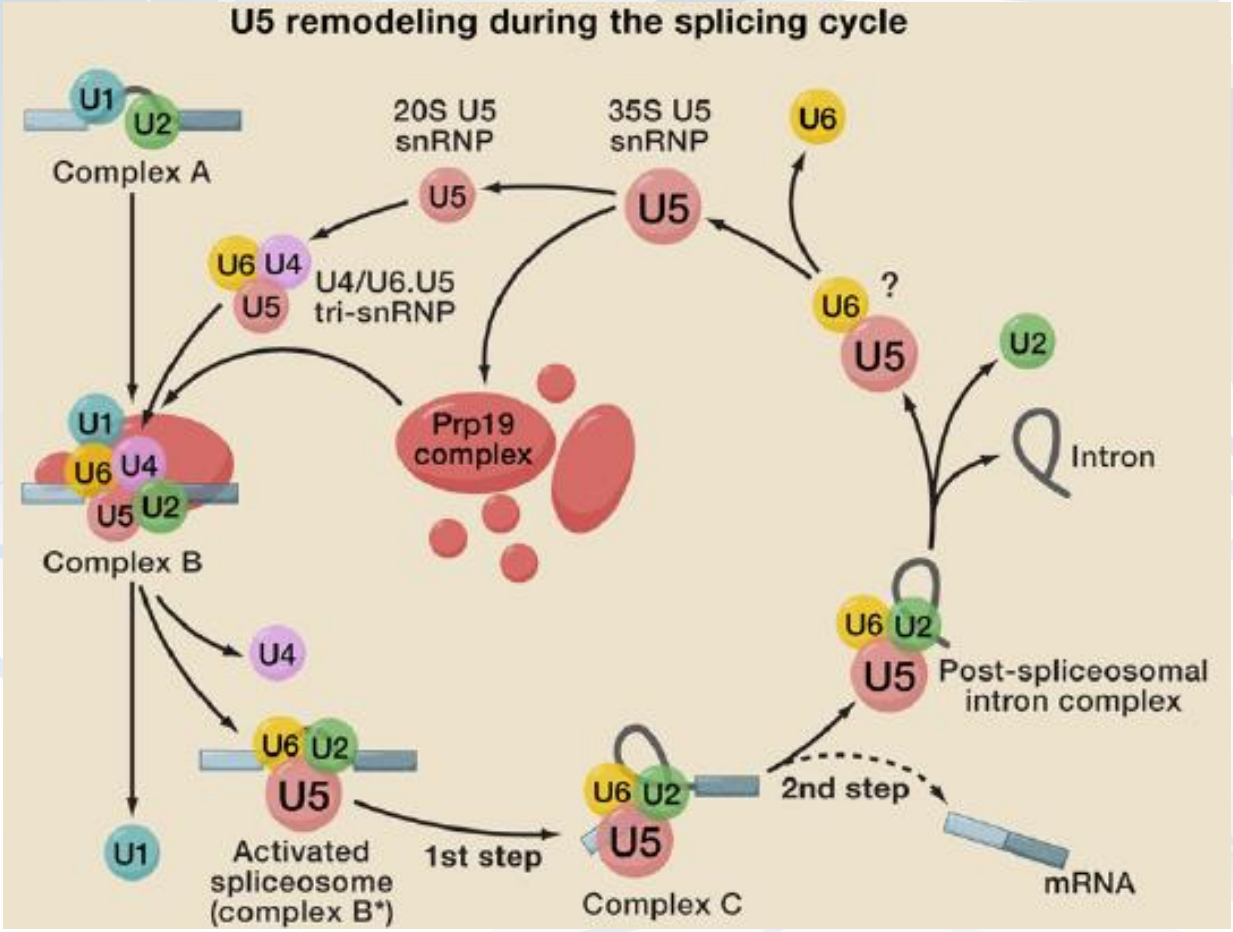

Complex A proteins
U1
U1 RNA
Sm
70K
A
C
FBP11
S164
p68
CA150
CBP80+20
hnRNP proteins
8
SR proteins
9
general mRNP proteins
8
U2
U2 RNA
Sm
A', B''
SF3a (3)
SF3b (7)
U2 related
U2AF65 + 35
PUF60
SPF30
SPF31
SPF45
CHERP
SR140
hPrp43
Prp19 complex
Prp19
CDC5
SPF27
PRL1
AD-002
Catenin β-like 1
Hsp73
NPW38
NPW38BP
Prp19 related
SKIP
hSyf1
hSyf3
hIsy1
PPIL1
CypE
MGC23918
RBM22
G10
KIAA0560
GCIP p29
RES complex
MGC13125
SNIP
CGI-79
U4/U6.U5 tri-snRNP
27K
hSad1
hSnu66
U5
U4/U6
U5 RNA
Sm
hSnu114
hBrr2
hPrp8
40K
hPrp6
hPrp28
hDib1
hSnu23
hPrp38
MGC20398
PPIL2
HSP27
Hskin17
Skiv2L2
hPRP4 kin
KIAA1604
hPrp2
GPKOW
U6 RNA
LSm 2-8
U4 RNA
Sm
hPrp31
CypH
hPrp4
hPrp3
hSnu13
Complex B proteins
THRAP3
MFAP1
UBL5
RED
hSmu1
U1
U6
U4
U5
U2
Complex B
~35 proteins
~35 proteins


Complex A proteins
U1
CBP80+20
hnRNP proteins 8
