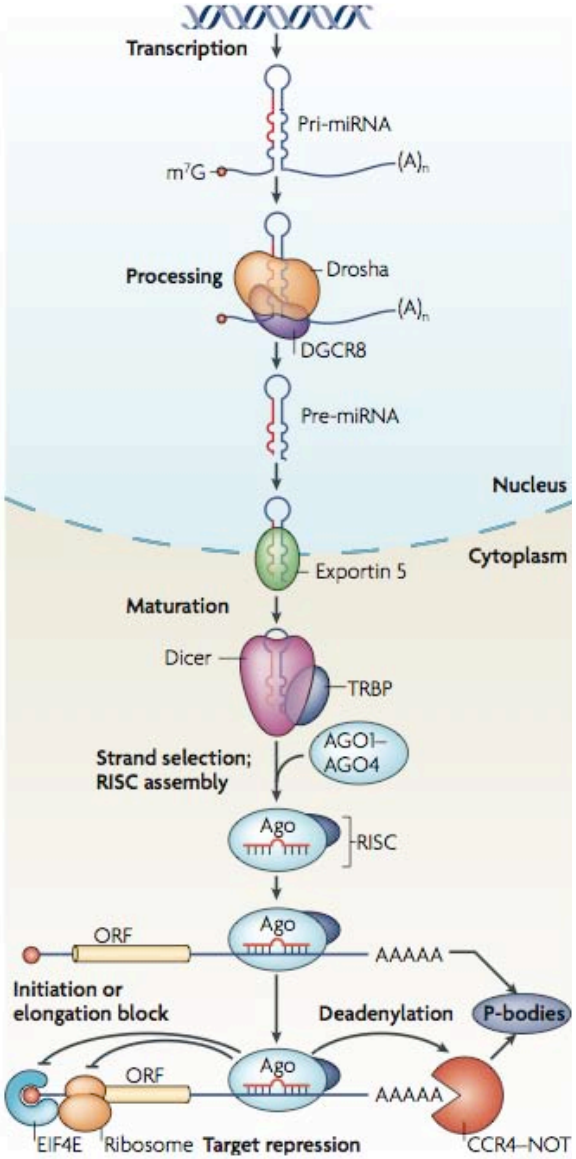
Cours du 21 novembre 2011

MicroRNA control of signal transduction

Inui M, Martello G, Piccolo S

Nat Rev Mol Cell Biol

2010 vol. 11 (4) pp. 252–63

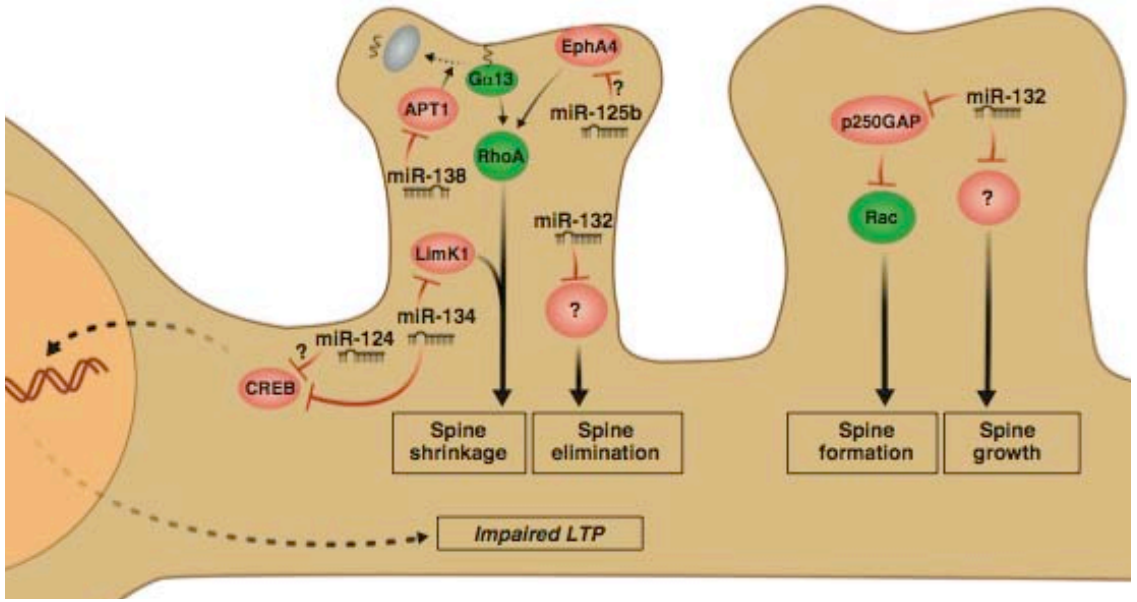


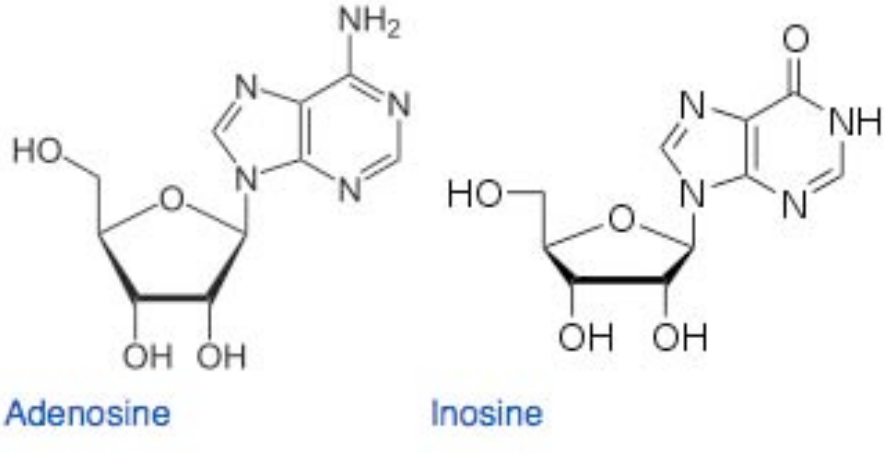
microRNAs in neurons: manifold regulatory roles at the synapse

Siegel G, Saba R, Schratt G

Current Opinion in Genetics & Development

2011 vol. 21 (4) pp. 491–7

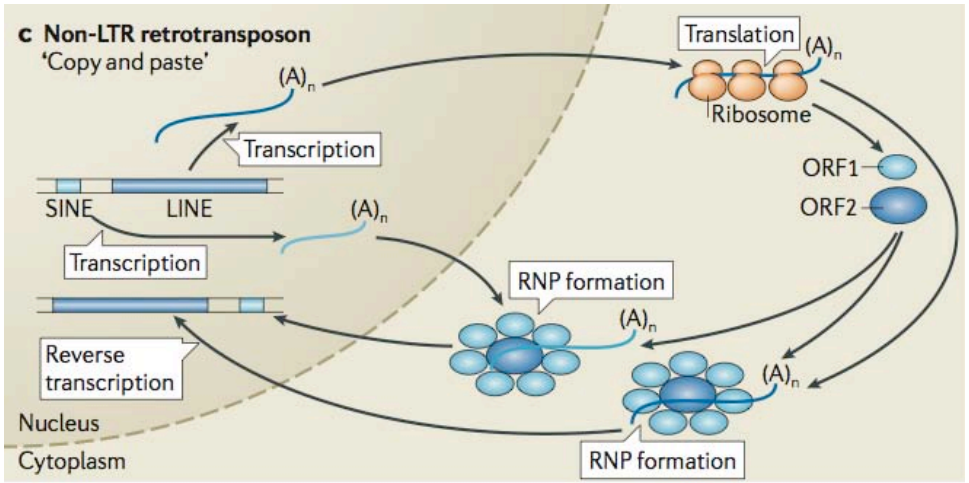




PIWI-interacting small RNAs: the vanguard of genome defence

Nat Rev Mol Cell Biol
2011 vol. 12 (4) pp. 246–58

Siomi MC, Sato K, Pezic D, Aravin AA



RNA editing, DNA recoding and the evolution of human cognition

Trends in Neurosciences
2008 vol. 31 (5) pp. 227–33

Mattick JS, Mehler MF

Table 1. Human A-to-I edited DNA repair enzymes: functional roles

Gene name	Comment	Functional categories
BRCA1		DSBR (NHEJ, HR); MMR; TCR
Claspin		DSBR (HR)
DDB2[a]		NER; GGR; MMR
DMC1	Rad51 family	Meiotic HR
FANCC[a]		DSBR (HR); TLS
FANCD2		DSBR (HR); TLS
MSH2	Mismatch repair enzymes	MMR; DSBR (HR)
MSH5	Mismatch repair enzymes	MMR; DSBR (HR)
NCoA6[a]		DSBR (NHEJ)
NEIL1		BER; TCR
POLM[a]	X family DNA polymerases	DSBR (NHEJ); TLS
Rad1		BER; TLS
Rad51		DSBR (HR); TLS
RecQL5		DSBR (HR); NER; TCR
Rev3L	Pol-ζ	TLS
TOP3A[a]		DSBR (HR); NER; MMR
UBE2B	Rad6 homolog; ubiquitin [E2]-conjugating enzyme	TLS
USP1[a]		DSBR (HR); TLS
XPA[a]		NER; GGR; TCR
XPB[a]	ERCC3	NER; GGR; TCR
XPV	Pol-η; Y family DNA polymerases	NER; GGR; TLS
XRCC6	Ku70	DSBR (NHEJ)

Abbreviations: DSBR, double-strand break repair; NHEJ, non-homologous end joining; HR, homologous recombination; NER, nucleotide excision repair; BER, base excision repair; MMR, mismatch repair; GGR, global general repair; TCR, transcription-coupled repair; TLS, trans-lesional synthesis.
[a]Gene loci specifically verified to have edited transcripts in neural tissues. Supporting information can be found in Refs [38–41].

