

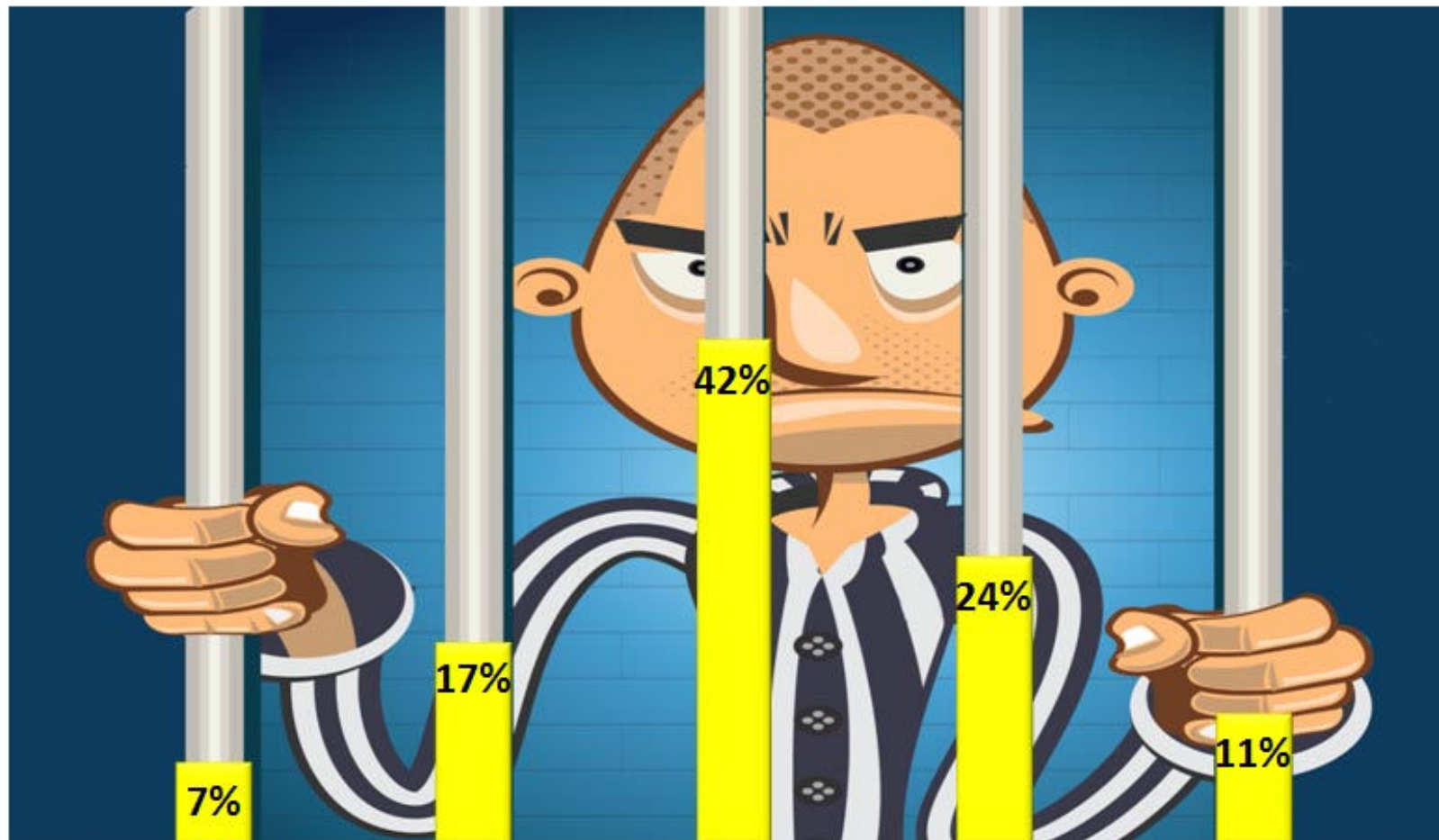
Geni, ambiente e comportamento (anti)sociale



