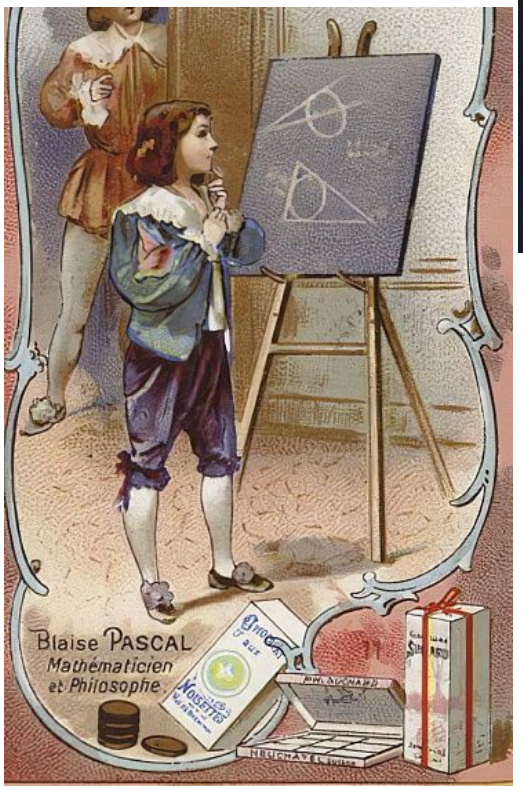

Blaise PASCAL
Mathématicien
et Philosophe

I “bastardi” di Rehoboth

Eugene Fischer 1874 - 1967, ’Istituto di Antropologia dell’Università di Berlino

nelle terre della Colonia del Capo a seguito dei contatti tra i coloni boeri e le popolazioni indigene (soprattutto donne di etnia nama).

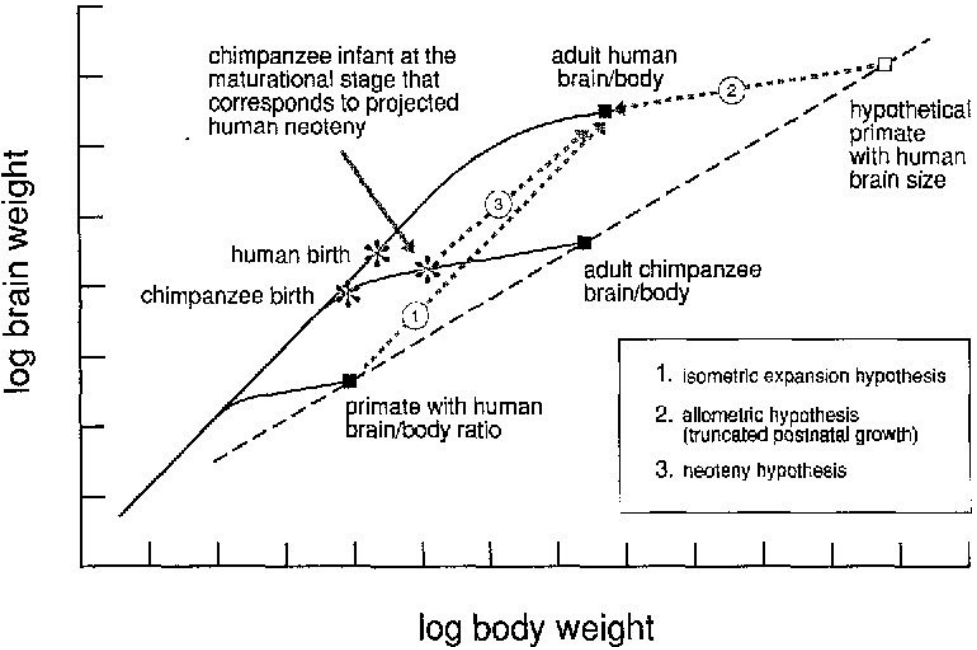
parlano l'afrikaans e, dal punto di vista culturale, si considerano più bianchi che neri. Praticanti il calvinismo, i basters sono molto religiosi (il loro motto è "Groei in Geloof", vale a dire "crescita nella fede") e vanno fieri del fatto di essere considerati "più olandesi degli stessi olandesi".

appello mondiale per impedire la prosecuzione di una "razza mista", e quindi il divieto del matrimonio inter-razziale. I discendenti meticci non avrebbero più dovuto continuare a riprodursi;

"scala Fischer-Saller". Questa scala si basava sui colori dei capelli; gradazioni di biondo = da A a J, gradazioni di marrone = da K a V, e marrone scuro e nero fino alla lettera Z, quindi gradazioni di rosso con la numerazione romana da I a VI. Gli esperimenti medici furono eseguiti su dei prigionieri vivi (zingari, ebrei e africani), compiendo su di loro numerosi prelievi di sangue, tessuti e misurazioni invasive dei loro crani.

i meticci di Rehoboth sono inferiori rispetto alle popolazioni "pure" sia bianche sia nere.

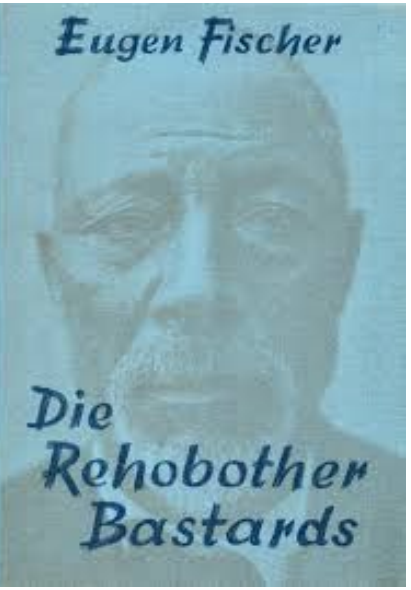
comportamenti come l'instabilità, l'inaffidabilità e una presunta predisposizione alla criminalità e alla degenerazione morale.



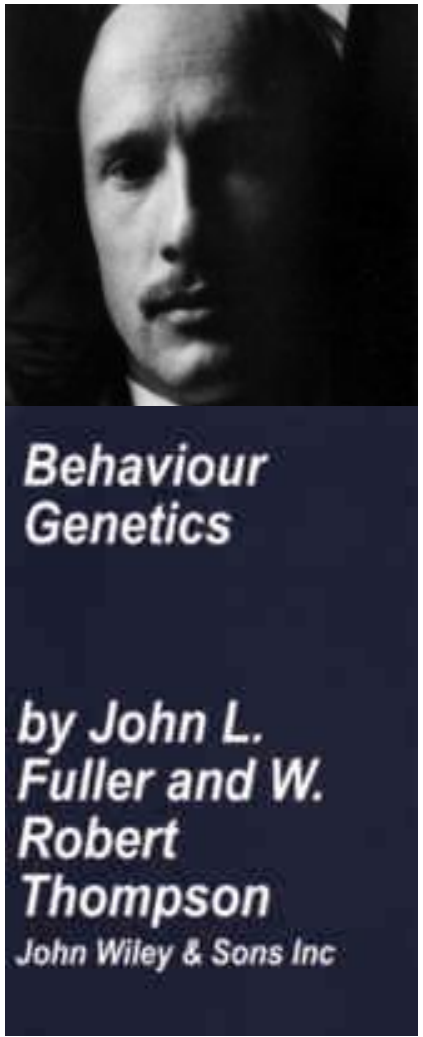
MA...

- L'ereditabilità dell'intelligenza aumenta da circa il 20% nell'infanzia a forse l'80% nella tarda età adulta.