SR proteins 9
general mRNP proteins 8
U2
U2 RNA
Sm
A', B''
SF3a (3)
SF3b (7)
U2 related
Prp19 complex
Prp19
CDC5
SPF27
PRL1
AD-002
Catenin β-like 1
Hsp73
Prp19 related
SKIP
hSyf1
hSyf3
hIsy1
PPIL1
CypE
MGC23918
RBM22
G10
KIAA0560
GCIP p29
RES complex
MGC13125
SNIP
CGI-79
U4/U6.U5 tri-snRNP
U5
hSnu66
U4/U6
U5 RNA
Sm
hSnu114
hBrr2
hPrp8
40K
hPrp6
hPrp28
U6 RNA
hSnu23
hPrp38
MGC20398
PPIL2
HSP27
Hskin17
Skiv2L2
hPRP4 kin
KIAA1604
hPrp2
GPKOW
Complex B proteins
hPrp43
TFIP11
EJC/TREX
Acinus
eIF4A3
Y14
Magoh
Aly
UAP56
THOC1 - 3
Complex C proteins
Abstrakt
Cactin
DDX35
Q9BRR8
Step II factors
hPrp17
Slu7
hPrp22
hPrp18
hPrp16
PPIases
Cyp64
PPIL3b
PPIG
NY-CO10
FRA10AC1
FRG1
MORG1
DGCR14
NOSIP
FLJ35382
FAM50A+B
FAM32A
RNF113A
CXorf56
C9orf78
CCDC130
Srm300
U6
U2
U5
Complex C

We have, then, a factory that reorganizes itself as it performs diverse operations…