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AGGRESSIVE / VIOLENT BEHAVIOR: *NATURE OR NURTURE?*

NO CLEAR-CUT OPINION WHETHER BORN THAT WAY OR LEARNED/TAUGHT



Completely
person's nature
(born this way)

Mostly
nature /
environment
plays small role

Nature &
environment
equal factors

Mostly
environment /
nature plays
small role

Completely
person's
environment
(learned/taught)

Prove a sostegno della ereditabilità del comportamento vengono dagli studi sui gemelli e sui soggetti adottati



STESSO AMBIENTE
DIVERSO GENOTIPO

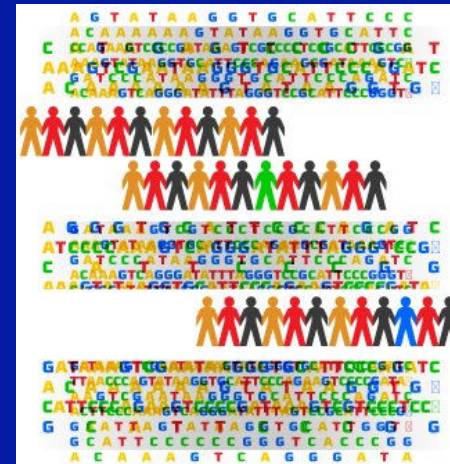
STESSO GENOTIPO
DIVERSO AMBIENTE



Dopo la decodifica del Genoma Umano



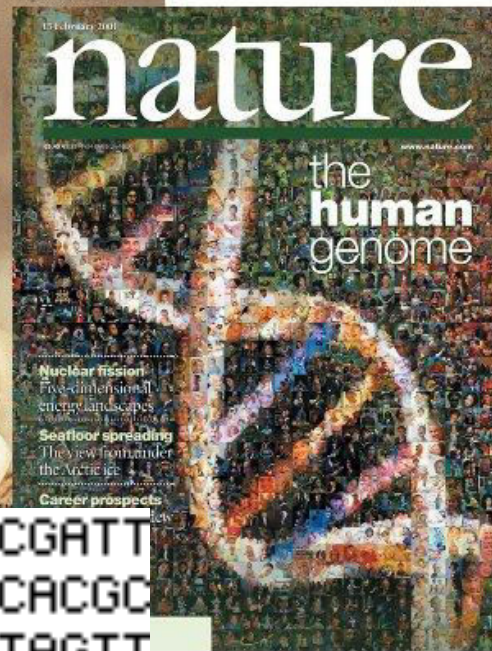
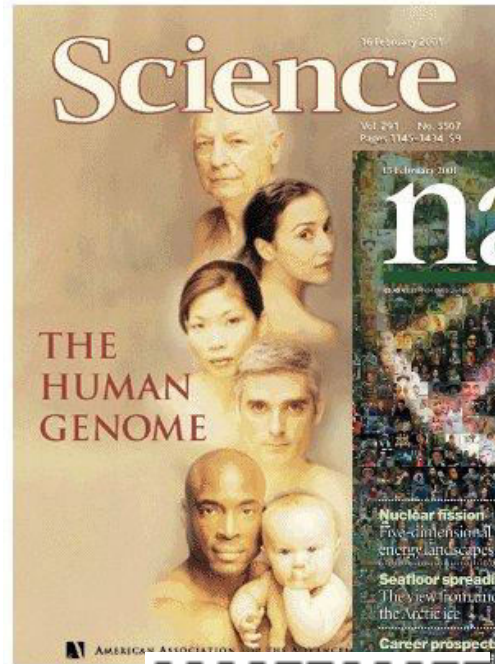
Alcune varianti genetiche



Sono state associate al comportamento antisociale

Progetto Genoma Umano

1990



stabilire con precisione
come sono disposte una
dopo l'altra le quattro basi
azotate del DNA

ACGATTTCGATT
CTCTAGCACGC
GCTAGTTAGTT
TACTACCTACG
ACTGAGATCGA

2003

VARIABILITA' DEL DNA UMANO

- Ogni essere umano ha una propria sequenza genomica individuale
- I genomi di due individui presi a caso contengono almeno 3 milioni di differenze (l'uno per mille)
- Solo gemelli identici possiedono lo stesso corredo di DNA