‘30



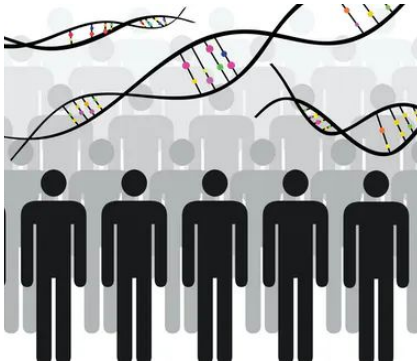
‘60



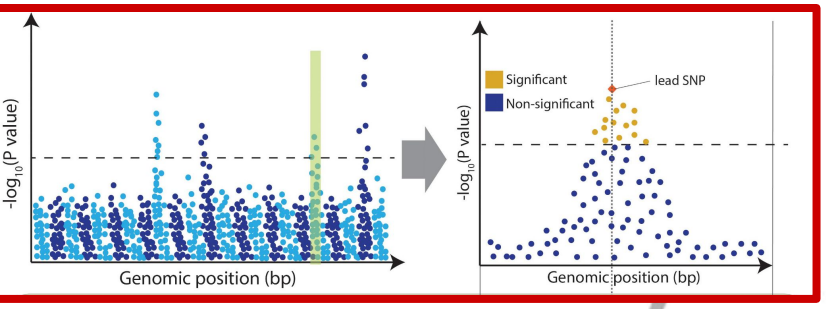
‘70

Twin studies

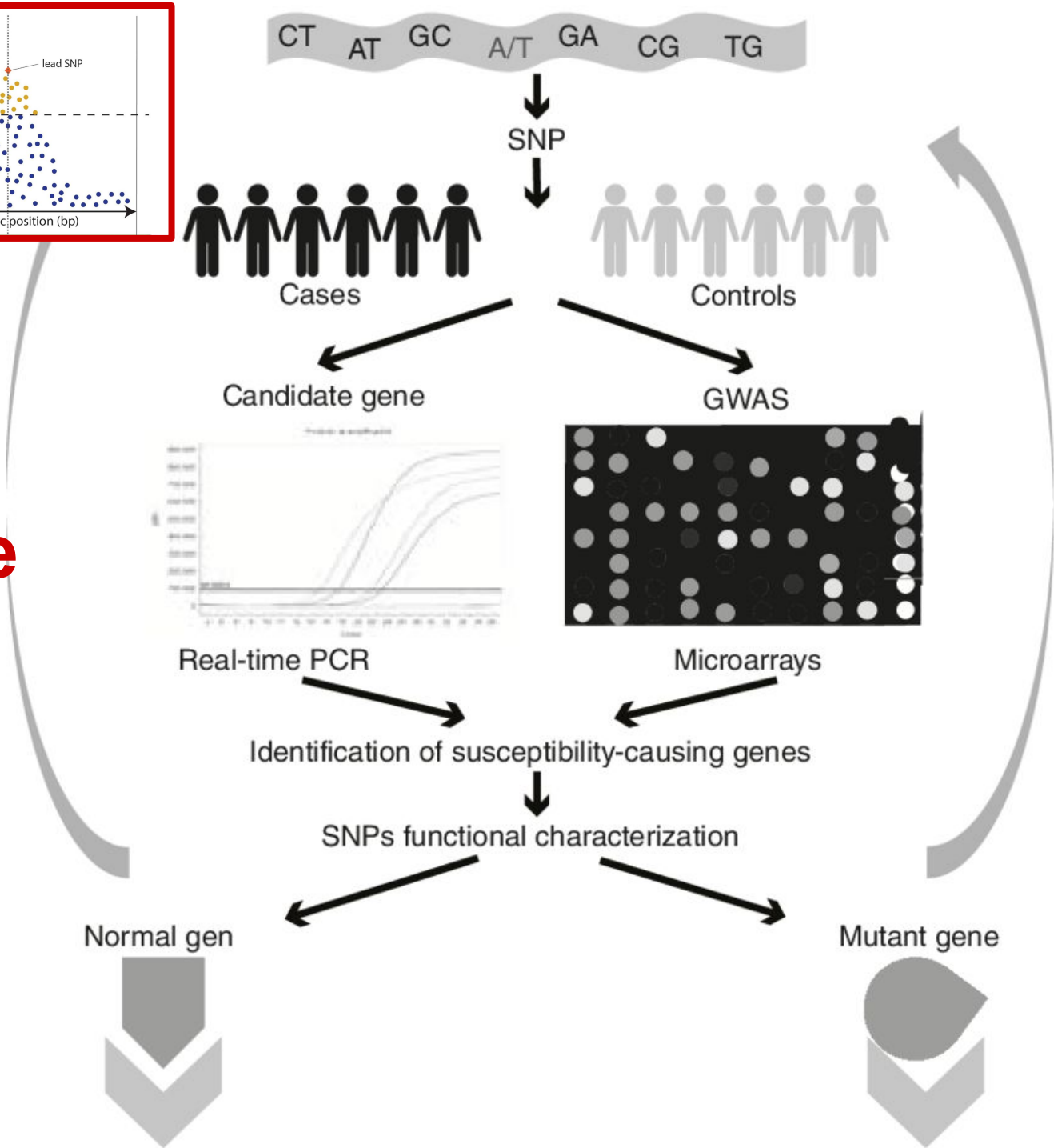
‘80



gene disease association studies



candidate gene vs **genome wide association** studies



Top 10 Replicated Findings From Behavioral Genetics

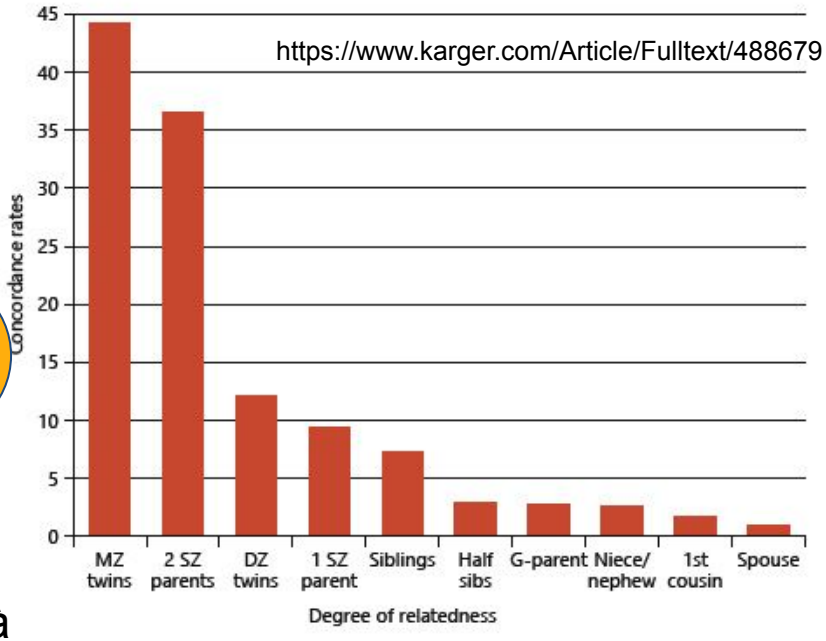
Robert Plomin[1], John C. DeFries[2], Valerie S. Knopik[3], and Jenae M. Neiderhiser[4]

Perspectives on Psychological Science
2016, Vol. 11(1) 3–23

DOI: 10.1177/1745691615617439
pps.sagepub.com
SAGE

https://scholar.google.it/scholar?hl=en&as_sdt=0%2C5&q=top+10+replicated+findings+from+behavioral+genetics&btnG=

1. "Tutti i tratti psicologici mostrano un'influenza genetica significativa e sostanziale"... ma
2. "Nessun tratto è ereditabile al 100%".... anzi…
3. "L'ereditabilità è causata da molti geni di piccolo effetto".
4. "La stabilità da età a età è dovuta principalmente alla genetica".
5. "La maggior parte delle associazioni tra fattori ambientali e tratti psicologici sono significativamente mediate geneticamente" ma anche che l'ambiente media l'associazione tra tr. psicologici e genetica
6. "gli effetti ambientali possono non essere condivisi dai bambini che crescono nella stessa famiglia".



psicosi porta alla dissociazione della personalità
Allucinazioni - percepite come reali, ma che non esistono realmente (ad esempio, udire voci o vedere cose che non ci sono). 1/200 persone affette, ereditabilità c.ca 60%

- Deliri - esperienze sensoriali inesistenti, credenze irrazionali o false che una persona può sostenere fermamente, anche quando sono contraddette dalle prove.
- Pensiero disordinato - difficoltà a organizzare i pensieri o a esprimersi in modo coerente.
- Movimenti disordinati - movimenti fisici ripetitivi o strani.

Comportamento bizzarro o violento o che non segue le norme sociali o culturali.

Gli animali non presentano la schizofrenia principalmente perché hanno strutture cerebrali diverse e non subiscono gli stessi fattori di rischio ambientali e genetici degli esseri umani.

https://www.nature.com/articles/s41586-022-04434-5

Article

Mapping genomic loci implicates genes and synaptic biology in schizophrenia

2022

Genome-wide association study of up to **76,755 individuals** with schizophrenia and **243,649 control** individuals

- Common variant associations at **287 distinct genomic loci**, concentrated in genes that are expressed in **excitatory and inhibitory neurons of the central nervous system**, but not in other tissues or cell types.
- We implicate fundamental processes related to **neuronal function, including synaptic organization, differentiation and transmission**.
- convergence of **common and rare variant associations** in schizophrenia and neurodevelopmental disorders
- We also show that **genes with high relative specificity for expression in almost all tested brain regions are enriched for genetic association**. This suggests that **abnormal neuronal function in schizophrenia is not confined to a small number of brain structures**, which in turn might explain its diverse **psychopathology, association with a broad range of cognitive impairments and lack of regional specificity in neuroimaging measures**.

Article

Rare coding variants in ten genes confer substantial risk for schizophrenia

https://www.nature.com/articles/s41586-022-04556-w

2022

Genetic study of more than **121,000 people** carried out by the Schizophrenia Exome Sequencing Meta-Analysis (SCHEMA) consortium (MIT and Harvard).

- Rare coding variation has historically provided the most direct connections between gene function and disease pathogenesis. By meta-analysing the whole exomes of **24,248 schizophrenia cases and 97,322 controls**, we implicate **ultra-rare coding variants** (URVs) in **10 genes** that strongly increase an individual's risk of developing schizophrenia — in one instance, by more than 20-fold.
- These genes have the **greatest expression in central nervous system neurons** and have functions that include the **formation, structure and function of the synapse**.
- The associations of the NMDA (N-methyl-D-aspartate) receptor subunit GRIN2A and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor subunit GRIA3 provide support for dysfunction of the glutamatergic system as a mechanistic hypothesis in the pathogenesis of schizophrenia.
- We observe an **overlap of rare variant risk among schizophrenia, autism spectrum disorders, epilepsy and severe neurodevelopmental disorders**, although different mutation types are implicated in some shared genes.
- Even after excluding significantly associated genes, schizophrenia cases still carry **a substantial excess of URVs**, which indicates that more risk genes await discovery using this approach.

GRIN2A, SP4, STAG1 and FAM120A as specific genes in which the convergence of rare and common variant associations strongly supports their pathogenic role in the disorder.

GRIN2A - glutamate ionotropic receptor N-methyl-D-aspartate (NMDA) type subunit 2A; a member of the glutamate-gated ion channel protein family; Disruption of this gene is associated with **focal epilepsy and speech disorder** with or without cognitive disability.

Sp4 Transcription Factor
bind to the GC promoter region of a variety of genes, including those of the photoreceptor signal transduction system.
This gene may be involved in **bipolar disorder and schizophrenia**.

FAM120A
Family With Sequence Similarity 120A
Enables RNA binding activity. Located in cytosol, **regulates activity of Src kinases** to protect cells from oxidative stress-induced apoptosis.

STAG1
Stromal Antigen 1, **encodes a component of cohesin**, a protein complex responsible for cohesion between portions of chromosomes during cell replication and is involved in DNA repair

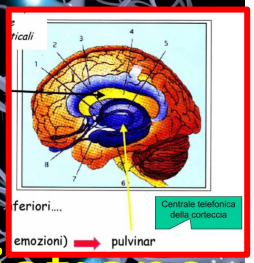
Non genetic factors

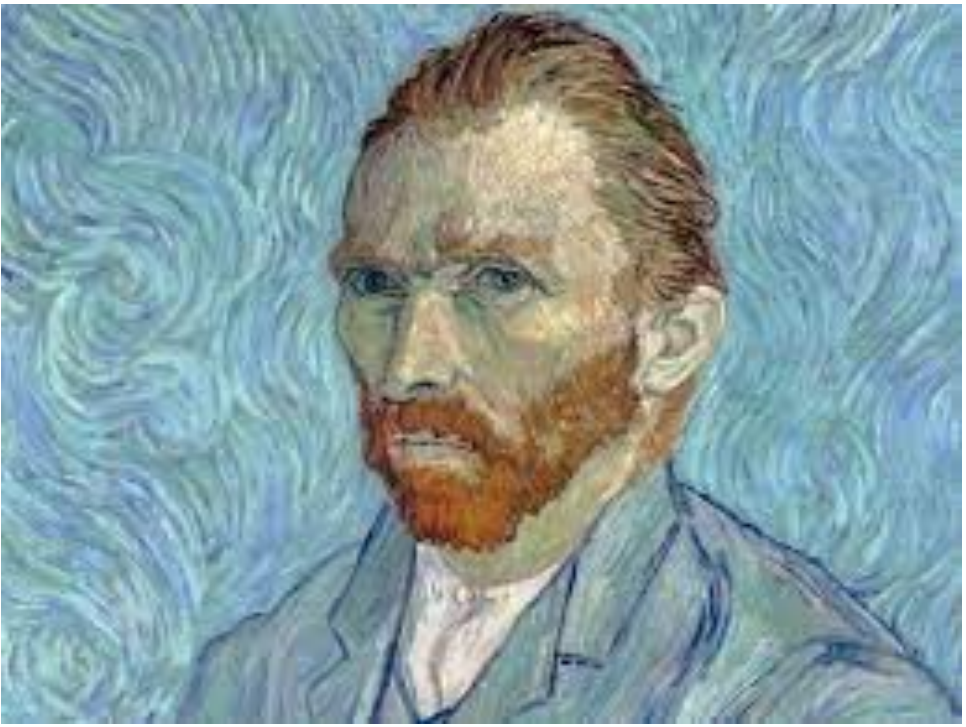
Chronic social adversity in childhood and in adulthood
migrant status
urban environment
pre- and perinatal factors
Drug abuse e.g. cannabis , psychostimulants, tobacco
maternal malnutrition

Evolutionary paradox
lower fitness of affected person but maintenance in the population

https://www.karger.com/Article/FullText/488679

dopamine receptor deficit in the thalamus?
less filter for mental associations





Differences in voice-hearing experiences of people with psychosis in the USA, India and Ghana: interview-based study

T. M. Luhrmann, R. Padmavati, H. Tharoor and A. Osei

The British Journal of Psychiatry (2015) 206, 41–44. doi: 10.1192/bjp.bp.113.139048

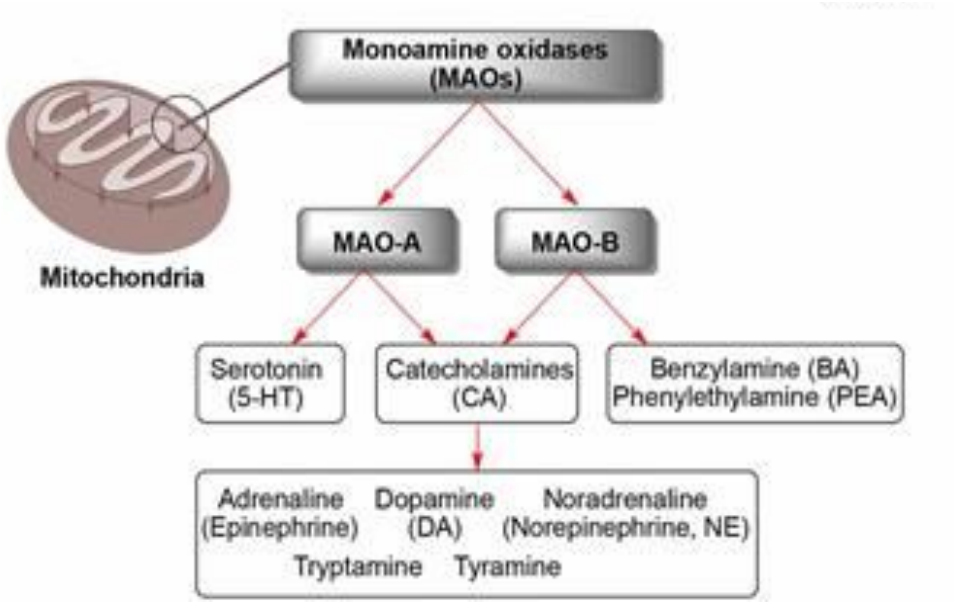
Negli **Stati Uniti** l'esperienza è vissuta come **qualcosa di negativo**, non dissociato dalla malattia, e le voci spesso accusano o provocano le persone affette da questo disturbo, con modalità aggressive e autoritarie. Le allucinazioni uditive sono spesso violente, come si legge nello studio «parlano di torture, o incitano le persone a compiere azioni terribili, come usare una forchetta per togliere un occhio a qualcuno, o rompergli la testa per bere il suo sangue». E nessuno dei pazienti negli Stati Uniti ha riportato esperienze uditive positive. Questo perché «nel campione americano la voce è vissuta come **un'intrusione nel proprio spazio mentale** perché nella loro cultura l'individuo si percepisce come un'entità autonoma che vuole mantenere il controllo della propria mente. Sentire una voce esterna è un'**aggressione alla propria identità, qualcosa fuori dal proprio controllo**.