Box 1. Categories/roles of edited genes involved in nervous system development and function

(a) System-wide adaptations
i. Neural induction (*SMAD1*; *IFNR1*)
ii. Anterior (forebrain) neural tube patterning (*FGFR1*; *Formin2*; *HHAT*)

(b) Adaptations of regional neural stem cell functions
i. Neural stem cell (NSC) self-renewal (*NuMA1*; *CD44*; *SNX1*)
ii. NSC asymmetric (neurogenic) cell divisions (*Nde1*)
iii. Modulation of NSC proliferation (*CDC2L5*; *RBBP7*; *PKCD1*; *SYK*)

(c) Adaptations of neuronal precursor (neuroblast) development
i. Neuronal precursor (neuroblast; NB) migration (*CXCL1*; *Foxp1*)
ii. NB cell-cycle kinetics (*Par6*; *CDK10*; *CDKL1*; *MCM3*; *DNM2*; *Cullin1*)
iii. Modulation of NB cell-cycle exit (*Sox13*)

(d) Adaptations of the process of neuronal maturation
i. Progressive neuronal differentiation (*TLE2*)
ii. Neuronal morphogenesis (*PAK4*; *SPARC*)
iii. Neuronal cell polarity/neurite process outgrowth (*Neuron navigator1*)
iv. Neuronal axon guidance (*Centaurin-γ2*)
v. Neuronal dendritogenesis (*δ2-Catenin*)
vi. Neuronal synaptogenesis (*Protocadherin* β)
vii. Neuronal subtype specification (*Lhx3*)
viii. Neuronal network connectivity (*Protocadherin α1, 2, 4–6, C1, 2*)

(e) Adaptations of mature neuronal functions
i. Neuronal viability (Beclin1; Casp9, 10; TRAP1; STAG-1; Fas inhibitory molecule 1)
ii. Neuronal excitability (Annexin A4; AMPAR1/GluR1; VDCCβ4; VDKC)
iii. Neuronal cell–cell and cell–environment interactions (Integrin β4)
iv. Cooperative clustering of synaptic neurotransmitter receptors (VDCCβ2)
v. Assembly of multimeric intracellular and cell–cell signaling scaffolds (Syncoilin)
vi. Organization of neuronal somadendritic microdomains (mGluR1)
vii. Neuronal signal transduction (Src homology domain containing E, SHE)
viii. Neuronal plasticity (CaM Kinase II; Synaptotagmin 2; α1-Adaptin; Complexin 1)
ix. Neuronal energy metabolism (CPT1A, C; Dynamin1-like)
x. Neuronal axodendritic transport (Kinesin 1B, 2, 3B, 6; Dynein 10)

Intégration

Noyau

c DNA

RT des LINES

ORF1
ORF2
→ Intégration du c DNA

Perte ou gain de régulation de la traduction
Modification de la protéine

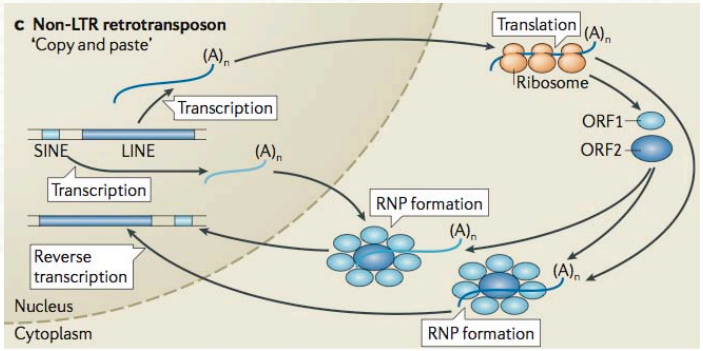
I

TA

mRNA ou SINE

mRNA

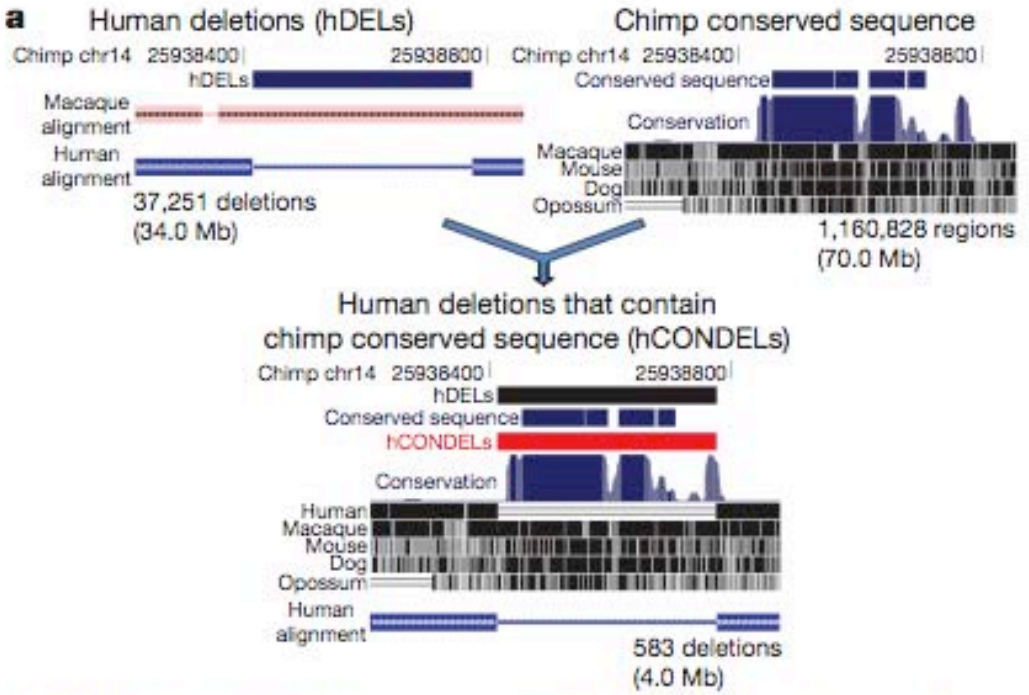
Activité

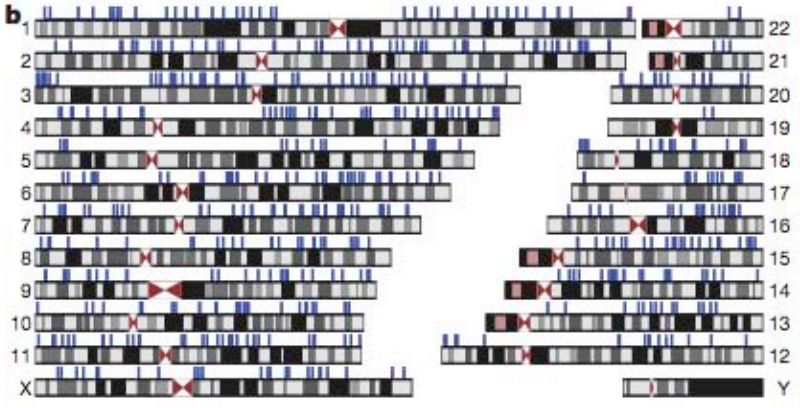


Human-specific loss of regulatory DNA and the evolution of human-specific traits

Mclean CY, Reno PL, Pollen AA, Bassan AI, Capellini TD, Guenther C, Indjeian VB, Lim X, Menke DB, Schaar BT, Wenger AM, Bejerano G, Kingsley DM

Nature
2011 vol. 471 (7337) pp. 216-9





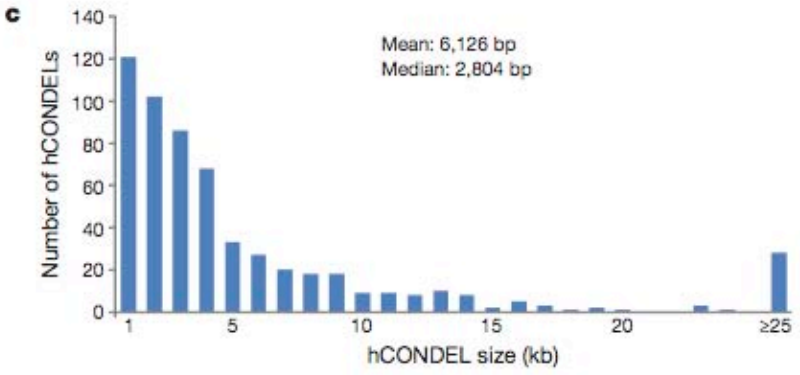
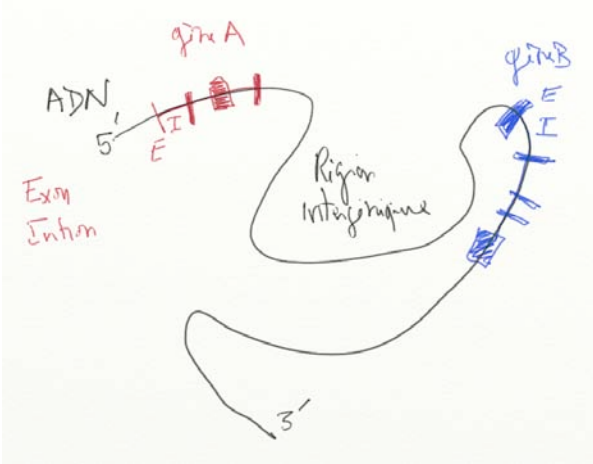


Table 1 | Summary of annotation enrichments of hCONDELs

Ontology: Term	Expected number of hCONDELs	Observed number of hCONDELs	Fold enrichment	Binomial *P*-value[19]
GO Molecular Function: Steroid hormone receptor activity	4.7	14	2.96	3.7×10^{-4}
Entrez Gene: Neural genes	141.3	180	1.27	1.1×10^{-4}
MGI Expression in Theiler Stage 21:				
Hindbrain	49.9	79	1.58	3.4×10^{-5}
Cerebral cortex	42.1	68	1.62	7.0×10^{-5}
Brain, ventricular layer	29.9	52	1.74	9.4×10^{-5}
Midbrain	30.5	52	1.70	1.6×10^{-4}
InterPro Protein Domains:				
Fibronectin, type III	16.7	34	2.03	1.0×10^{-4}
CD80-like, immunoglobulin C2-set	2.1	8	3.84	1.4×10^{-3}

Showing only non-redundant terms that are enriched after accounting for both multiple testing and for the tendency of conserved elements to be found near particular classes of genes (Supplementary Information).