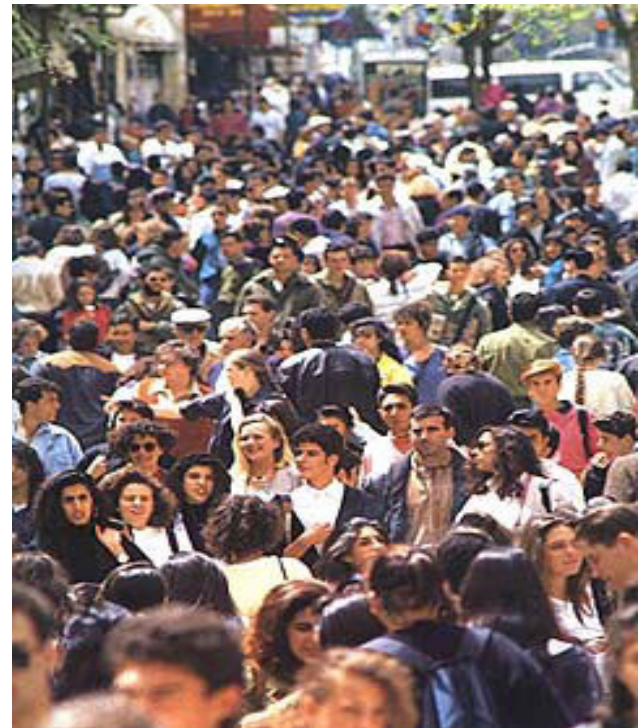


Non siamo tutti uguali...



Non esiste un' unica sequenza del genoma umano, ma circa 3 milioni dei 3 miliardi di nucleotidi che compongono il genoma di un individuo variano rispetto al genoma di un altro individuo e costituiscono dei