In **India e Ghana** invece le persone affette da schizofrenia vivono la stessa esperienza **in maniera più positiva**: per loro si tratta quasi sempre di **sentire un amico o un parente o una divinità** che dà consigli o suggerimenti. nelle culture orientali e africane c'è una maggior propensione ai rapporti sociali e al collettivismo. È per questo motivo che l'esperienza della voce viene vissuta come un estensione della già fitta rete sociale del paziente affette da schizofrenia. I partecipanti allo studio hanno dichiarato di avere **un rapporto talmente positivo con le proprie voci, da non collegarlo nemmeno alla diagnosi di disturbo fatta dal medico.**

The violence gene: one variant - one behavior

Monoaminoxydase-a

- MAO, protein family of flavin-containing amine oxidoreductases,catalyze the oxidation of monoamines,
- bound to the outer membrane of mitochondria in most cell types of the body.
- MAO genes located on the short arm of cromosoma X



In humans there are two types of MAO: MAO-A and MAO-B

- Both are found in neurons and astroglia.
- Outside the central nervous system:
  - MAO-A is also found in the liver, pulmonary vascular endothelium, gastrointestinal tract, and placenta.
  - MAO-B is mostly found in blood platelets.

unusually high or low levels of MAOs in the body have been associated with schizophrenia,depression, attention deficit disorder,[substance abuse,[migraines,and irregular sexual maturation

The violence gene: one variant - one behavior

Science

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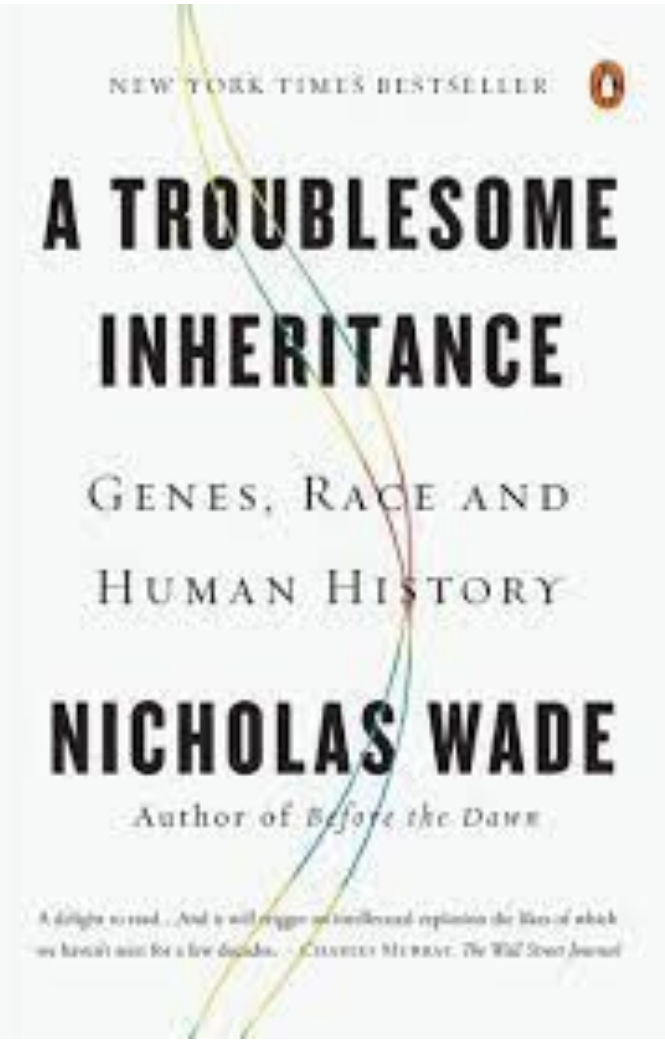
Volume 262(5133) 22 October 1993 pp 578-580

Abnormal Behavior Associated with a Point Mutation in the Structural Gene for Monoamine Oxidase A

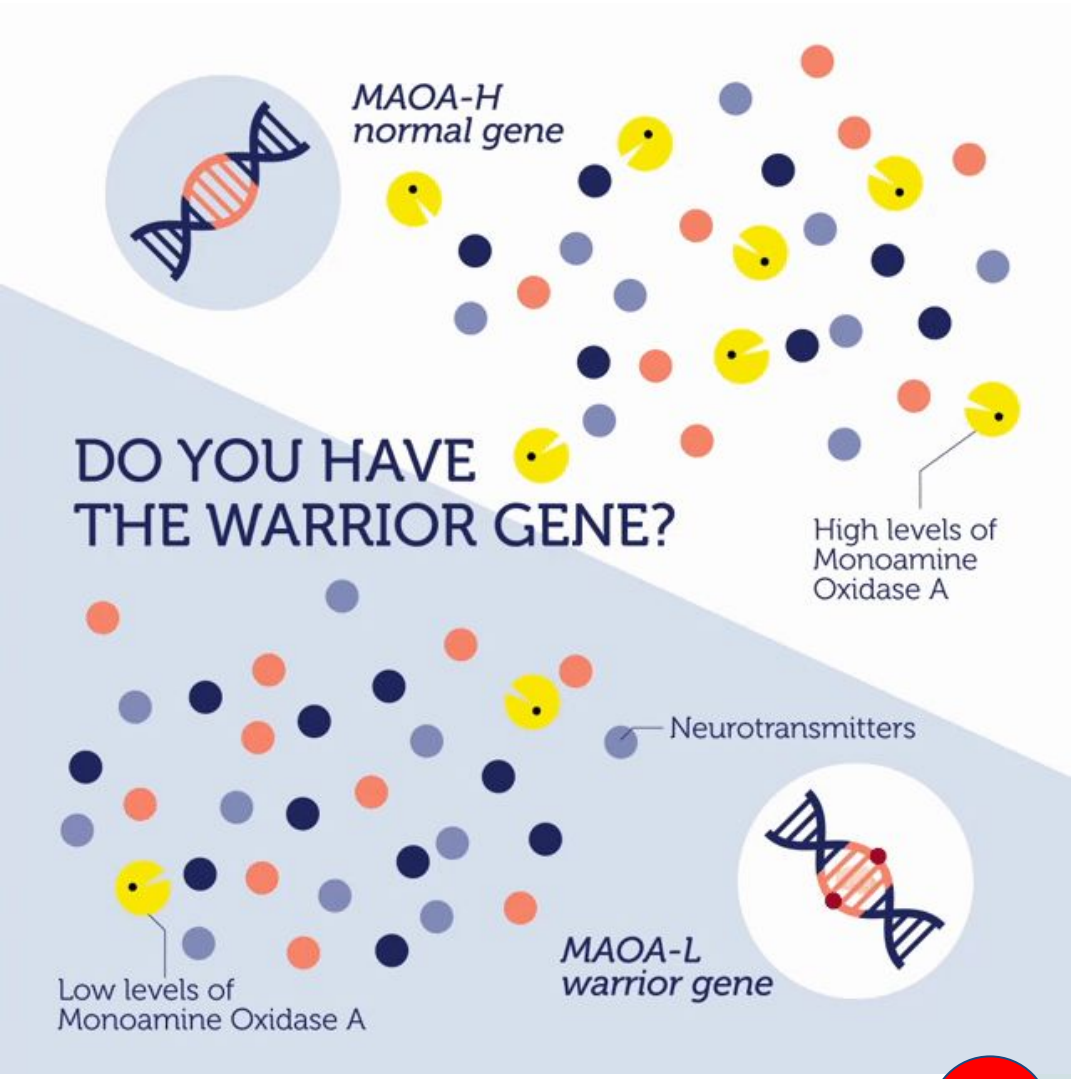
[Reports]

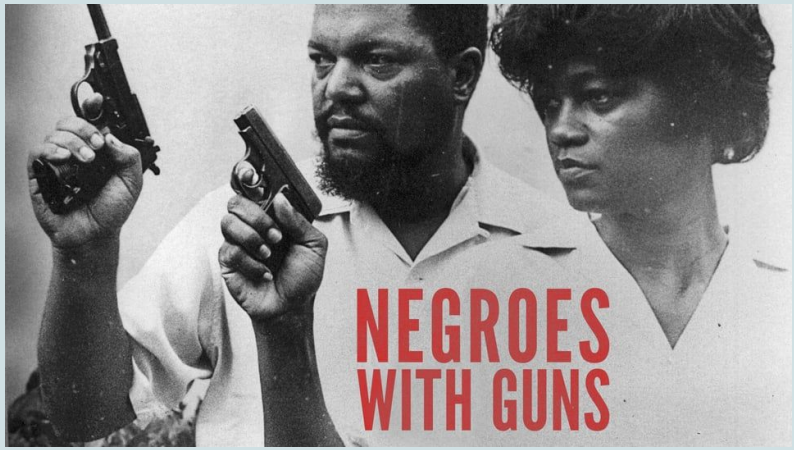
Brunner, H. G.*; Nelen, M.; Breakefield, X. O.; Ropers, H. H.; van Oost, B. A.

Analysis of 24-hour urine samples indicated markedly disturbed monoamine metabolism. This syndrome was associated with a complete and **selective deficiency of enzymatic activity of monoamine oxidase A** (MAOA). In each of five affected males, a point mutation was identified in the eighth exon of the MAOA structural gene, which **changes a glutamine to a termination codon**. Thus, isolated complete MAOA deficiency in this family is **associated with a recognizable behavioral phenotype that includes disturbed regulation of impulsive aggression**.



The violence gene: one variant - one behavior





RESEARCH ARTICLE

Genotypes Do Not Confer Risk For Delinquency ut Rather Alter Susceptibility to Positive and Negative Environmental Factors: Gene-Environment Interactions of *BDNF* Val66Met, 5-*HTTLPR*, and *MAOA*-uVNTR

Kent W Nilsson, MD; Erika Comasco, MD; Sheilagh Hodgins, MD; Lars Oreland, MD; Cecilia Åslund, MD

International Journal of Neuropsychopharmacology, 2015, 1–10

doi:10.1093/ijnp/pyu107
Research Article

https://academic.oup.com/ijnp/article/18/5/pyu107/786166

- Study of the interactions between the **brainderived neurotrophic factor gene** (BDNF Val66Met), the **serotonin transporter gene-linked polymorphic region** (5-HTTLPR), the **monoamine oxidase A** (MAOA-uVNTR) polymorphisms, **family conflict, sexual abuse, the quality of the child-parent relationship, and teenage delinquency.**
- 337 high-school students, aged 17– 18 years, anonymously completed questionnaires and provided saliva samples for DNA analyses.
- **Teenage delinquency** was associated with two-, three-, and four-way interactions of each of the genotypes and the three environmental factors. Significant four-way interactions were found for **BDNF Val66Met × 5-HTTLPR×MAOA-uVNTR × family conflicts** and for **BDNF Val66Met × 5-HTTLPR×MAOA-uVNTR × sexual abuse.** Further, the two genotype combinations that differed the most in expression levels (BDNF Val66Met Val, 5-HTTLPR LL, MAOA-uVNTR LL [girls] and L [boys] vs BDNF Val66Met Val/Met, 5-HTTLPR S/LS, MAOA-uVNTR S/SS/LS) in interaction with family conflict and sexual abuse were associated with the highest delinquency scores.
- The genetic variants previously shown to confer vulnerability for delinquency **(BDNF Val66Met Val/Met × 5-HTTLPR S × MAOA-uVNTR S**) were **associated with the lowest delinquency scores in interaction with a positive child-parent relationship**.
- Functional variants of the MAOA-uVNTR, 5-HTTLPR, and BDNF Val66Met, either alone or in interaction with each other, may be best conceptualized as **modifying sensitivity to environmental factors that confer either risk or protection for teenage delinquency**.