Human-specific loss of regulatory DNA and the evolution of human-specific traits

Mclean CY, Reno PL, Pollen AA, Bassan AI, Capellini TD, Guenther C, Indjeian VB, Lim X, Menke DB, Schaar BT, Wenger AM, Bejerano G, Kingsley DM

Nature
2011 vol. 471 (7337) pp. 216-9

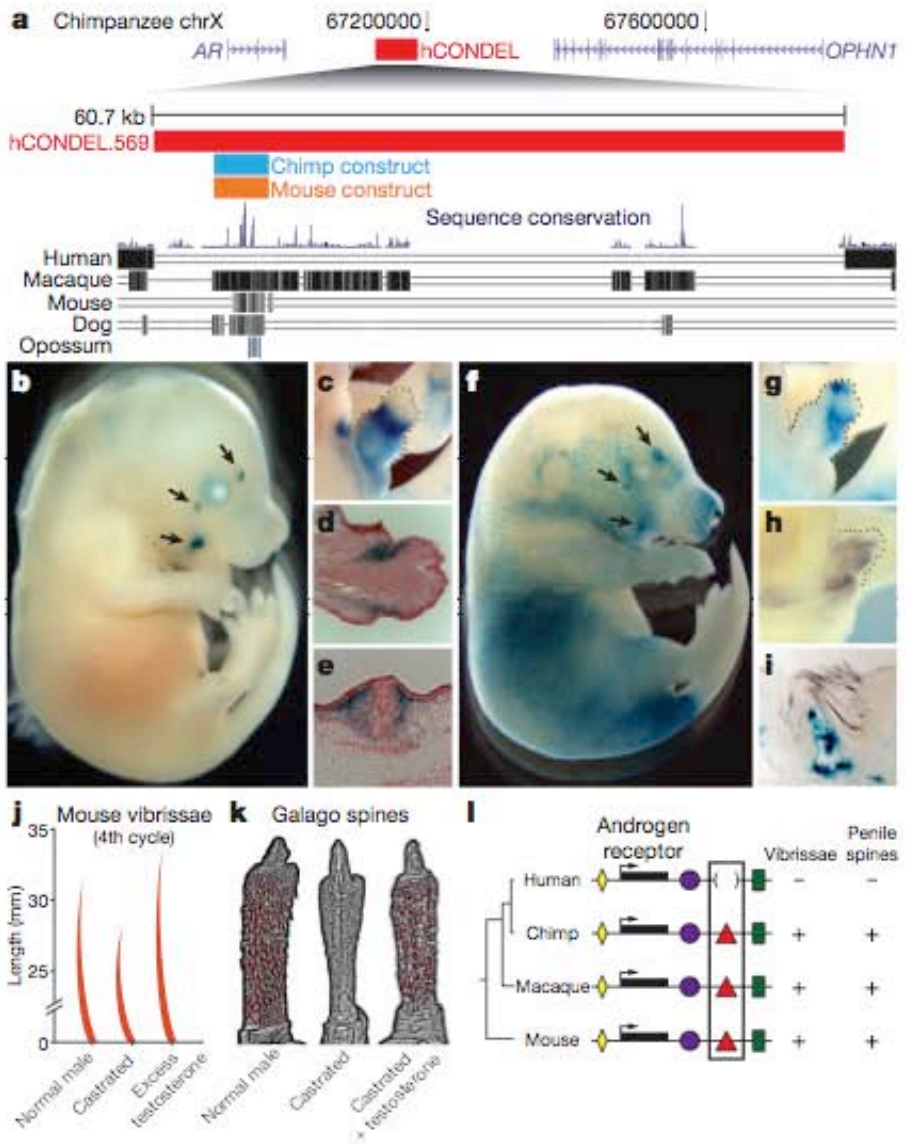
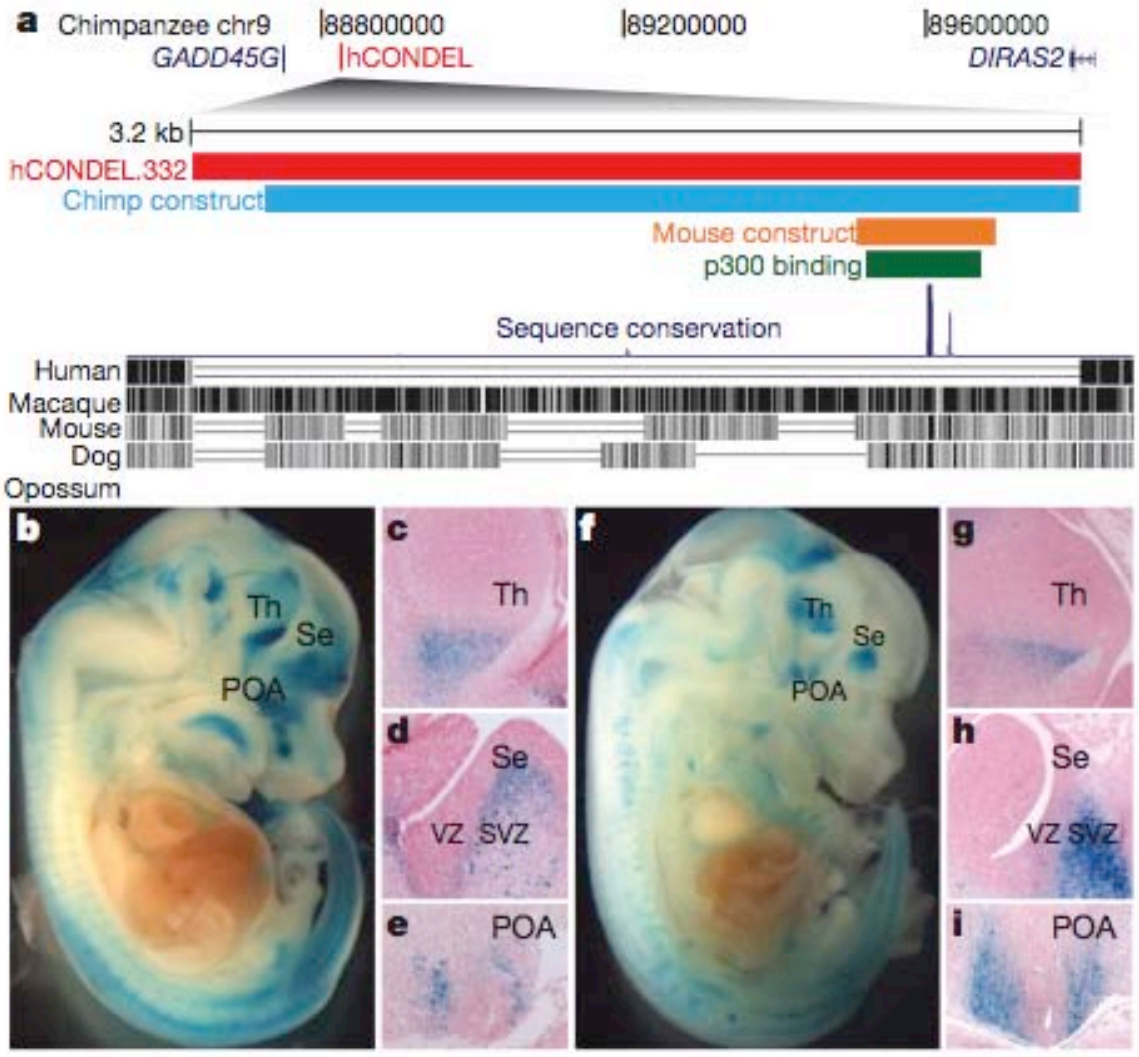


Figure 2 | Transgenic analysis of a chimpanzee and mouse *AR* enhancer region missing in humans. **a**, Top panel: 1.1 Mb region of the chimpanzee X chromosome. The red bar shows the position of a 60.7-kb human deletion removing a well-conserved chimpanzee enhancer between the *AR* and *OPHN1* genes. Bottom panel: multiple species comparison of the deleted region, showing sequences aligned between chimpanzee and other mammals. Blue and orange bars represent chimpanzee and mouse sequences tested for enhancer activity in transgenic mice. The chimpanzee sequence drives *lacZ* expression in **b**, facial vibrissae (arrows), and **c**, genital tubercle (dotted line) of E16.5 mouse embryos. Histological sections reveal strongest staining in superficial mesenchyme of **d**, the prospective glans of the genital tubercle, and **e**, dermis surrounding the base of sensory vibrissae. The mouse enhancer also drives consistent expression in **f**, facial vibrissae, **g**, genital tubercle, and hair follicles of E16.5 embryos. **h**, Endogenous *AR* is expressed in the genital tubercle (dotted line) as demonstrated by *in situ* hybridization. **i**, Histological section of a 60-day-old transgenic mouse penis showing postnatal *lacZ* expression in dermis of penile spines. Vibrissae and penile spines are androgen-dependent, as shown by **j**, changes in vibrissae length in castrated and testosterone-treated mice and **k**, loss and recovery of penile spines of a castrated and testosterone-treated primate (*Galago crassicaudatus*) (modified from refs 23 and 24). **l**, Model depicting multiple conserved tissue-specific enhancers (coloured shapes) surrounding *AR* coding sequences (black bars) of different species. Loss of an ancestral vibrissae/penile spine enhancer in humans is correlated with corresponding loss of sensory vibrissae and penile spines.

tion in our species relative to chimpanzees[20]. This fits with an adaptive suite, including feminization of the male canine dentition, moderate-sized testes with low sperm motility, and concealed ovulation with permanently enlarged mammary glands[20], that suggests our ancestors evolved numerous morphological characteristics associated with pair-bonding and increased paternal care[21].