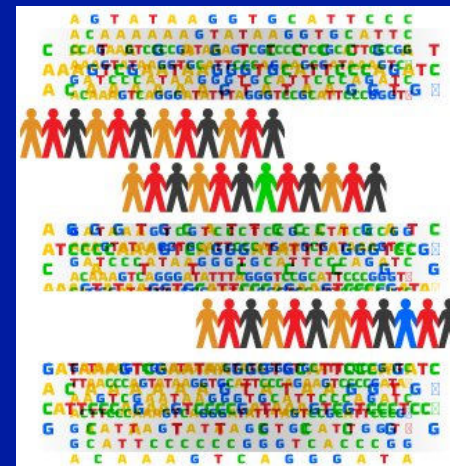
POLIMORFISMI GENETICI



Dopo la decodifica del Genoma Umano

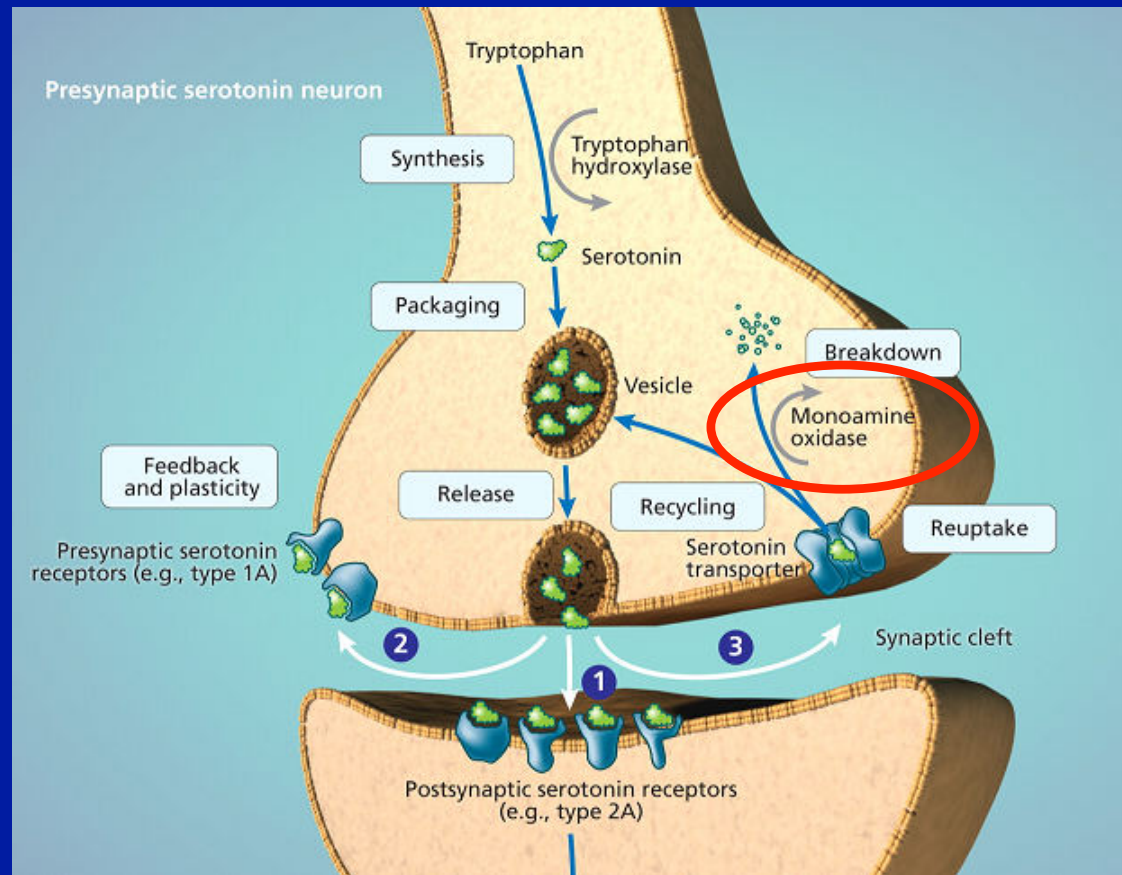


Alcune varianti genetiche



Sono state associate al comportamento antisociale

MAOA (monoamine oxidase A) Il gene “guerriero”



(aan het Rot et al., 2009)

X-Linked Borderline Mental Retardation with Prominent Behavioral Disturbance: Phenotype, Genetic Localization, and Evidence for Disturbed Monoamine Metabolism

H. G. Brunner,* M. R. Nelen,* P. van Zandvoort,* N. G. G. Abeling,† A. H. van Gennip,† E. C. Wolters,‡ M. A. Kuiper,‡ H. H. Ropers,* and B. A. van Oost*

*Department of Human Genetics, Nijmegen; †Departments of Pediatrics and Clinical Chemistry, Academic Medical Center, University of Amsterdam; and ‡Department of Neurology, Free University, Amsterdam