Comportamento innato nell'uomo?
le cose si complicano...

Emozioni universali

rabbia, disgusto, paura, gioia, tristezza, sorpresa.
Eckman 1987

divertimento, stupore, contentezza, desiderio, imbarazzo, dolore, sollievo e simpatia (espressioni facciali e vocali).
noia, confusione, interesse, orgoglio e vergogna, disprezzo, sollievo (espressioni facciali),
trionfo (espressioni vocali)

Cordaro e Keltner 2016

https://doi.apa.org/doiLanding?doi=10.1037/emo0000302

Le espressioni emotive sono una "lingua universale", ma diversi "accenti"o "dialetti" possono variare in modo sottile **attraverso le culture.**

Comportamento innato nell'uomo?
le cose si complicano...

Le espressioni emotive sono una "lingua universale", ma diversi "accenti"o "dialetti" possono variare in modo sottile **attraverso le culture.**

... **display rules**, cioè regole sociali di esibizione delle emozioni, culturalmente apprese, prescrivono il controllo e la modificazione delle espressioni emozionali a seconda della circostanza sociale: **intensificazione, attenuazione inibizione, mascheramento**.

Giapponesi vs statunitensi: risposte espressive in assenza e in presenza di un osservatore
individualismo vs collettivismo

INTENSIFICAZIONE, esagera la manifestazione;
ATTENUAZIONE, che la minimizza;
INIBIZIONE, che sopprime
MASCHERAMENTO l'espressione di una emozione che non si sente in quel momento.

Quindi…

- geni vs ambiente
- ambiente inteso come?
- cultura?
- c’è un ruolo per la fortuna?

Cosa significa essere umani … il corpo

ChapGPT4 31 march 2023	
Postura eretta: Gli esseri umani camminano in posizione eretta su due gambe, il che consente di liberare le mani per l'uso di utensili e altre attività.	Adattamenti scheletrici Basi neurali Basi sociali …Bizzarre idee di “devolution”
Cervello di grandi dimensioni: Il cervello umano è molto più grande e complesso di quello degli altri primati ed è responsabile di molte delle caratteristiche uniche associate all'essere umano.	Grande ma anche stipato Associazione e integrazione… neuroni di connessione Rapporto tra massa e cervello nella crescita (basi sociali) Plasticità e diversità umana
Pollici opponibili: Gli esseri umani hanno pollici in grado di opporsi alle altre dita, il che consente un maggior grado di destrezza e precisione nei compiti manuali.	non solo un tratto anatomico, la mano come organo di senso ed estensione della mente
Capacità di linguaggio: Il tratto vocale umano è specializzato per la parola e gli esseri umani sono gli unici animali in grado di usare il linguaggio per comunicare idee e concetti complessi	Basi anatomiche, neurali, sociali
cosa si può aggiungere? altri elementi anatomici che marcano gli esseri umani? cranio, mano, piede, bacino, cinto toracico,	

Cosa significa essere umani 2 **…la mente**

ChapGPT4 31 march 2023	
Consapevolezza di sé: La capacità di riflettere sui propri pensieri e sentimenti e di comprendere se stessi come individui.	siamo davvero unici?
Razionalità: La capacità di pensare logicamente, di risolvere i problemi e di prendere decisioni.all'essere umano.	siamo davvero unici?
Creatività: La capacità di immaginare e creare nuove idee, arte e cultura.	Congo
Comunicazione: La capacità di trasmettere informazioni e idee attraverso il linguaggio e altre forme di espressione.	Il linguaggio come attività “sociale” L’importanza della "joint attention” e della “Teoria della mente” Nei primati non umani https://www.scuolafilosofica.com/5646/i-primati-non-umani-ci-leggono-la-mente

1. Humans vs apes

2. Detecting meaningful differences

3. Biomedical implications and prospects

1. Humans vs apes

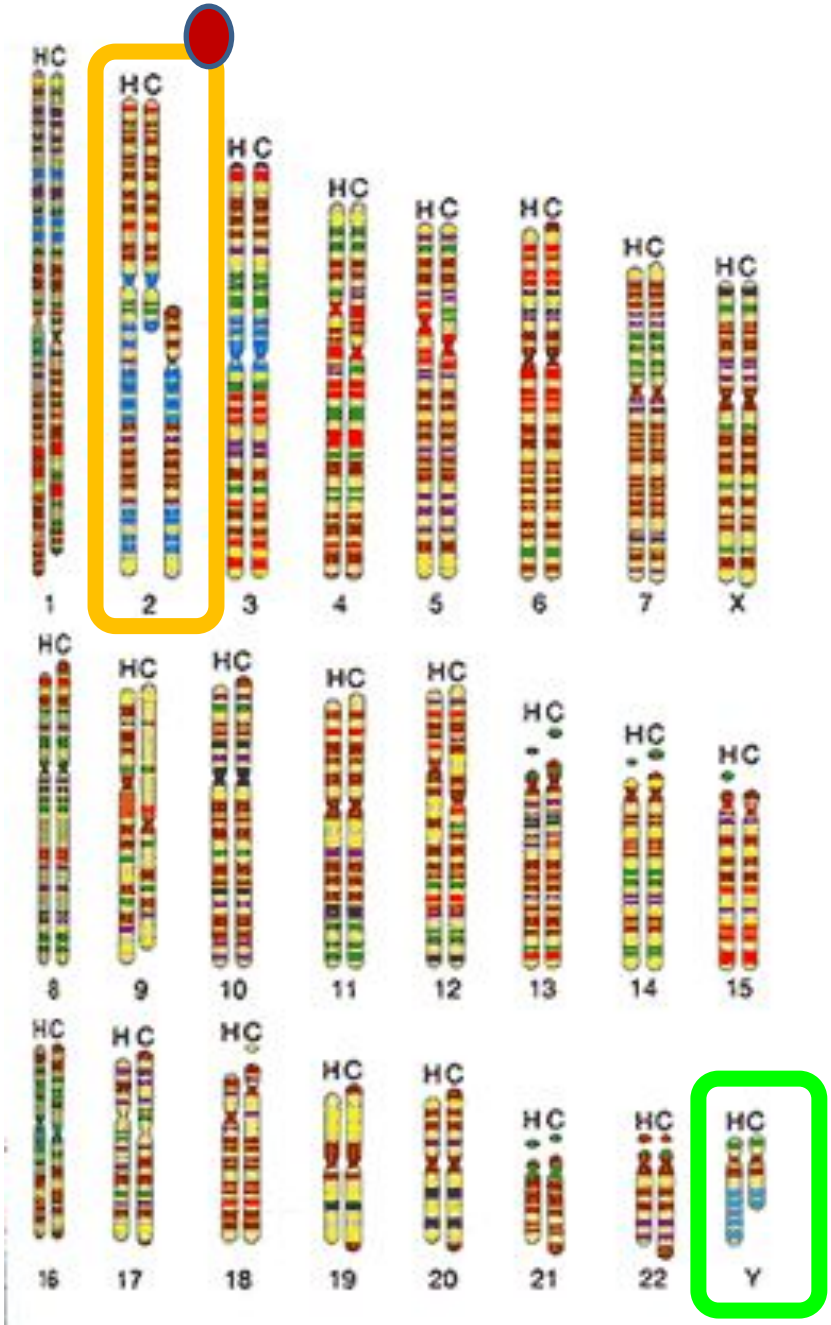
1. Structural DNA diversity (chromosomes)
2. Rough diversity estimates (DNA-DNA Hybridization)
3. DNA sequencing (autosomes, mtDNA and Y)
4. Proteins
5. Comparison of genetic diversity in apes and humans

1. Diversity of chromosomes

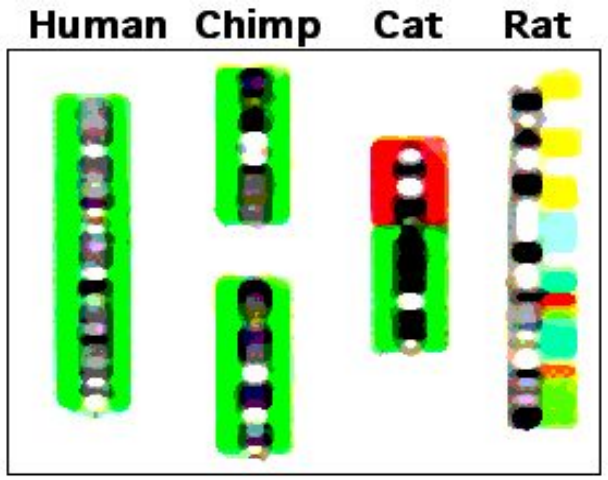
1. They change very slowly (constrained by homologue pairing)

2. Provide a global view of genome

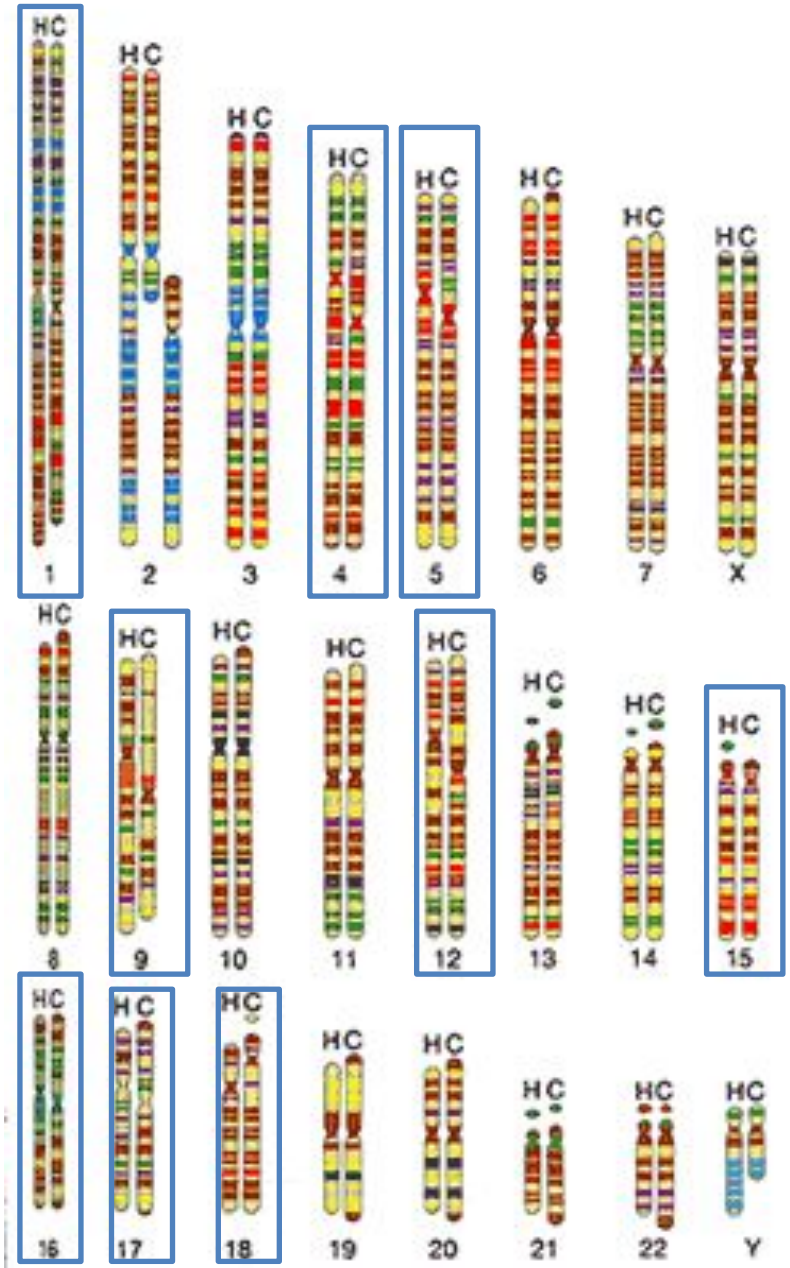
3. Ease of comparison: simple and reproducible methods



Humans have 23 pairs of chromosomes and other g**reat apes have 24 pairs** of chromosomes, but with a comparable total size (3,100 Mbp[1] (mega-basepairs) per haploid genome 6,200 Mbp total (diploid).