Chimp

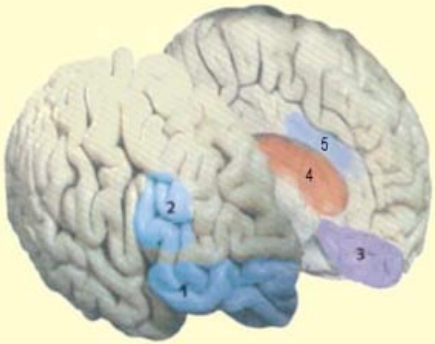
Mouse

Human-specific loss of regulatory DNA and the evolution of human-specific traits

Mclean CY, Reno PL, Pollen AA, Bassan AI, Capellini TD, Guenther C, Indjeian VB, Lim X, Menke DB, Schaar BT, Wenger AM, Bejerano G, Kingsley DM

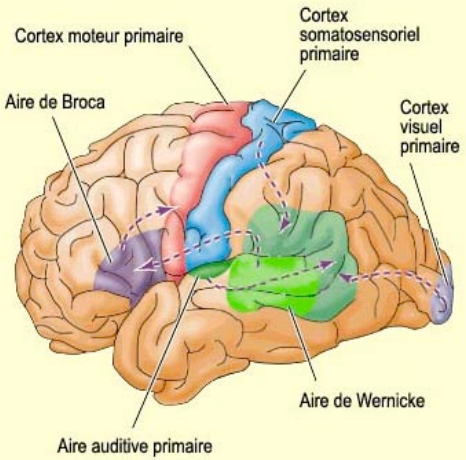
Nature
2011 vol. 471 (7337) pp. 216-9

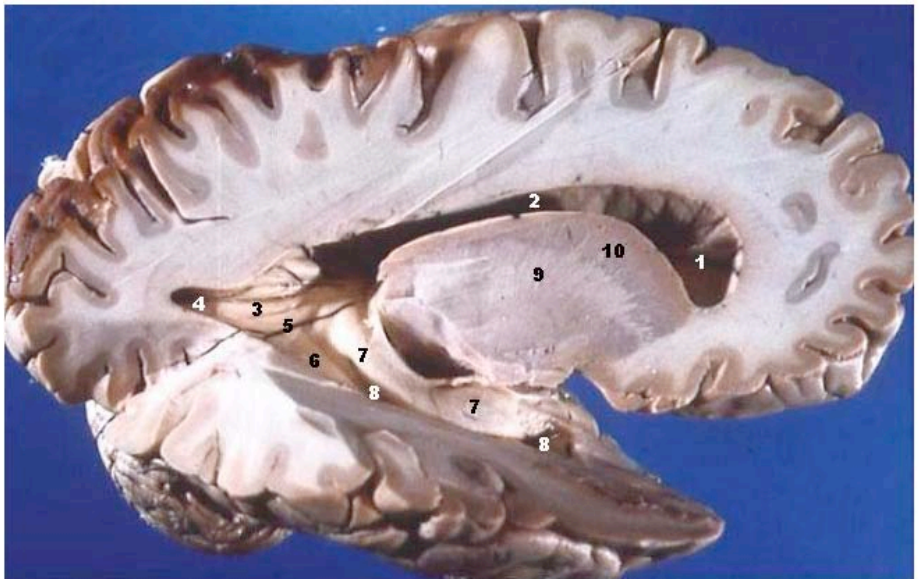
Figure 3 | Transgenic analysis of a chimpanzee and mouse forebrain enhancer missing from a tumour suppressor gene in humans. **a**, Top panel: 1.3 Mb region of the chimpanzee chromosome 9. The red bar illustrates a 3,181 bp human-specific deletion removing a conserved chimpanzee enhancer located downstream of *GADD45G*. Bottom panel: multiple species comparison of the deleted region, showing sequences aligned between chimpanzee and other mammals. The green bar represents a mouse forebrain-specific p300 binding site[18], and the blue and orange bars represent chimpanzee and mouse sequences tested for enhancer activity in transgenic mice. The chimpanzee (**b**–**e**) and mouse sequence (**f**–**i**) both drive consistent *lacZ* expression in E14.5 mouse embryos in the ventral thalamus (**c**, **g**), the SVZ of the septum (**d**, **h**), and the preoptic area (**e**, **i**). Increased production of neuronal subtypes from these regions may contribute to thalamic and cortical expansion in humans[27–30]. All sections are sagittal with anterior to right. POA, preoptic area; Se, septum; SVZ, subventricular zone; Th, thalamus; VZ, ventricular zone.

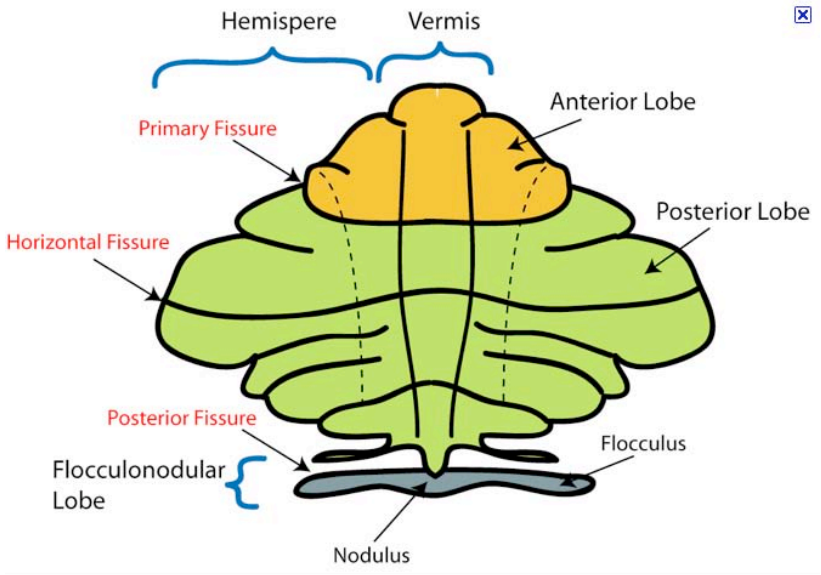


1) cortex orbitofrontal
2) cortex préfrontal latéral
3) cortex ventromédian
4) système limbique
5) cortex cingulaire antérieur

Source: Suzanne Stensaas et O.E. Millhouse, The Digital Slice of Life





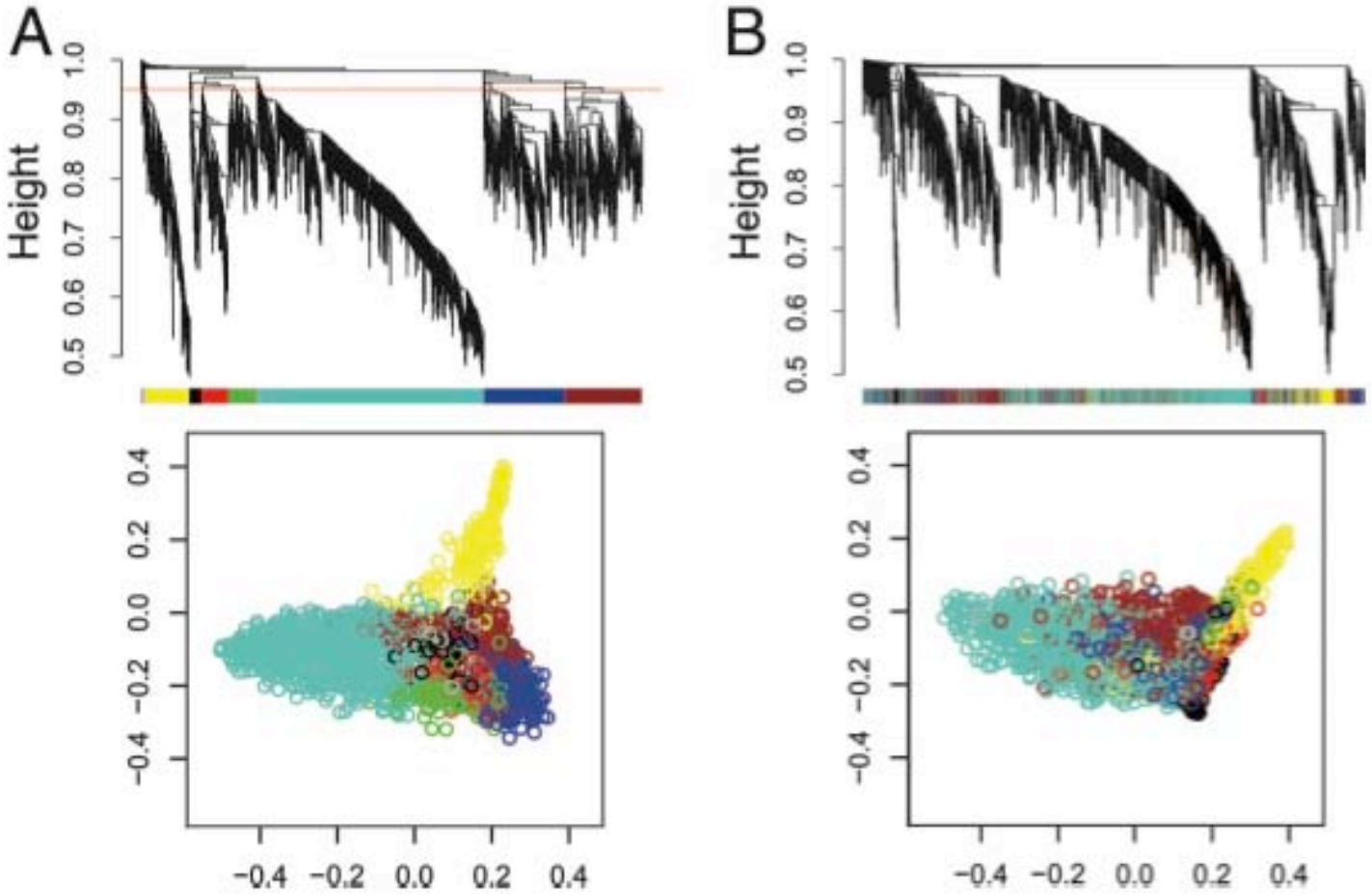


Conservation and evolution of gene coexpression networks in human and chimpanzee brains