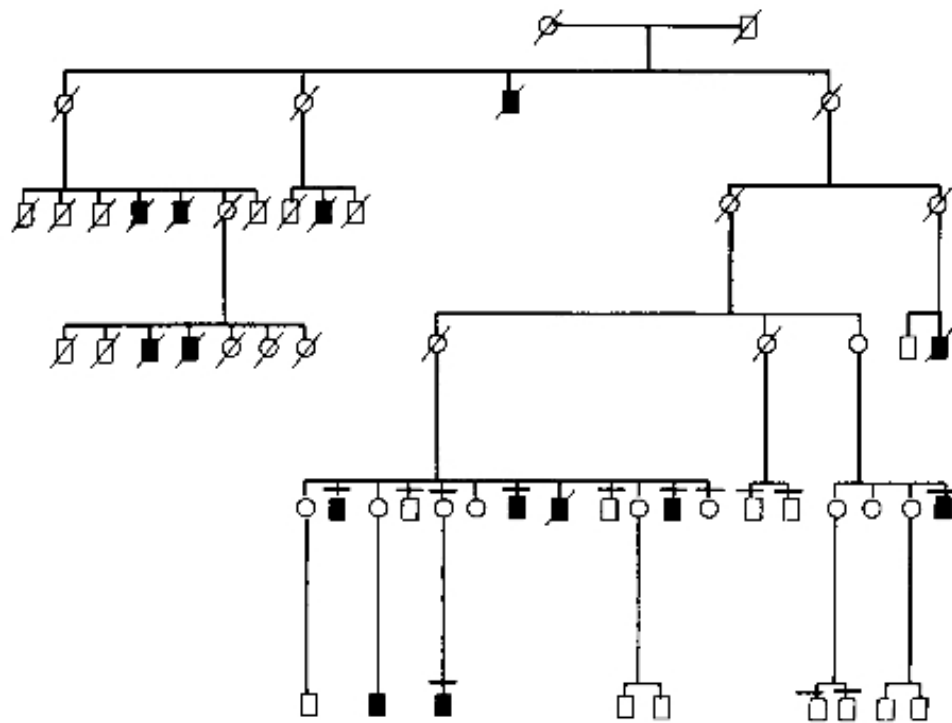
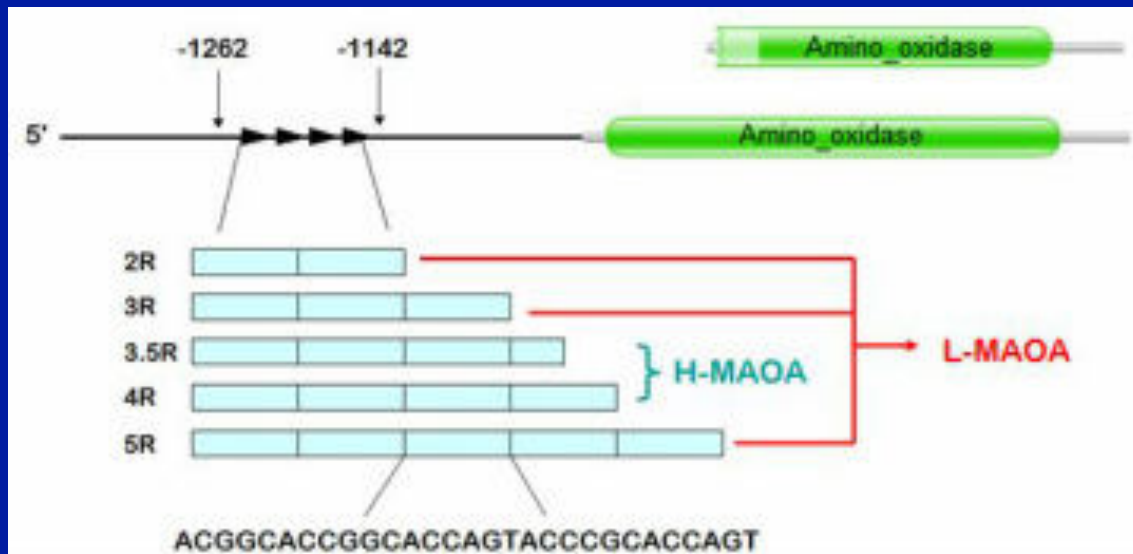
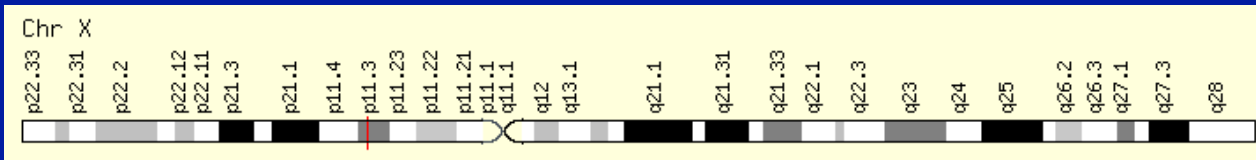


Figure 1 Pedigree of family with borderline mental retardation with prominent behavioral disturbance. Only individuals known to be at genetic risk are shown. Blackened squares denote affected males. Clinically evaluated individuals are indicated by a horizontal line above the symbol.