Parts of human chromosome 2 (green) are scattered among parts of several cat and rat chromosomes in these species that are more distantly related to humans

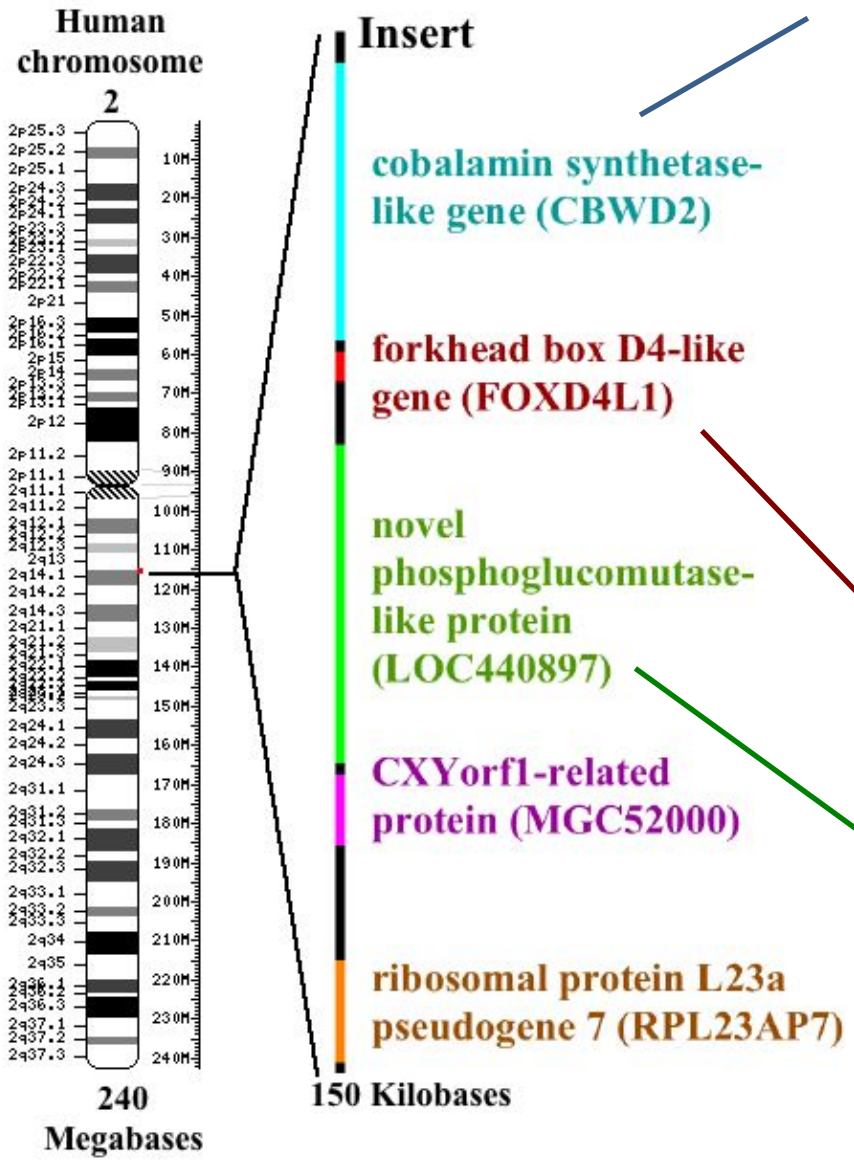


Other **major chromosomal differences**: chromosome pericentric segment inversions on human chromosomes 1, 4, 5, 9, 12, 15, 16, 17, and 18 and Y.

Differences in the chromosomal organization of pericentric, paracentric, intercalary and Y type **heterochromatin**.

The majority of chimpanzee's chromosomes contain **subterminal constitutive heterochromatin** (C-band) blocks (SCBs) that are absent in human chromosomes.

https://bmcgenomics.biomedcentral.com/articles/10.1186/s12864-020-06962-8



derived from **a bacterial enzyme that makes vitamin B_{12}.** A major change in human development is greater post-natal brain growth than is observed in other apes. Vitamin B_{12} is important for brain development, and vitamin B_{12} deficiency during brain development results in severe neurological defects in human children.

an example of an intronless gene.,may code for a transcription control protein.

The phosphoglucomutase-like gene of human chromosome 2, incomplete and may not produce a functional transcript.

Role of chromosomal changes in speciation

No “valid”hybrid between human and chimps

Most karyotipic differences: hybrid viable (+/-) but sterile

Uncertainty about chrom. rearrangements and speciation

Did human karyotype become 46 before or after human emergence?

Humans vs apes

1. Structural DNA diversity (chromosomes)
2. Rough diversity estimates (DNA-DNA Hybridization)
3. DNA sequencing (autosomes, mtDNA and Y)
4. proteins
5. Comparison of genetic diversity in apes and humans

2. Rough diversity estimates

(DNA DNA hybridization; 80s)

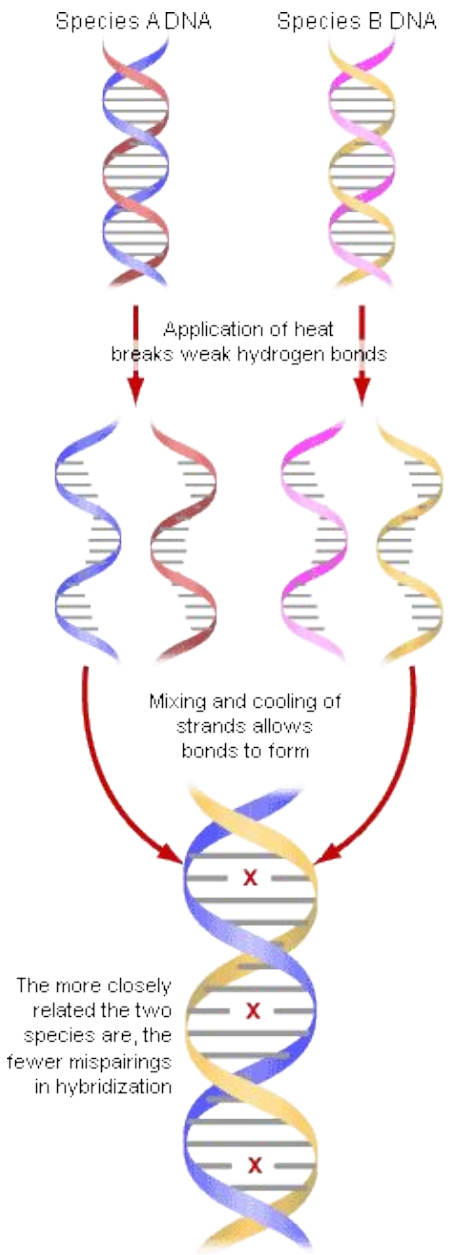
1. compare the entire single copy components of two genomes; picks up only single base substitution.

2. a sort of preliminary assessment

3. from thermal stability to genetic distances

4. still used in microbiology to help identify bacteria

DNA DNA hybridization



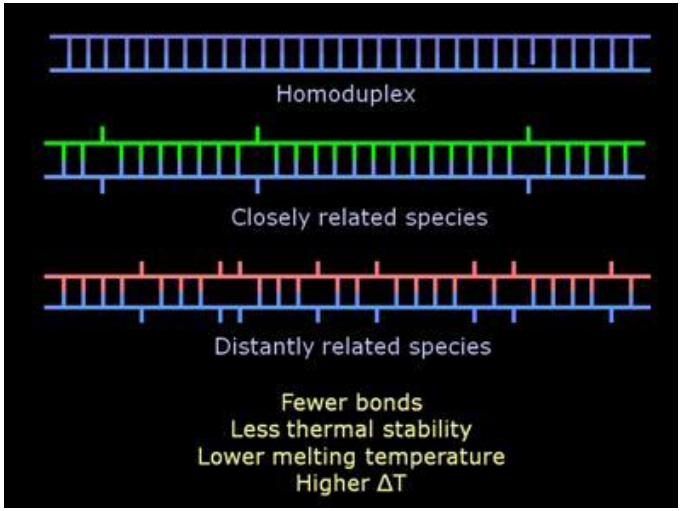
1. Extract and purify DNA from cell nuclei

2. Shear long-chain DNA strands into fragments ca. 400 - 600 bases in length.

3. Remove repeated sequences to produce "single-copy" DNA

4. "Label" the single-copy DNA with a radioactive

5. Combine the single-stranded DNA of the two species to obtain homoduplex (same species) and heteroduplexes.

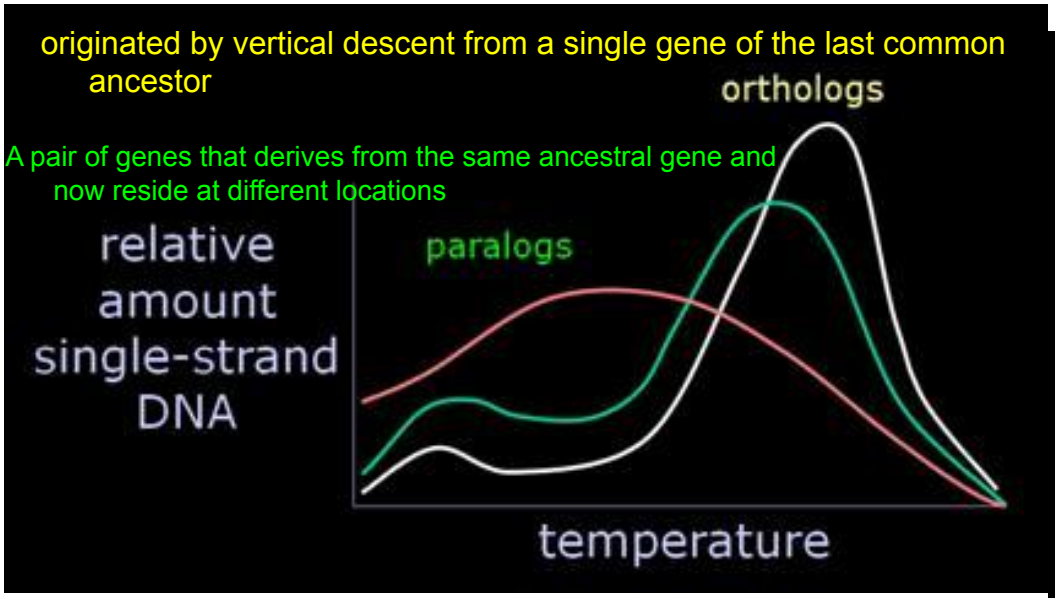


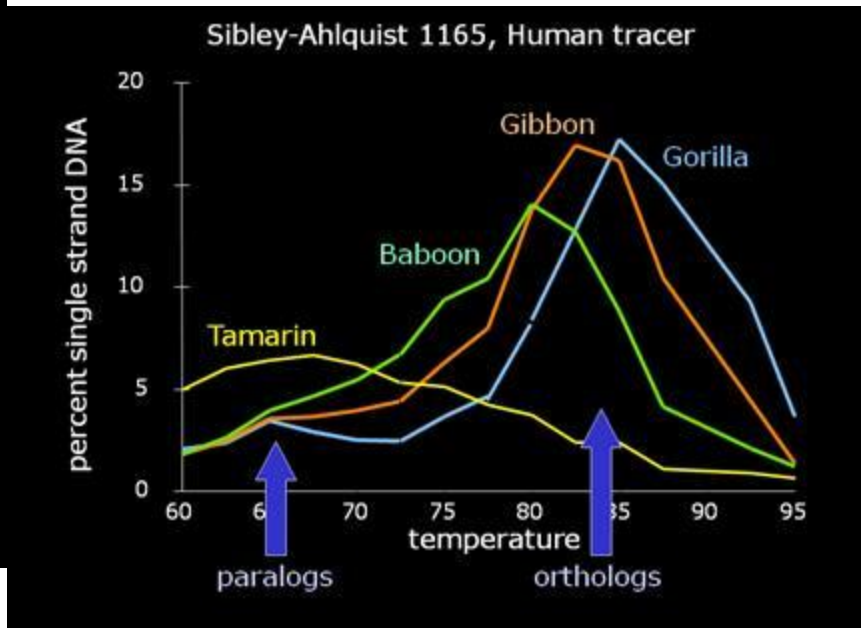
6. Place the DNA-DNA hybrids on hydroxyapatite (HAP) columns.

mostra colonna

7. Move to a heated waterbath and raise the temperature in 2.5 C increments from 55 to 95 C

8. Use the amount of radioactivity ("counts") in each sample to construct melting curves and to calculate genetic distance values.