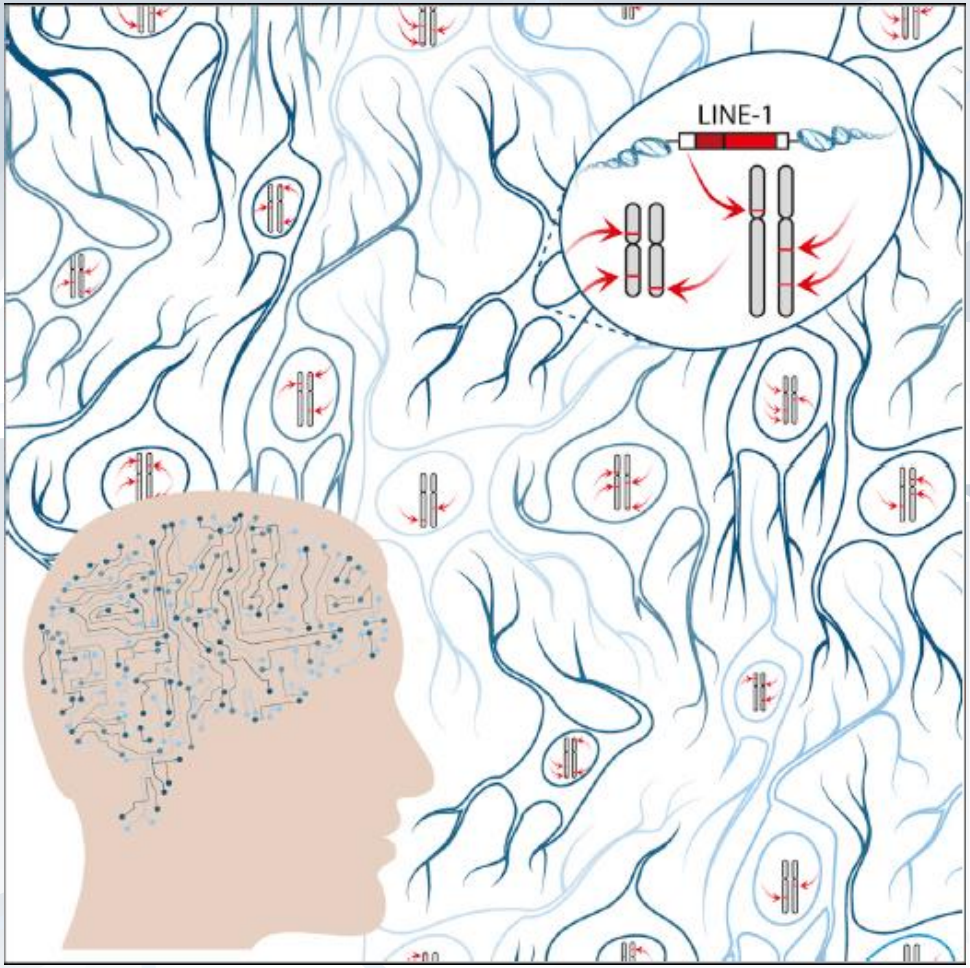


…a series of decision-making procedures that are mediated by a meta-dynamic network.



The mappings that are effected by the spliceosome are not directed by a static instruction set. *What*, then, guides this process? *Where* are its specifications?

Not even our DNA code-letters are static, for they are changed in development.



An estimated 13.7 somatic L1 insertions occur per hippocampal neuron, on average

Target-primed reverse transcription drives somatic L1 retrotransposition

Somatic L1 insertions sense oriented to introns are depleted in neurons and glia

Hippocampus genes and enhancers are strikingly enriched for somatic L1 insertions