Oldham M, Horvath S, Geschwind DH

Proc Natl Acad Sci USA
2006 vol. 103 (47) pp. 17973–8

Fig. 1. Network analysis of gene expression in human and chimpanzee brains identifies distinct modules of coexpressed genes in human (*A*) and chimpanzee (*B*). (*A*) Dendrograms produced by average linkage hierarchical clustering of 2,241 genes based on TO (see *Supporting Text*). The red line in the human dendrogram indicates the height at which the tree was cut (0.95) to define modules. Modules were assigned colors as indicated in the horizontal bar beneath the human dendrogram. Genes in the chimpanzee network are depicted by using human module colors to represent the extent of module conservation. (*B*) Classical multidimensional scaling plots in three dimensions (color-coded as in *A*) depict the relative size and cohesion of modules in humans and chimpanzees.



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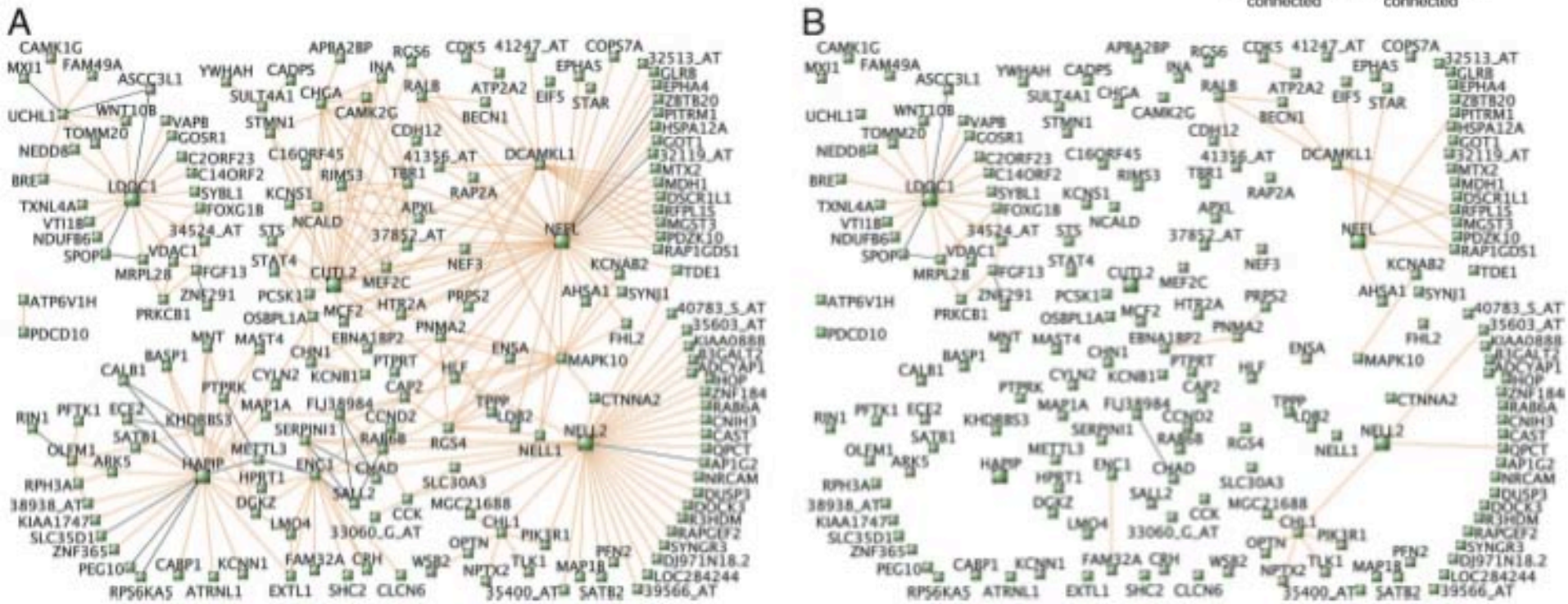

Fig. 3. Module visualization identifies hub genes and human-specific connections. (*A*) Three hundred pairs of genes with the greatest TO in humans are depicted for cortex (brown module). Genes with expression levels that are negatively correlated are connected by black lines. Where gene symbols are unknown, Affymetrix probe set IDs are shown (e.g., 37158_at). (*B*) Connections from *A* that are present in humans but absent in chimpanzees (see *Materials and Methods*).

NRG1: Glycoprotéine de 44kD, signalisation, développement, impliquées dans plusieurs maladies dont cancer, schizophrénie and psychose maniaco-dépressive

LDOC1 : Protéine nucléaire, développement, cancer

EYA1 : Facteur de transcription développement, vision (œil)

LECT1 : Glycoprotéine, angiogenèse, vascularisation au cours du développement

PGAM2 : Phosphoglycerate mutase (PGAM), stockage du glycogène

COX5A : Protéine mitochondriale, ETC

COX6A2 : Protéine mitochondriale, ETC

UQCRFS1 : Protéine mitochondriale, cancer , schizophrénie

IMMT : Protéine mitochondries, morphologie des mitochondries, interagit avec DISC1 (Disrupted in Schizophrenia 1)

DNM1L : Membre de la superfamille des dynamin sf GTPases, morphologie mitochondriale

DTNA1 : Dystrobrevin A1, muscle, CNS, développement de l'œil, de l'oreille interne, de l'hypophyse, de la barrière hémato méningée, plus d'autres régions cérébrales.

RAB3A : Exocytose, fusion des vésicules

ABI2 : Cytosquelette actine

CYFIP2 : Cytosquelette, interagit avec FRMP, retard mental

MAP1B : Polymérisation des microtubules

FGF12 : Membre de la famille des FGF avec localisation nucléaire

SLC30A9 : Transporteur, Zinc

ANKMY2 : Ankyrin repeat, pourrait être impliquée dans le transport de protéines de signalisation par les cils

KIAA1279 : Famille des kinésines (moteur moléculaire), transport des mitochondries, mutations associées au Goldberg-Shprintzen megacolon syndrome (maladie rare, affectant aussi le SNC)

Human brain evolution: harnessing the genomics (r)evolution to link genes, cognition, and behavior

Konopka G, Geschwind DH

Neuron
2010 vol. 68 (2) pp. 231–44

Studying the brain from an evolutionary perspective and combining these results with those from development and pathology, connecting genetic variation to neural circuit development and functioning, will yield the best approximation of how natural forces shaped this organ. Aside from satisfying basic curiosity about the origins of our abilities, such endeavors have enormous implications for understanding human diseases involving cognition and behavior, ranging from intellectual disability and autism to neurodegenerative dementias.

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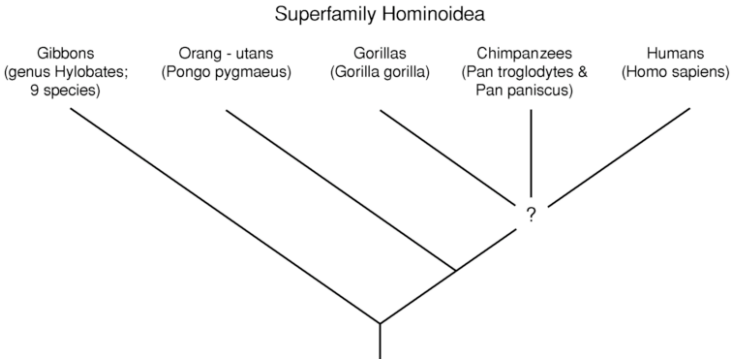
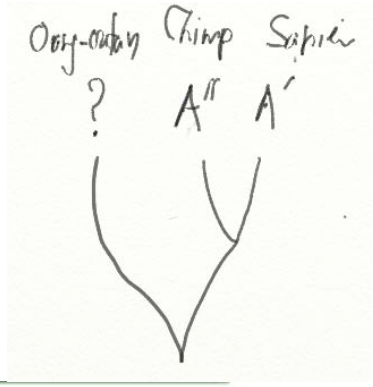