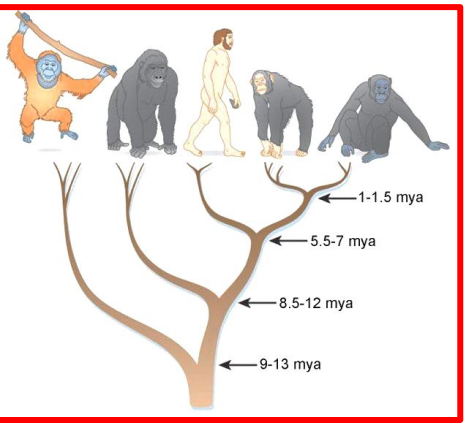




only about one-half occurred along the way to becoming human

both noncoding and coding regions

many base pair differences simply represent polymorphisms within either species



99.2% 98.5%

Gibbon Orangutan Gorilla Common chimp Pygmy chimp Human

cDNA sequence identity = 99.31% ± 0.38

pred. aminoacid identity = 99.36% ± 0.66

Humans vs apes

1. Structural DNA diversity (chromosomes)
2. Rough diversity estimates (DNA-DNA Hybridization)
3. DNA sequencing (autosomes, mtDNA and Y)
4. proteins
5. Comparison of genetic diversity in apes and humans

Autosomes

Divergence between samples of chimpanzee and human DNA sequences is 5%, counting indels

Roy J. Britten*

California Institute of Technology, 101 Dahlia Avenue, Corona del Mar, CA 92625

Contributed by Roy J. Britten, August 22, 2002

Five chimpanzee bacterial artificial chromosome (BAC) sequences (described in GenBank) have been compared with the best matching regions of the human genome sequence to assay the amount and kind of DNA divergence. The conclusion is the old saw that we share 98.5% of our DNA sequence with chimpanzee is probably in error. For this sample, a better estimate would be that 95% of the base pairs are exactly shared between chimpanzee and human DNA. In this sample of 779 kb, the divergence due to base substitution is 1.4%, and there is an additional 3.4% difference due to the presence of indels. The gaps in alignment are present in about equal amounts in the chimp and human sequences. They occur equally in repeated and nonrepeated sequences, as detected by REPEATMASKER (http://ftp.genome.washington.edu/RM/RepeatMasker.html).

what about indels?

a glance--- only 779 kb (out of 3 billions)

data confirmed comparing human and chimp draft genome

PNAS October 15, **2002** vol. 99 no. 21 13633–13635 EV

The Chimpanzee Sequencing and Analysis Consortium (2005). "Initial sequence of the chimpanzee genome and comparison with the human genome". *Nature* **437** (1 September **2005**): 69–87

- Availability of draft genomes for **chimp**, **bonobo**, **orangutan** and **gorilla**
- **2400 million bases** (of ~3160 million bases) sequenced and assembled well enough to be compared to the human genome
- **1.23% differences in alignable sequences** due to single-base substitutions (35 million single-nucleotide substitutions)
- **1.06% or less represent fixed differences** between the species (the rest being variant sites in humans or chimpanzees)
- **3%** of the complete genomes differ by **deletions, insertions and duplications…**

The Chimpanzee Sequencing and Analysis Consortium (2005). "Initial sequence of the chimpanzee genome and comparison with the human genome". *Nature* **437** (1 September 2005): 69–87

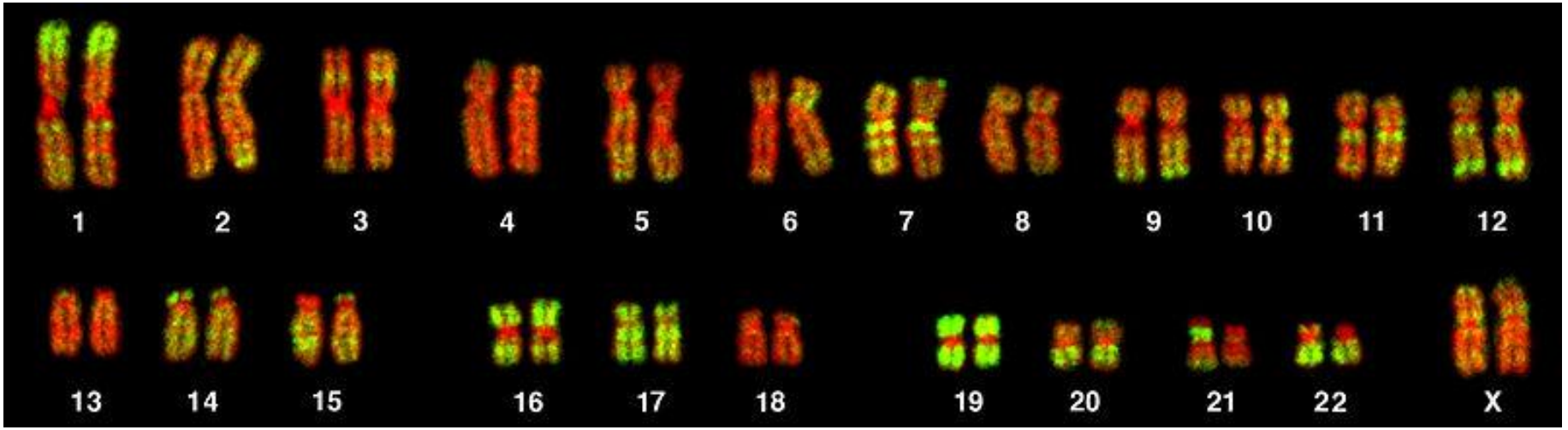
- 3% of the complete genomes differ by deletions, insertions and duplications…
- five million insertion/deletion (~15% of differences) but contributed ~1.5% of unique sequence to each genome
- Segmental duplications*: a total of 2.7% of euchromatic sequence had been differentially duplicated in one or the other lineage. The comparable variation within human populations is 0.5 percent
- single-base-pair substitutions account for about half as much genetic change as does gene duplication

*a duplication of a DNA segment equal to or longer than 1 kb with a high level of sequence identity (> 90%) between copies transposed to new locations

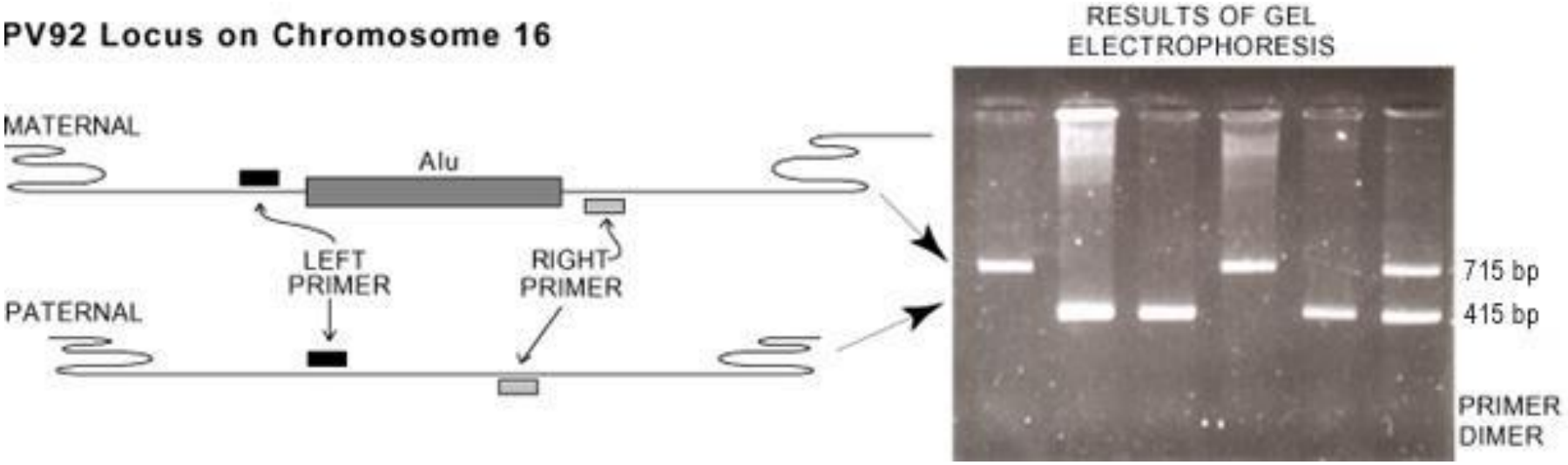
Percentage sequence divergence between humans and other hominids*

	Human-Chimp	Human-Gorilla	Human-Orangutan
Alu elements	2	-	-
Pseudogenes (autosomal)	1.64 ± 0.10	1.87 ± 0.11	-
Pseudogenes (Chr. X)	1.47 ± 0.17	-	-
Noncoding (autosomal)	1.24 ± 0.07	1.62 ± 0.08	3.08 ± 0.11
Genes (K_s)	1.11	1.48	2.98
Introns	0.93 ± 0.08	1.23 ± 0.09	-
Subtotal for X chromosome	1.16 ± 0.07	1.47 ± 0.08	-
Genes (K_a)	0.8	0.93	1.96

*substitutional differences only



Karyotype from a female human lymphocyte (46, XX). Chromosomes were hybridized with a probe for Alu sequences (green) and counterstained with TOPRO-3 (red). Alu sequences were used as a marker for chromosomes and chromosome bands rich in genes



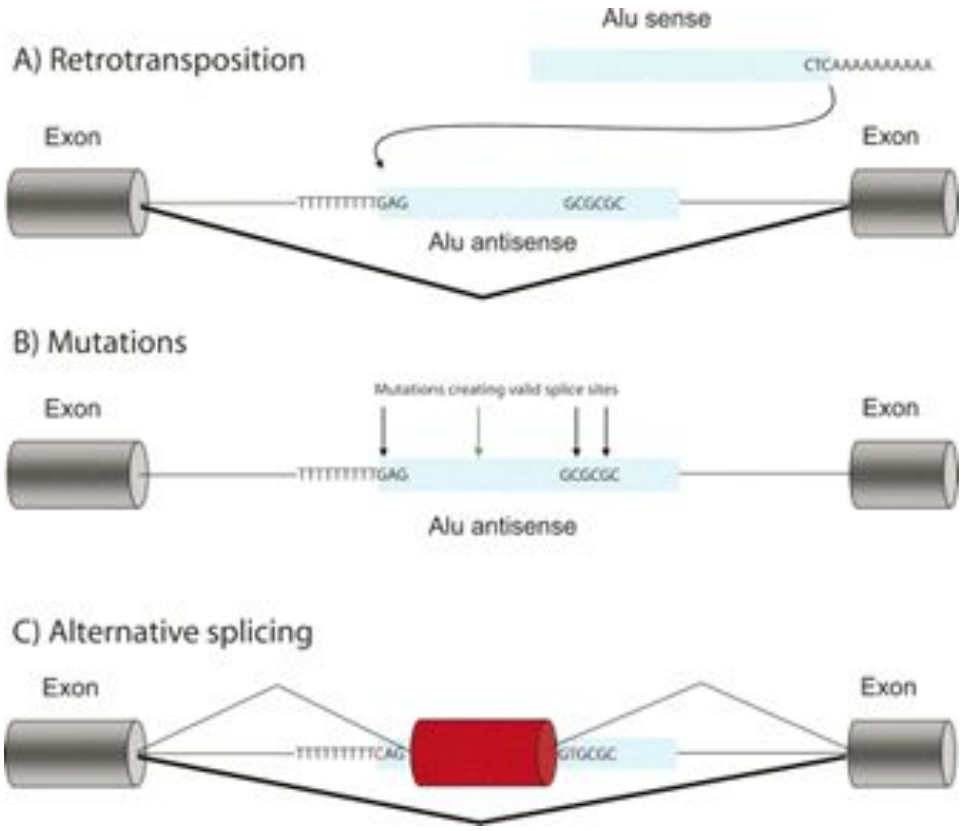
2. Inserzioni di elementi trasponibili (Alu)

- SINEs: retrotrasposoni Alu (dall'enzima di restr. di **A**rthrobacter **lu**teus)
- elementi di 290 bp
- presenti solo nei Primati (a partire da 65 MYA)
- elementi ripetuti e dispersi più abbondanti: 11% del genoma umano
- < 0.5% sono polimorfici
- stato ancestrale (assenza di inserzione) e origine unica
- 5530 inserzioni Alu specie specifiche nell'uomo
- non solo "Junk DNA": stimolazione della traduzione proteica, in particolare in circostanze cellulari stressanti e formazione di nuovi geni o combinazioni di geni aggiunta di nuove funzionalità a geni già esistenti (esonizzazione); responsabili di circa il 62% di tutti i nuovi esoni in *Homo sapiens* (effetti moderati dal splicing alternativo)

(A) *Alu* is inserted into introns of primate genes by retrotransposition.