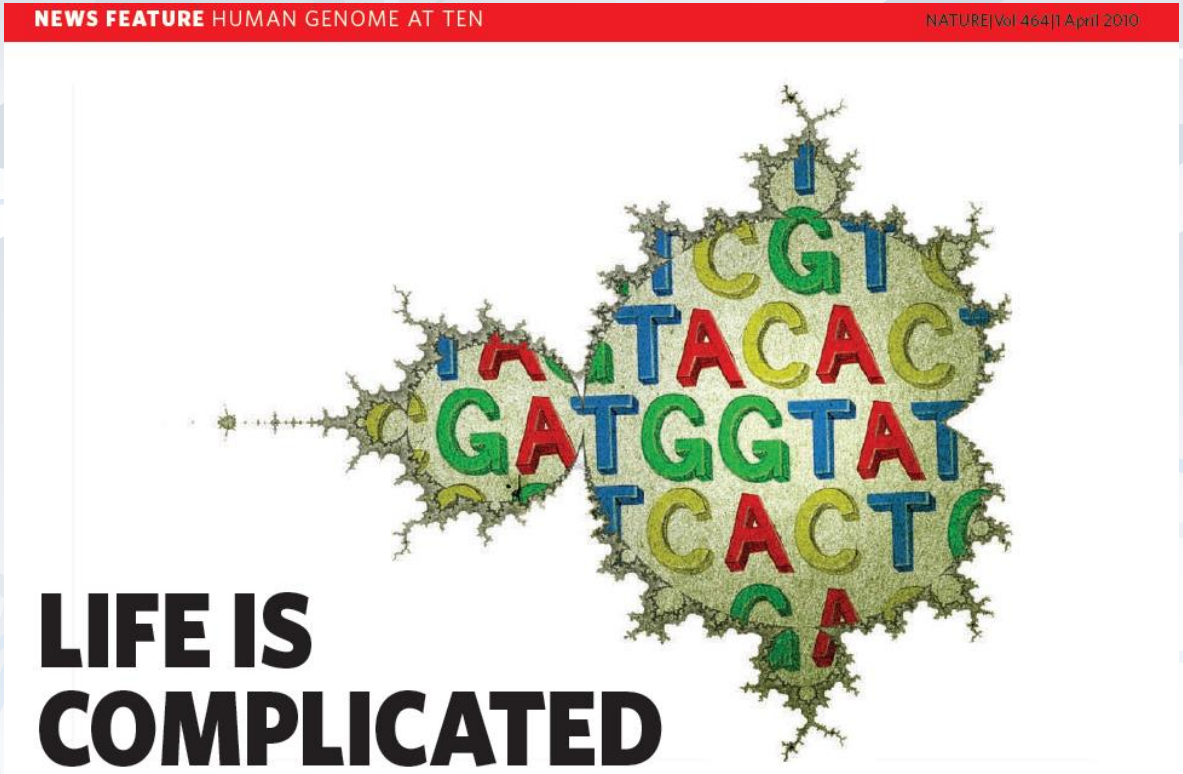
In Brief

Somatic genome mosaicism among neurons has the potential to impact brain function. L1 retrotransposons mobilize extensively in hippocampal neurons, preferentially in hippocampally expressed loci, and are depleted from mature neurons when oriented in the most deleterious configuration to host genes, suggesting functional significance.

Ubiquitous L1 Mosaicism in Hippocampal Neurons

Kyle R. Upton,[1,6] Daniel J. Gerhardt,[1,6] J. Samuel Jesuadian,[1,6] Sandra R. Richardson,[1] Francisco J. Sánchez-Luque,[1] Gabriela O. Bodea,[1] Adam D. Ewing,[1] Carmen Salvador-Palomeque,[1] Marjo S. van der Knaap,[2] Paul M. Brennan,[3] Adeline Vanderver,[4] and Geoffrey J. Faulkner[1,5,*]

Cell *161*, 228–239, April 9, 2015



And as more aspects of our genome's "infinite complexity" are unraveled, we can only expect the number of differences that make a difference to grow.

…and I think we have to attribute the "informing" principle to something other than DNA.

The epigenome and top-down causation

P. C. W. Davies*

Interface Focus (2012) **2**, 42–48
doi:10.1098/rsfs.2011.0070

THE EPIGENOME AS A VIRTUAL OBJECT

. . . we will look in vain for any particular physical object within the cell that we can identify as 'the epigenome.' In the case of epigenetics, *there is no physical headquarters*, no localized commanding officers issuing orders, no geographical nerve centre where the epigenomic 'programme' is stored and from where epigenomic instructions emanate to help run the cell. The epigenome is not to be found at a place and the ultimate information source of epigenetics cannot be located anywhere specifically; rather, it is distributed throughout the cell. To be sure, the epigenome is *manifested* in particular structures (histone tails, nucleosome patterns, methylation patterns, chromatin packing . . .), but it does not *originate* there. The epigenome is everywhere and nowhere; it is a global, systemic entity. Expressed more starkly, *the epigenome is a virtual object*. Given that it calls many, if not most, of the biological shots, its non-existence as a specific physical entity is deeply significant.

. . . Undeniably the genome provides the words, but the epigenome writes the play! For those