Common Name	Species	Original Date Sequenced	Unique Features
Mouse	*Mus musculus*	2002	Common model system for neurobehavioral/ neurogenetic experiments
Human	*Homo sapiens*	2001	
Rat	*Rattus norvegicus*	2003	Common model system for neurobehavioral experiments; now available for genetic manipulations
Fly	*Drosophila melanogaster*	2003	Common model system for neurobehavioral/ neurogenetic experiments
Worm	*Caenorhabditis elegans*	2004	Aging and longevity
Chimpanzee	*Pan troglodytes*	2005	Great ape; most similar to human on genome level
Zebrafish	*Danio rerio*	2005	Easy to visualize brain development; behavior; genetically malleable
Rhesus macaque	*Macaca mulatta*	2006	Old world monkey; bred in the USA for behavior and neurophysiology experiments
Honey bee	*Apis mellifera*	2006	Social behavior; aggression
Orangutan	*Pongo pygmaeus abelii*	2007	Great ape; useful for outgroup comparison with human/chimp
Elephant shark	*Callorhinchus milii*	2007	Outgroup for zebrafish and mouse comparisons
Dolphin	*Tursiops truncatus*	2008	Evidence for vocalization and self-awareness
Zebra finch	*Taeniopygia guttata*	2008	Patterned vocalization
Sea hare	*Aplysia californica*	2008	Learning and memory
Elephant	*Loxodonta africana*	2009	Evidence for vocalization and self-awareness
Pig	*Sus scrofa*	2009	Gyrencephalic cortex
Bat	*Myotis lucifugus*	2010	Echolocation
Ferret	*Mustela putorius furo*	in progress	Gyrencephalic cortex
Cichlids	*Tilapia nilotica*	in progress	"Natural" mutants for the study of evolution
Marmoset	*Callithrix jacchus*	in progress	New world monkey

Human brain evolution: harnessing the genomics (r)evolution to link genes, cognition, and behavior

Konopka G, Geschwind DH

Neuron
2010 vol. 68 (2) pp. 231–44

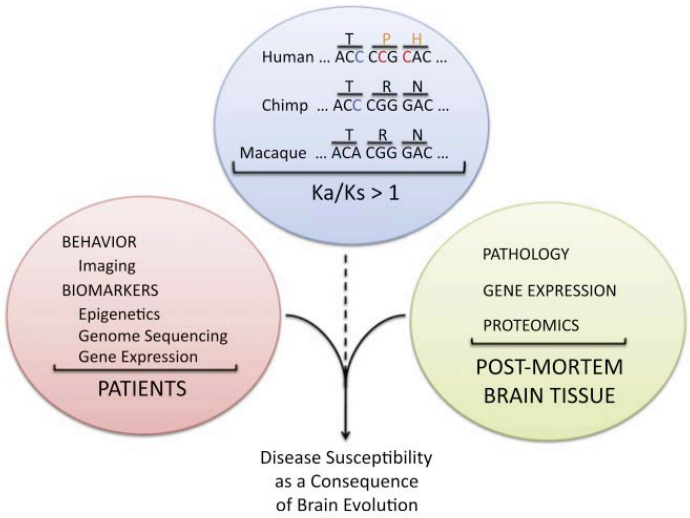


Figure 1. Combining Comparative Genomics with Phenotype and Expression Data Leads to Disease Insights

Measures of positive selection are typically calculated by dividing the number of nonsynonymous changes (depicted in red) by the number of synonymous changes (depicted in blue); a value greater than one is used as evidence for positive selection. It should be emphasized that this is arbitrary and only takes into account known protein coding regions. Screening genomes for genes under positive selection is one important step; however, other measures such as links to behavior and expression need to be incorporated. Furthermore, a gene does not have to have undergone positive selection to be a disease-susceptibility gene. Other changes in evolution such as timing or location of expression could make a gene or signaling pathway vulnerable in disease.

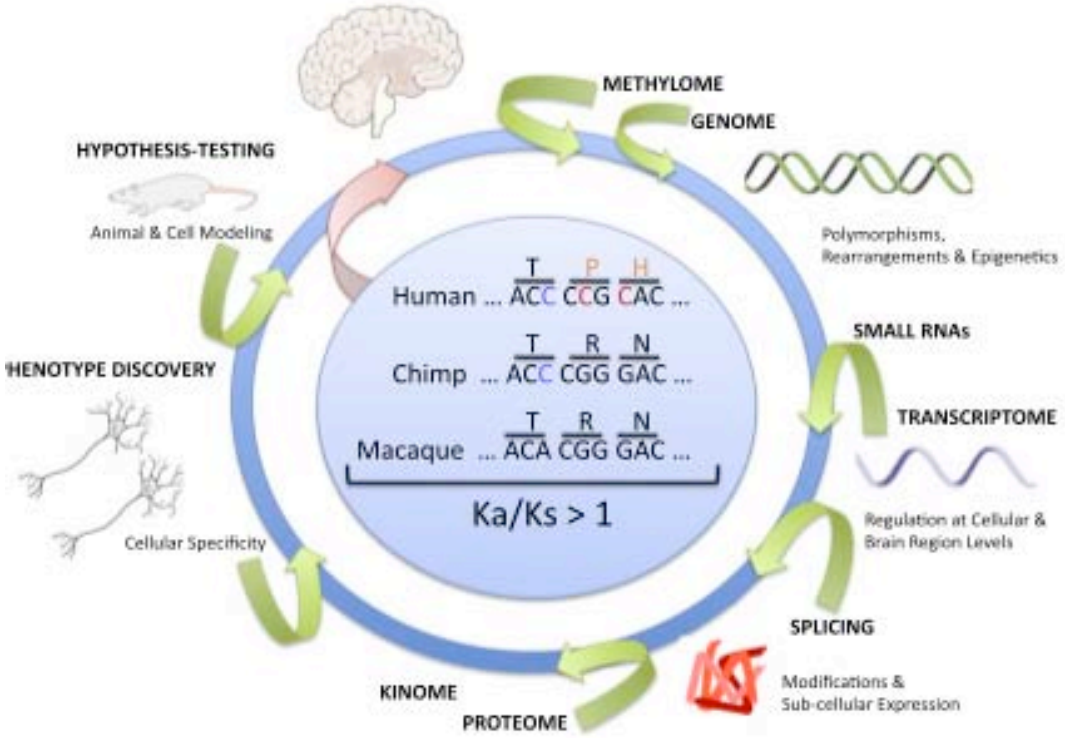


Figure 2. Multiple Layers of Regulation Underlie Human Brain Evolution

More than genomic comparisons need to be considered when building our understanding of human brain evolution. Regulation at the level of the epigenome (e.g., methylome), regulation of expression by changes in transcription or small RNA regulation, novel isoforms through differential splicing, changes in regional and subcellular expression, and posttranslational modifications (e.g., kinome) all need to be taken into account, and many of these changes can be queried using NGS techniques. Also, the incorporation of animal models and cell-specific lines of inquiry need to undertaken. Finally, the integration of all of these data will lead to phenotype discovery and hypothesis-testing that ultimately will inform polymorphism discovery in human brain diseases. In this manner, modern neurogenetic investigations are not only an exercise in advanced data analysis, but comprehensive data integration.

Both noncoding and protein-coding RNAs contribute to gene expression evolution in the primate brain

Genome Biol Evol
2010 vol. 2 pp. 67–79

Babbitt CC, Fedrigo O, Pfefferle AD, Boyle AP, Horvath JE, Furey TS, Wray G

Categorical Enrichment To determine functional category enrichment for the differentially expressed genes, we employed the PANTHER (HMM Library Version 6.0; Mi et al. 2005) and GO (The Gene Ontology Consortium, 2000) gene ontology databases. Our background set of genes were those genes measured in our tissue samples. PANTHER and GO category enrichment scores were computed using the top 5% of the hypergeometric probability distribution. Python code used to perform all enrichments is available at: http://www.duke.edu/~ofedrigo/Olivier_Fedrigo/PythonScripts.html.

Categorical Enrichments for Differentially Expressed Genes between the Human and Chimpanzee Individuals

Category	*P* value	Top 5.0%	Total
PANTHER			
DNA repair	8.06×10^{-05}	17	119
DNA metabolism	9.58×10^{-05}	26	233
Intracellular protein traffic	0.0001132	61	759
Electron transport	0.007361	16	163
Neurotransmitter release	0.01398	10	90
Oxidative phosphorylation	0.01562	7	53
Induction of apoptosis	0.01983	10	95
Endocytosis	0.02428	17	202
Extracellular transport and import	0.03121	6	48
Protein targeting and localization	0.03184	14	162
Nuclear transport	0.03957	7	64
Cytokinesis	0.04562	7	66
GO			
Translational elongation	0.0004988	11	68
Viral genome replication	0.002211	4	12
Protein import into nucleus, docking	0.008714	4	17
Phospholipid metabolic process	0.01311	4	19
Transport	0.0139	34	460
Glutamate signaling pathway	0.01946	3	12
Induction of apoptosis	0.02269	10	97
Intracellular protein transport	0.02412	14	156
tRNA aminoacylation for protein translation	0.02438	3	13
Lipid catabolic process	0.02472	7	58
Nucleocytoplasmic transport	0.0299	3	14
Regulation of GTPase activity	0.03603	3	15
Electron transport chain	0.04029	8	78
RNA processing	0.04054	6	51
Base-excision repair	0.04274	3	16
Inactivation of MAPK activity	0.04274	3	16
Protein stabilization	0.04274	3	16
DNA repair	0.04792	11	125
Phospholipid biosynthetic process	0.04874	4	28

NOTE.—The results for the biological process domain of both the GO and PANTHER ontologies are shown. Categorical enrichments are for the top 5% of a hypergeometric probability distribution. The right-hand columns show the number of genes in the top 5%, as well as the total number of genes evaluated. Categories that evaluated less than 10 genes total are not shown. Categories are further colored according to hierarchically related ontology terms: nucleic acid metabolism (green), electron transport (yellow), neuronal activity (blue), transport, extra- and intracellular protein traffic (pink), and lipid metabolism (purple).