(B) During the course of evolution, mutations within pseudo-splice sites in the intronic *Alu* activate these sites (black arrows). Mutations changing splicing regulatory elements are also possible (green arrow).

(C) Following these mutations, part of the *Alu* sequence is recognized as a new exon (\"exonized\"), and spliced into the transcript.



I riarrangiamenti genomici indotti dall'inserimento di Alu sono responsabili di circa lo **0,1%** delle **malattie umane** e le delezioni genomiche da “Alu recombination-mediated deletions (ARMD) sono sono responsabili di circa lo **0,3% delle malattie genetiche umane**.

http://dx.doi.org/10.5808/GI.2016.14.3.70

Table 1. A list of *Alu*-mediated genetic disorder in recent studies

Gene	Position	Subfamily	Mechanism	Disease	Reference
ACE	Chr 17	*AluY*a5	Insertion	Alzheimer's disease	[39]
ALMS1	Chr 2	*AluY*a5	Insertion	Alström syndrome	[40]
BMPR2	Chr 2	*AluY* *AluS*	ARMD_NAHR NHEJ	Pulmonary arterial hypertension	[41]
CDSN	Chr 6	*AluS*	ARMD_NHEJ	Peeling skin disease	[42]
COL4A5	Chr X	*AluY*	Insertion	Alport syndrome	[43]
FA	Chr X	*AluY*	ARMD_NAHR	Fanconi anemia	[44]
GBA1	Chr 1	*AluS*x	ARMD_NAHR	Gaucher disease	[45]
GGA	Chr 17	*AluS*	ARMD_NAHR	Pomp disease	[46]
GLA	Chr X	*Alu*	Insertion mediated deletion	Fabry disease	[47]
MUTYH	Chr 1	*AluY*b8	Insertion	Breast cancer/gastric cancer	[48]
PMP22	Chr 17	*AluY*/*AluS*c	ARMD_NAHR	Charcot-Marie-Tooth disease	[49]
SOX10	Chr 22	*AluS*	FoSTes/MMBIR	Waardenburg syndrome type 4	[50]
SPAST	Chr 2 Chr 2	*AluY*/*AluS* *AluY*	FoSTes/MMBIR	Hereditary spastic paraplegia	[51]
SPG11	Chr 15 Chr 15	*AluY*/*AluS* *AluS*	ARMD_NAHR	Spastic paraplegias	[52]
STK11	Chr 19	*AluY*	ARMD_NAHR	Peutz-Jeghers syndrome	[53]

ARMD, *Alu* recombination-mediated deletions; NAHR, nonallelic homologous recombination; NHEJ, nonhomologous end-joining mediated deletion; FoSTeS/MMBIR, fork stalling and template switching/microhomology-mediated break-induced replication.

TABLE 7.1:
PERCENTAGE SEQUENCE DIVERGENCES (JUKES–CANTOR DISTANCES) BETWEEN HOMINOIDS

Locus	H-C	H-G	C-G	H-O	C-O	G-O
Noncoding (Chr Y)	1.68 ± 0.19	2.33 ± 0.2	2.78 ± 0.25	5.63 ± 0.35	6.02 ± 0.37	6.17 ± 0.37
Pseudogenes (autosomal)	1.64 ± 0.10	1.87 ± 0.11	2.14 ± 0.11	–	–	–
Pseudogenes (Chr X)	1.47 ± 0.17	–	–	–	–	–
Noncoding (autosomal)	1.24 ± 0.07	1.62 ± 0.08	1.63 ± 0.08	3.08 ± 0.11	3.12 ± 0.11	3.09 ± 0.11
Genes (dS)	1.11	1.48	1.64	2.98	3.05	2.95
Introns	0.93 ± 0.08	1.23 ± 0.09	1.21 ± 0.09	–	–	–
Noncoding (Chr X)	0.92 ± 0.10	1.42 ± 0.12	1.41 ± 0.12	3.00 ± 0.18	2.99 ± 0.17	2.96 ± 0.17
Genes (dN)	0.80	0.93	0.90	1.96	1.93	1.77
Genomewide	1.37	1.75	1.81	3.40	3.44	3.50

H, human; C, chimpanzee; G, gorilla; O, orangutan. Data from Chen FC & LI WH (2001) *Am. J. Hum. Genet.* 68, 444; Scally A et al. (2012) *Nature* 483, 169; and references therein.

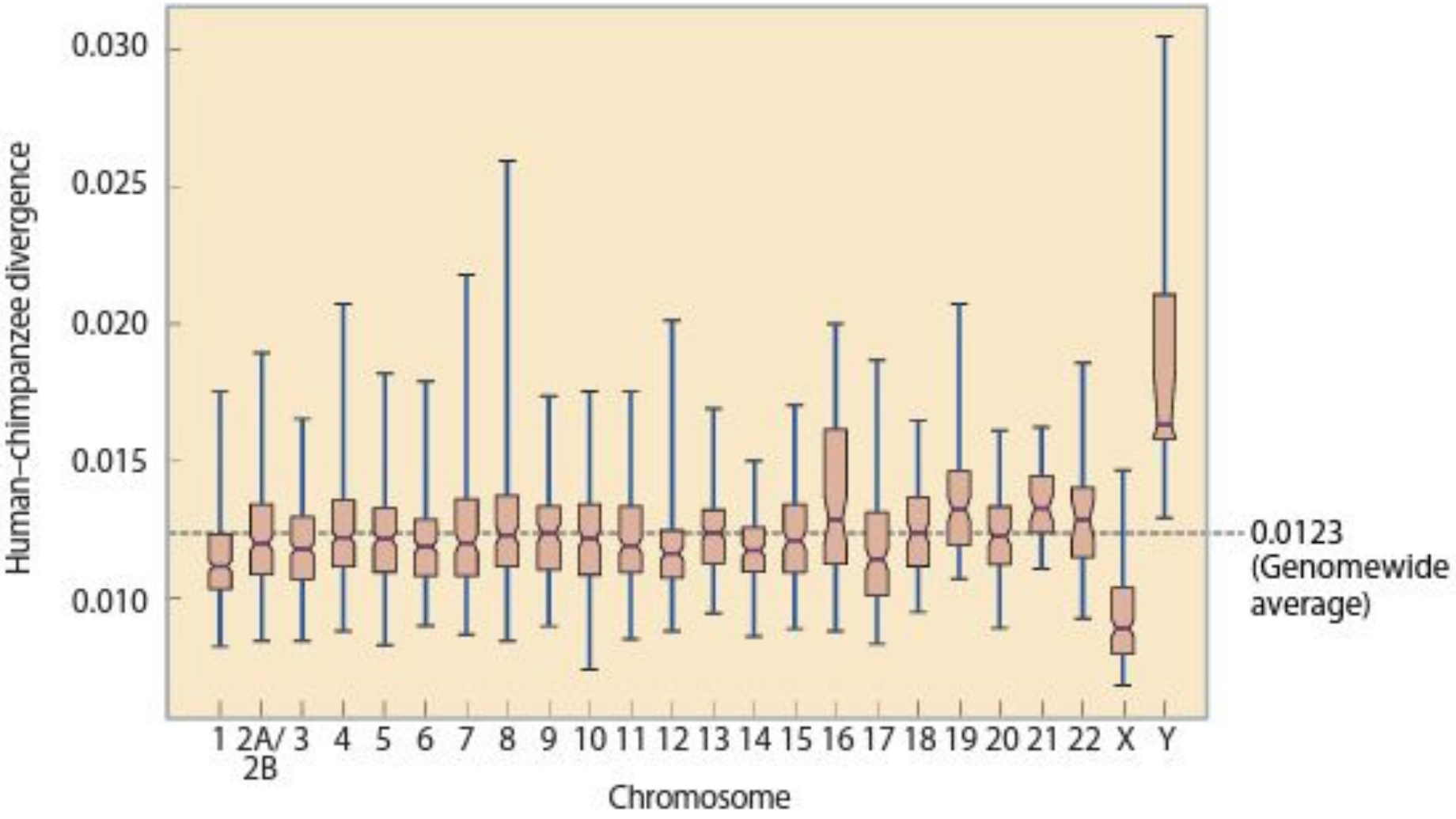
The Jukes–Cantor method corrects for multiple substitutions of the same site but not for different mutational probabilities that depend on the type (A, G, T, or C) and position of the nucleotide.

53 functional human genes that are either completely or partially deleted in the chimpanzee. In total, the **amount of lineage-specific gains or losses of functional sequence** in humans, gorillas, and chimpanzees is **3–7 Mb per species**. The most common targets of loss and gain appear to be **olfactory receptor genes** and genes related to **immunity or male fertility**.

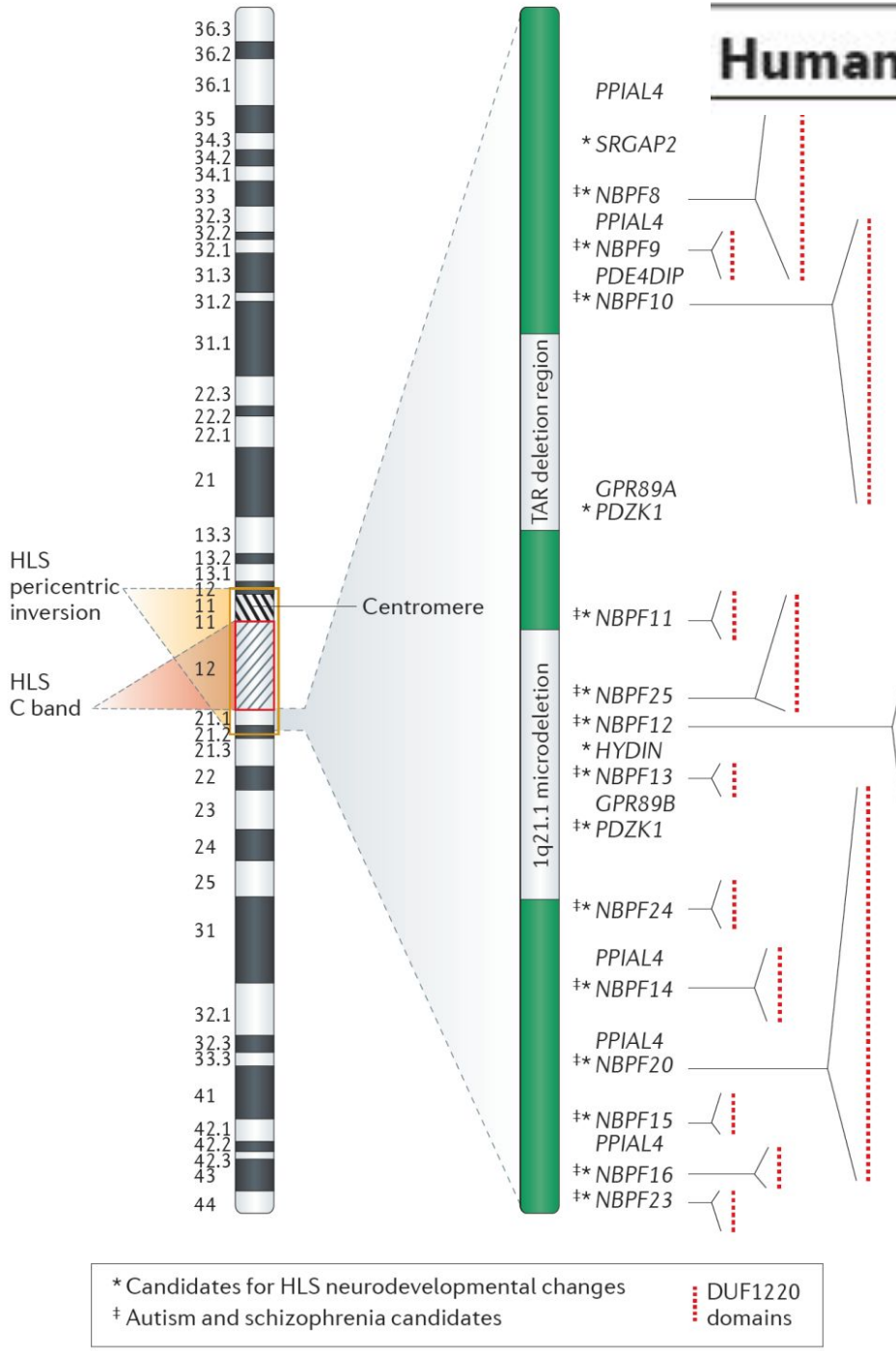
600 genes under strong positive selection in the human and chimp lineages; many of these genes are involved in immune system defense against microbial disease (example: granulysin is protective against *Mycobacterium tuberculosis*) or are targeted receptors of pathogenic microorganisms (example: Glycophorin C and *Plasmodium falciparum*).