MAOA uVNTR

Cromosoma Xp11.3



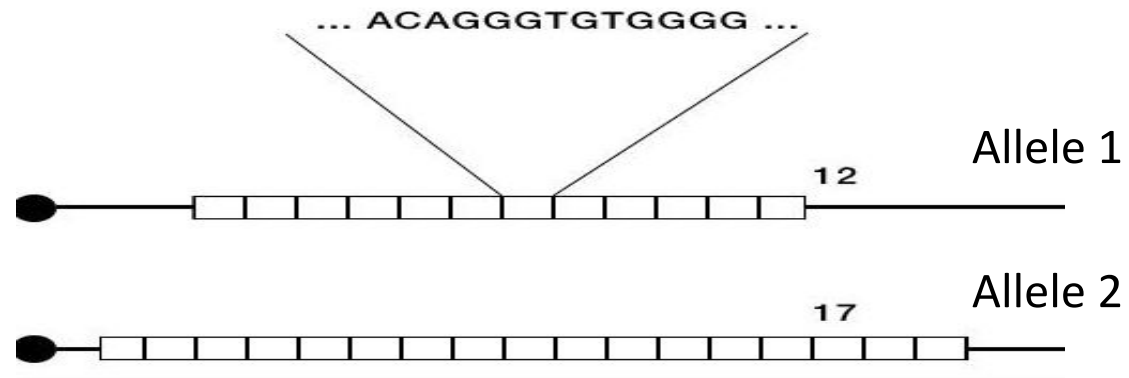
ATTIVITA':

H (high) → 3.5 o 4 ripetizioni

L (low) → 2, 3 o 5 ripetizioni

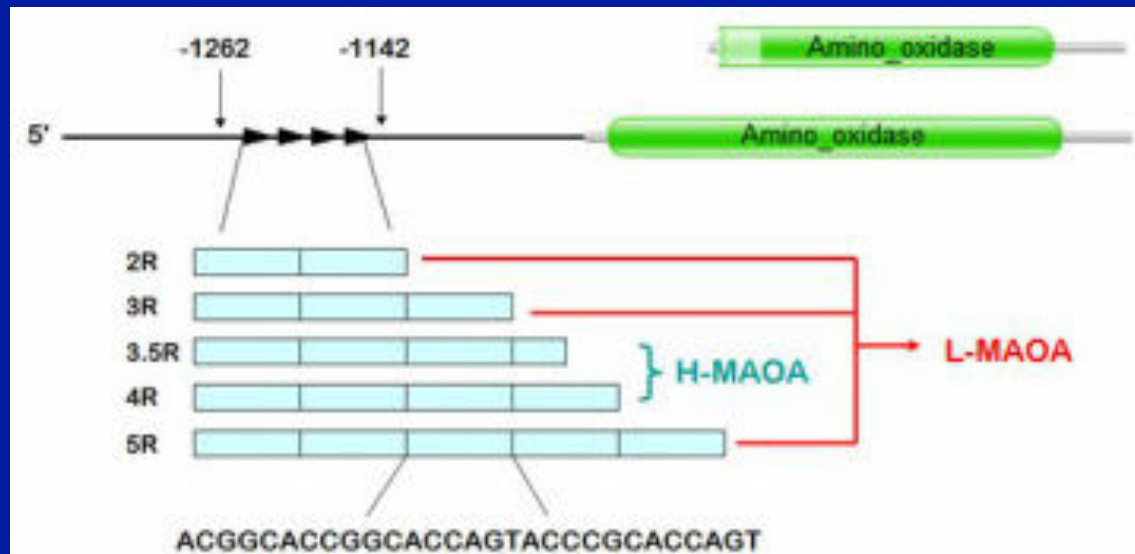
(Sabol et al., 1998)

VNTR (Variable Number Tandem): tratti di sequenza lunghi 15-40 nucleotidi ripetuti in tandem un numero variabile di volte.