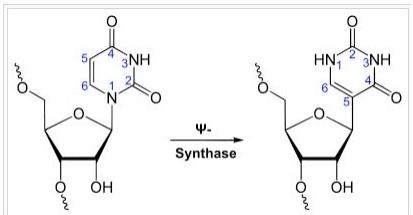
Table 1 | **Types of ncRNAs***

Name	Size	Location	Number in humans	Functions	Illustrative examples	Refs
Short ncRNAs						
miRNAs	19–24 bp	Encoded at widespread locations	>1,424	Targeting of mRNAs and many others	miR-15/16, miR-124a, miR-34b/c, miR-200	3–8
piRNAs	26–31bp	Clusters, intragenic	23,439	Transposon repression, DNA methylation	piRNAs targeting *RASGRF1* and LINE1 and IAP elements	13–19
tiRNAs	17–18bp	Downstream of TSSs	>5,000	Regulation of transcription?	Associated with the *CAP1* gene	37
Mid-size ncRNAs						
snoRNAs	60–300 bp	Intronic	>300	rRNA modifications	U50, SNORD	20–22
PASRs	22–200 bp	5′ regions of protein-coding genes	>10,000	Unknown	Half of protein-coding genes	10
TSSa-RNAs	20–90 bp	–250 and +50 bp of TSSs	>10,000	Maintenance of transcription?	Associated with *RNF12* and *CCDC52* genes	35
PROMPTs	<200 bp	–205 bp and –5 kb of TSSs	Unknown	Activation of transcription?	Associated with *EXT1* and *RBM39* genes	36
Long ncRNAs						
lincRNAs	>200 bp	Widespread loci	>1,000	Examples include scaffold DNA–chromatin complexes	*HOTAIR*, *HOTTIP*, *lincRNA-p21*	2,28–30
T-UCRs	>200 bp	Widespread loci	>350	Regulation of miRNA and mRNA levels?	uc.283+, uc.338, uc160+	31–34
Other lncRNAs	>200 bp	Widespread loci	>3,000	Examples include X-chromosome inactivation, telomere regulation, imprinting	*XIST*, *TSIX*, TERRAs, *p15AS*, *H19*, *HYMAI*	2,23–25

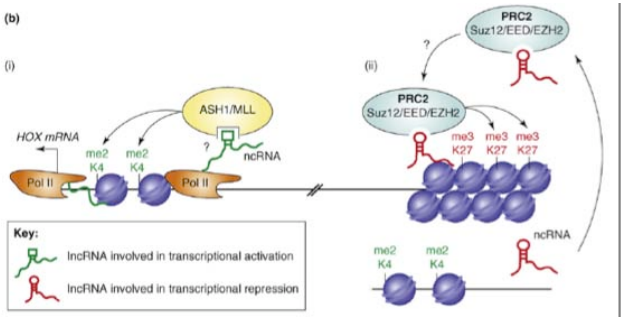
Non-coding RNAs in human disease

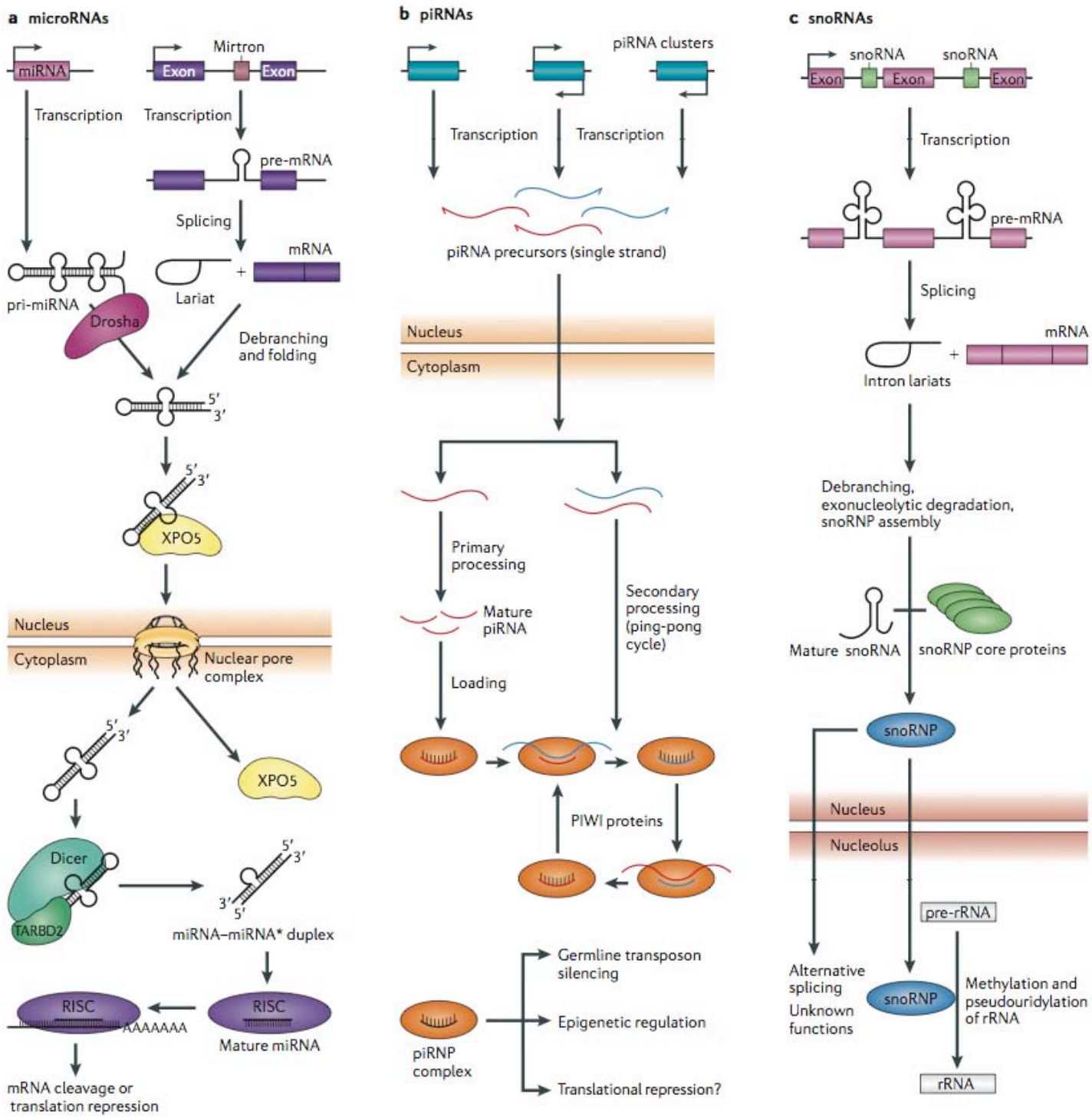
Esteller M

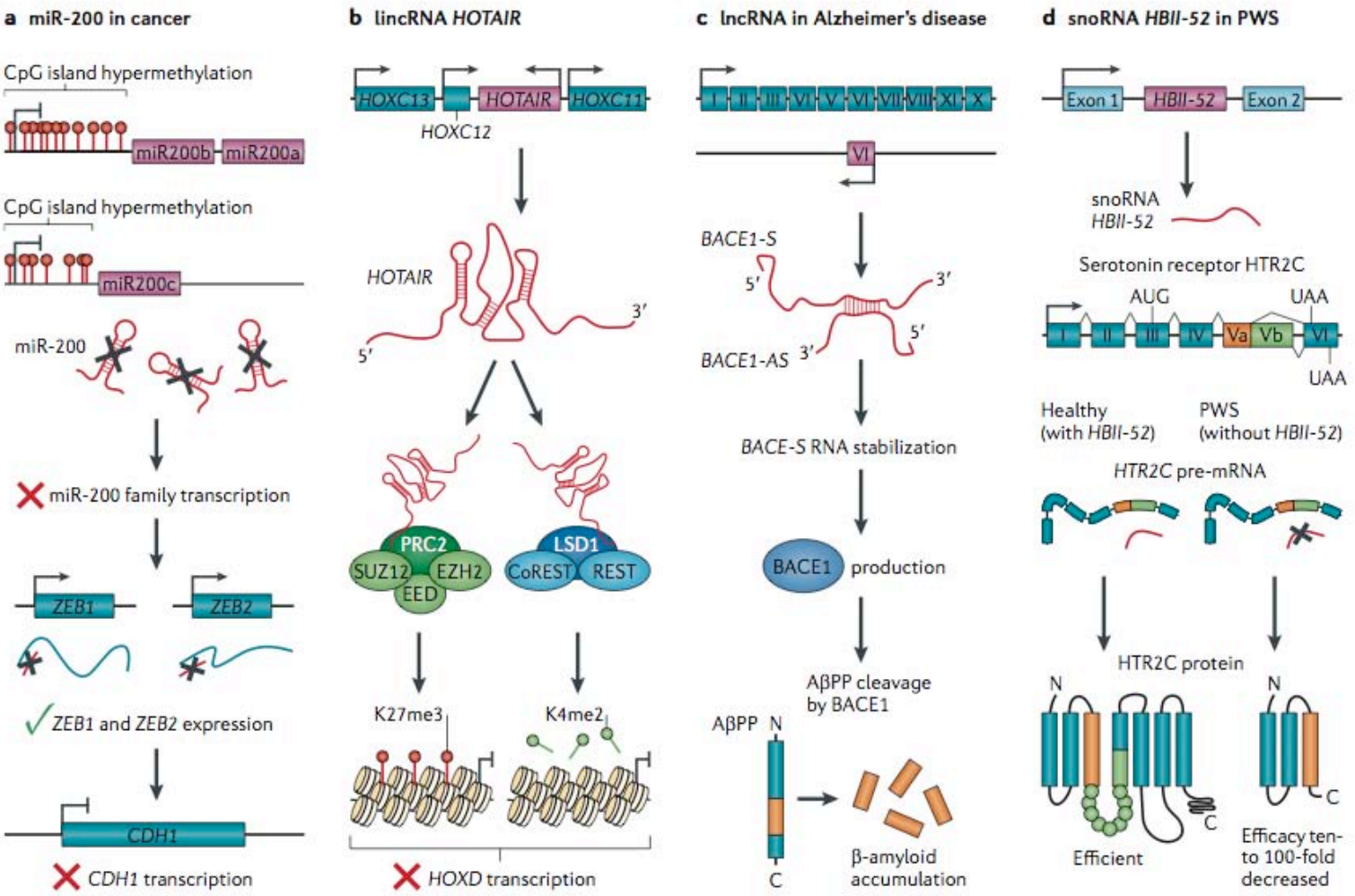
Nature Reviews Genetics 12, 861 (2011). doi: 10.1038/nrg3074