By comparing human and chimp genes to the genes of other mammals, it has been found that **genes coding for transcription factors**, such as forkhead-box P2 (FOXP2), have often evolved faster in the human relative to chimp; relatively small changes in these genes may account for the morphological differences between humans and chimps.

A set of **348 transcription factor genes code for proteins** with an average of about 50 percent more amino acid changes in the human lineage than in the chimp lineage.


Human–chimpanzee divergence
0.030
0.025
0.020
0.015
0.010
0.0123
(Genomewide
average)
1
2A/
2B
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
X
Y
Chromosome

Human-lineage-specific changes at 1q21.1



Large citogenetically visible changes are frequently adjacent to regions greatly enriched for evolutionarily recent genes duplications and that often function as **gene nurseries**

1q21.1 region close to the HLS chromosome 1 pericentric inversion, with numerous **HLS copy number expansions** (green band) including DUF1220 protein (Domain of unknown function) domains and other genes candidate to explain **neurodevelopmental changes and cognitive disorders**

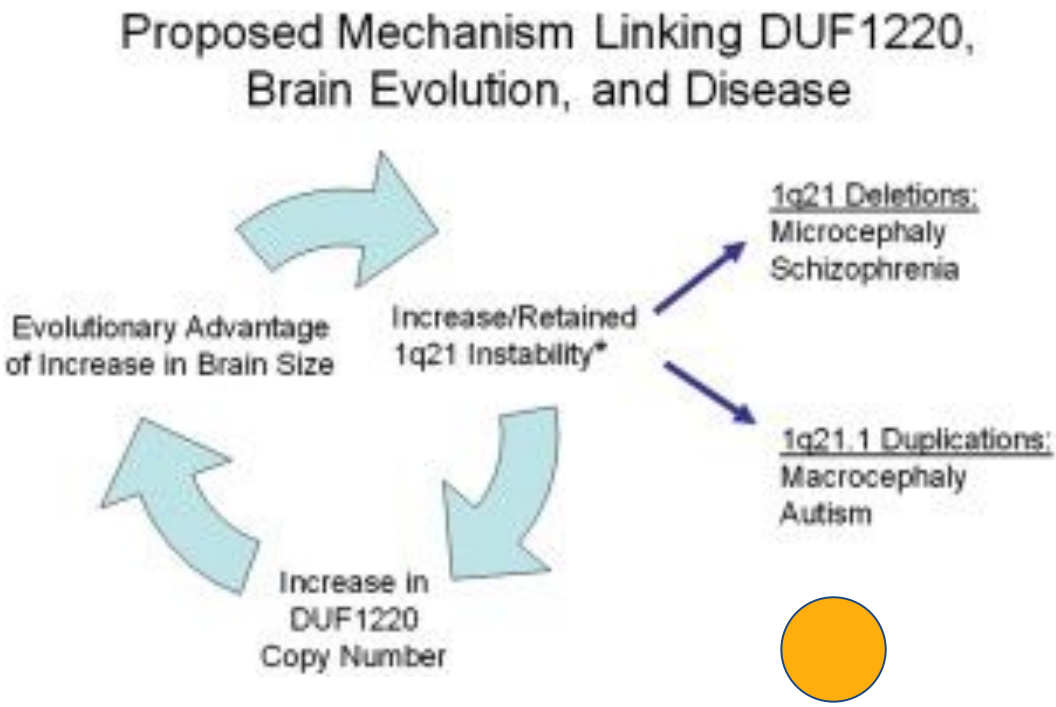
The **Olduvai domain**, known until 2018 as **DUF1220** (domain of unknown function 1220)

In 2018, it was named by its discoverers after Olduvai Gorge in Tanzania, one of the most important archaeological sites for early humans, to reflect data indicating its role in human brain size and evolution

Olduvai domains form the core of the **neuroblastoma breaking point family (***NBPF*) genes, which first appeared in placental mammals and experienced a rapid expansion in monkeys (simians) through duplication to reach over 20 genes in humans. In humans, Olduvai domains are repeated often dozens of times within these genes.

The most striking example of this process has been reported for the DUF1220 protein domain, which shows the largest HLS copy number increase of any protein-coding region in the human genome[8,41,42]. DUF1220 domains are encoded within genes of the neuroblastoma breakpoint family (NBPF)[43,44], and although there are several HLS NBPF genes found in the human genome, the great majority of HLS copies of DUF1220 have arisen by intragenic domain hyper-amplification[42]. With 272 copies, humans have more than twice the copy number of chimpanzees (which have 126 copies, the next highest number), whereas mice and rats have only one copy. It is estimated that, on average, 28 additional copies of DUF1220 domains have been added specifically to the human genome every million years since the human and *Pan* lineages diverged[42]. Recent correlative data from evolutionary studies and studies of brain size in normal and pathological populations (such as studies of individuals with microcephaly and macrocephaly) support the view that DUF1220 copy number is a general effector of brain size and may be largely responsible for the dramatic evolutionary expansion in brain size that occurred in the human lineage[45,46].

DUF1220 domains show t**he largesthuman-lineage-specific increase in copy number of any protein-coding region in the human genome** and map primarily to 1q21, where deletions and reciprocal duplications have been associated with **microcephaly and macro-cephaly, respectively.**



it appears to function to increase the number of **neural stem cells** by **prolonging the developmental period of neurons**. When Olduvai copy number is reduced, neurons appear to mature faster and divide less. Conversely, when Olduvai copy number is increased, neurons appear to mature for longer and divide in higher numbers.[6]

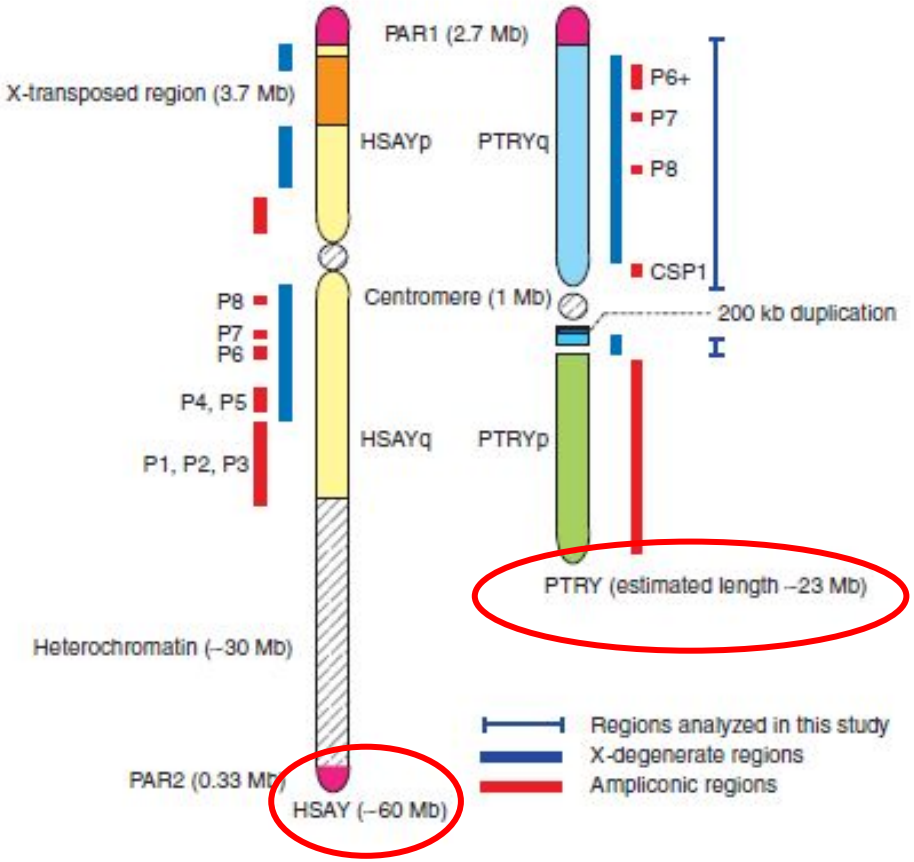
DUF1220 copy number is associated with schizophrenia risk and severity: implications for understanding autism and schizophrenia as related diseases

https://www.nature.com/articles/tp2015192

Y chromosome

Comparative analysis of chimpanzee and human Y chromosomes unveils complex evolutionary pathway

NATURE GENETICS doi:10.1038/ng1729 2006



Accelerated evolutionary rate
Greater sequence divergence between the human Y chromosome (HSAY) and PTRY (1.78%) than between their respective whole genomes (1.23%)

Relaxation of selective constraint and/or positive selection
Each of the 19 PTRY protein-coding genes analyzed had at least one nonsynonymous substitution, and 11 genes had higher nonsynonymous substitution rates than synonymous ones,

Lineage-specific changes,
Deletion of a 200-kb fragment from the pericentromeric region of HSAY, expansion of young Alu families in HSAY and accumulation of young L1 elements and long terminal repeat retrotransposons in PTRY.

Y chromosome

Dynamic evolution of great ape Y chromosomes

Monika Cechova[a,1,2], Rahulsimham Vegesna[a,b,2,3], Marta Tomaszkiewicz[a], Robert S. Harris[a], Di Chen[a], Samarth Rangavittal[a,b], Paul Medvedev[c,d,4], and Kateryna D. Makova[a,4]

https://www.pnas.org/doi/epdf/10.1073/pnas.2001749117

October 5, 2020

The **Y chromosomes of great apes** represent a particular **puzzle**: their gene content is **more similar between human and gorilla** than between human and chimpanzee, even though human and chimpanzee share a more recent common ancestor.

We found that **the genus Pan**, which includes chimpanzee and bonobo, **experienced accelerated substitution rates**. Pan also exhibited elevated gene death rates. These observations are consistent with **high levels of sperm competition in Pan**.

Selection to produce more sperm can also select for the **evolution of larger testes** in chimp than in gorillas

Furthermore, we inferred that the **great ape common ancestor already possessed multicopy sequences homologous to most human and chimpanzee palindromes**. Nonetheless, each species also acquired distinct ampliconic sequences.

mtDNA

	Homo sapiens	*Pan troglodytes t.*
length	16,569	16 556 bp
coding genes	13	13
tRNA genes	22	22
rRNA genes	2	2
transition/transversions (control region)	15	15

Diff. Human-chimp= 1462 bp (out of 16500) = 8,8%

why more divergence human chimps for unilinear markers?