MAOA uVNTR

Cromosoma Xp11.3



ATTIVITA':

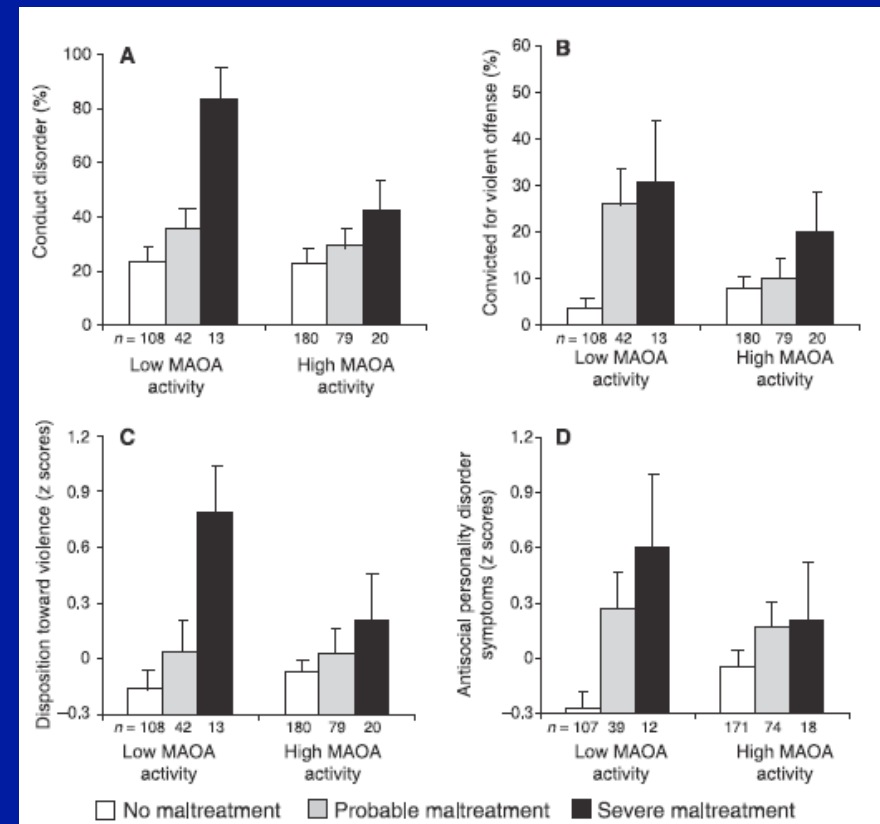
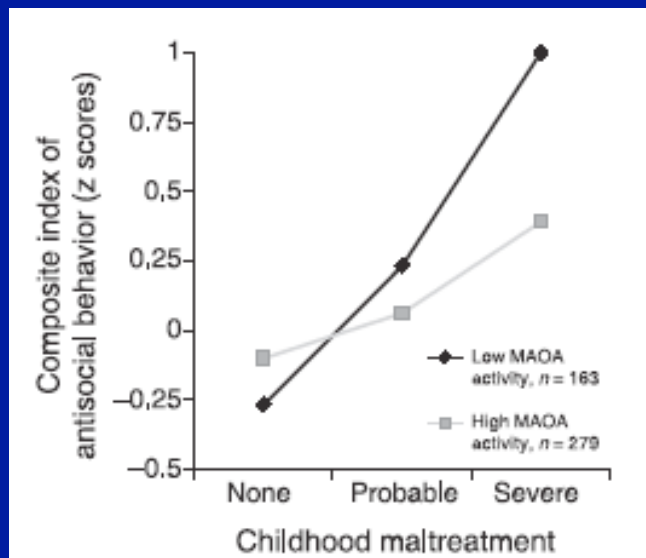
H (high) → 3.5 o 4 ripetizioni