Pseudouridine is biosynthesized from uridine via the action of Ψ synthases.




a microRNAs
miRNA
Mirtron
Exon
Exon
Transcription
Transcription
pre-mRNA
Splicing
mRNA
pri-miRNA
Drosha
Lariat
Debranching and folding
5′ 3′
XPO5
Nucleus
Cytoplasm
Nuclear pore complex
XPO5
Dicer
TARBD2
miRNA–miRNA* duplex
RISC
AAAAAAA
RISC
Mature miRNA
mRNA cleavage or translation repression
b piRNAs
piRNA clusters
Transcription
Transcription
piRNA precursors (single strand)
Nucleus
Cytoplasm
Primary processing
Mature piRNA
Loading
Secondary processing (ping-pong cycle)
PIWI proteins
piRNP complex
Germline transposon silencing
Epigenetic regulation
Translational repression?
c snoRNAs
snoRNA
snoRNA
Exon
Exon
Exon
Transcription
pre-mRNA
Splicing
mRNA
Intron lariats
Debranching, exonucleolytic degradation, snoRNP assembly
Mature snoRNA
snoRNP core proteins
snoRNP
Nucleus
Nucleolus
pre-rRNA
Alternative splicing
Unknown functions
snoRNP
Methylation and pseudouridylation of rRNA
rRNA

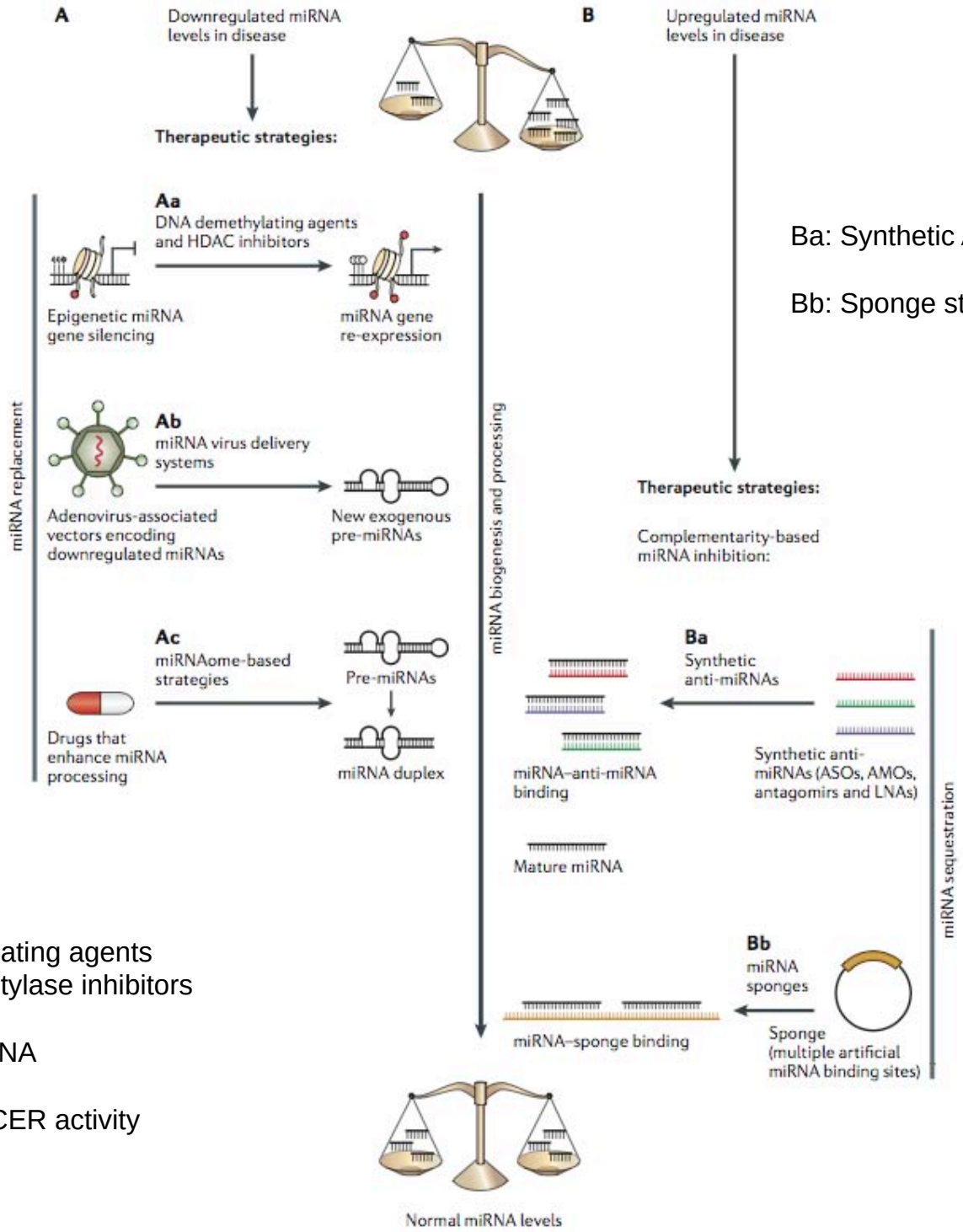


invasiveness. **c** | lncRNA targeting of β-secretase 1 (BACE1) has a role in the pathophysiology of Alzheimer's disease. An antisense lncRNA, *BACE1-AS*, regulates the expression of the sense *BACE1* gene (labelled *BACE1-S* in the figure) through the stabilization of its mRNA. *BACE1-AS* is elevated in Alzheimer's disease, increasing the amount of BACE1 protein and, subsequently, the production of β-amyloid peptide. **d** | The role of the snoRNA in Prader–Willi syndrome (PWS). The loss of the snoRNA in PWS changes the alternative splicing of the serotonin receptor *HTR2C* precursor mRNA (pre-mRNA), resulting in a protein with reduced function. AβPP, amyloid-β precursor protein; CoREST, REST corepressor.

Table 3 | **Illustrative list of ncRNAs that are disrupted in non-tumoural disorders**

Disease	Involved ncRNAs	ncRNA type	Refs
Spinal motor neuron disease	miR-9	miRNA	87
Spinocerebellar ataxia type 1	miR-19, miR-101, miR-100	miRNA	88
Amyotropic lateral sclerosis	miR-206	miRNA	86
Arrhytmia and hypertension	miR-1	miRNA	98
Atheromatosis and atherosclerosis	miR-10a, miR-145, mR-143 and miR-126	miRNA	100–102
Atheromatosis and atherosclerosis	Circular ncRNA linked to the CDKN2A locus	lncRNA	119
Cardiac hypertrophy	miR-21	miRNA	144
Rett's syndrome	miR-146a, miR-146b, miR-29 and miR-382	miRNA	108,109
5q syndrome	miR-145 and miR-146a	miRNA	106
ICF syndrome	miR-34b, miR-34c, miR-99b, let-7e and miR-125a	miRNA	107
Crohn's disease	miR-196	miRNA	110
Prader–Willi and Angelman syndromes	snoRNA cluster at 15q11–q13 imprinted locus	snoRNA	114–116
Beckwith–Wiedeman syndrome	lncRNAs *H19* and *KCNQ1OT1*	lncRNA	145
Uniparental disomy 14	snoRNA cluster at 14q32.2 imprinted locus	snoRNA	145
Silver–Russell syndrome	lncRNA *H19*	lncRNA	145
Silver–Russell syndrome	miR-675	miRNA	145
McCune–Albright syndrome	lncRNA *NESP-AS*	lncRNA	145
Deafness	miR-96	miRNA	111
Alzheimer's disease	miR-29, miR-146 and miR-107	miRNA	89–91
Alzheimer's disease	ncRNA antisense transcript for *BACE1*	lncRNA	112
Parkinson's disease	miR-7, miR-184 and let-7	miRNA	82
Down's syndrome	mir-155 and miR-802	miRNA	83
Idiopathic neurodevelopmental disease	T-UCRs uc.195, uc.392, uc.46 and uc.222	T-UCR	113
Rheumatoid arthritis	miR-146a	miRNA	147
Transient neonatal diabetes mellitus	lncRNA *HYMAI*	lncRNA	148
Pseudohypoparathyroidism	lncRNA *NESP-AS*	lncRNA	146

BACE1, β-secretase 1; CDKN2A, cyclin-dependent kinase inhibitor 2A; *HYMAI*, hydatidiform mole associated and imprinted; ICF syndrome, immunodeficiency, centromeric region instability and facial anomalies syndrome; KCNQ1OT1, KCNQ1 opposite strand/antisense transcript 1; lncRNA, long non-coding; miRNA, microRNA; NESP, also known as GNAS; NESP-AS, NESP antisense; ncRNA, non-coding RNA; snoRNA, small nucleolar RNA; T-UCR, transcribed ultraconserved region.



Ba: Synthetic Antisens strategy

Bb: Sponge strategy

Aa: DNA demethylating agents and histone deacetylase inhibitors

Ab: Delivery of µRNA

Ac: Enhancing DICER activity

Source: Suzanne Stensaas et O.E. Millhouse, The Digital Slice of Life