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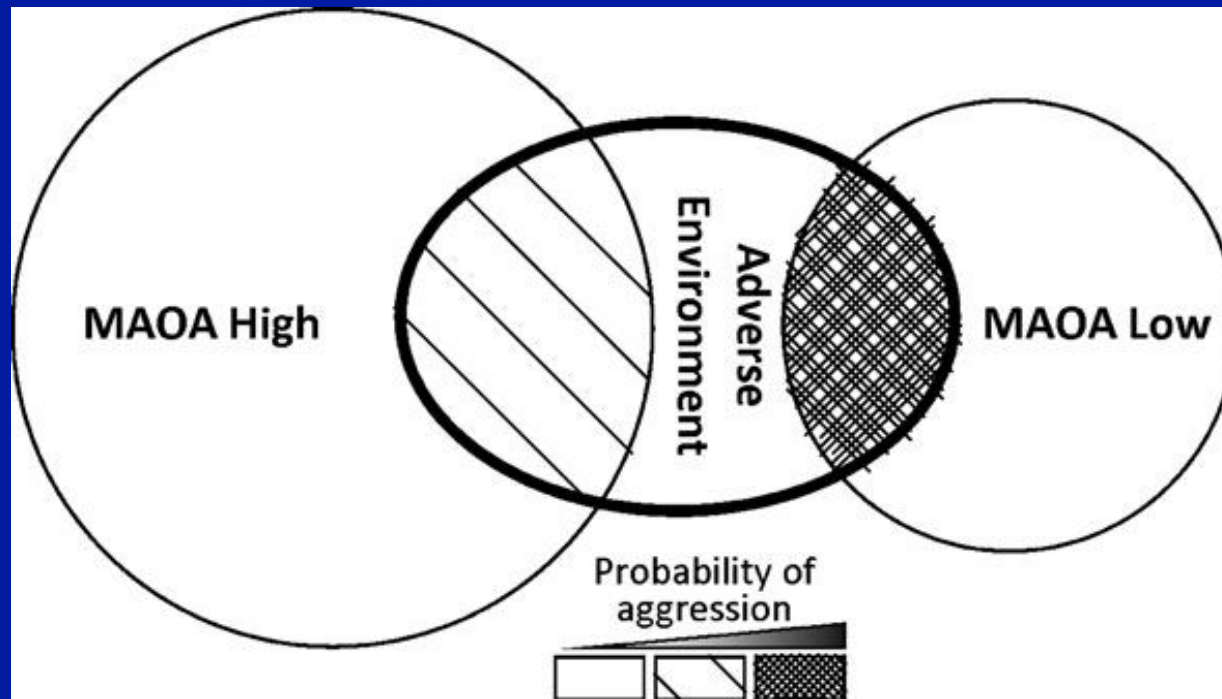
(Sabol et al., 1998)

Role of Genotype in the Cycle of Violence in Maltreated Children

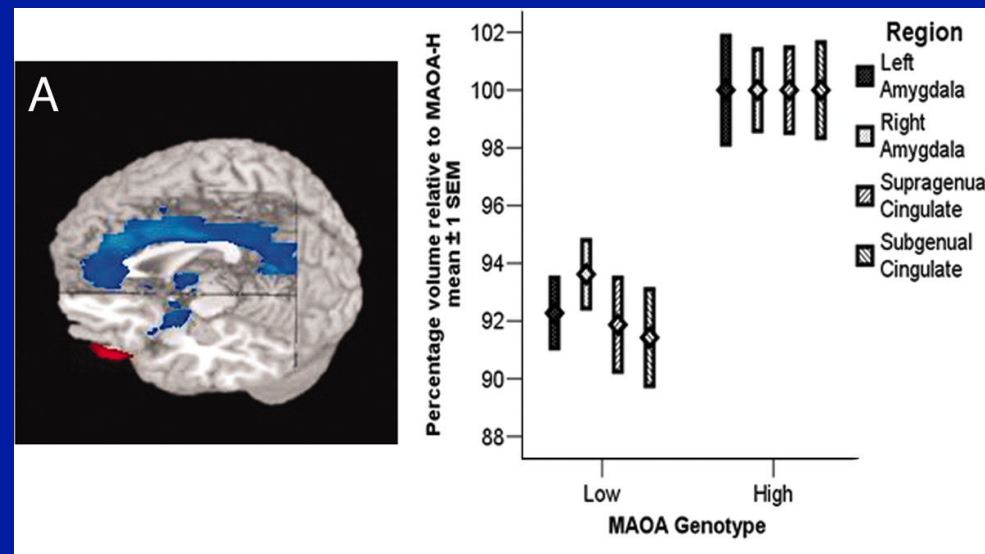
Avshalom Caspi,^{1,2} Joseph McClay,¹ Terrie E. Moffitt,^{1,2*}
Jonathan Mill,¹ Judy Martin,³ Ian W. Craig,¹ Alan Taylor,¹
Richie Poulton³



Interazione gene-ambiente

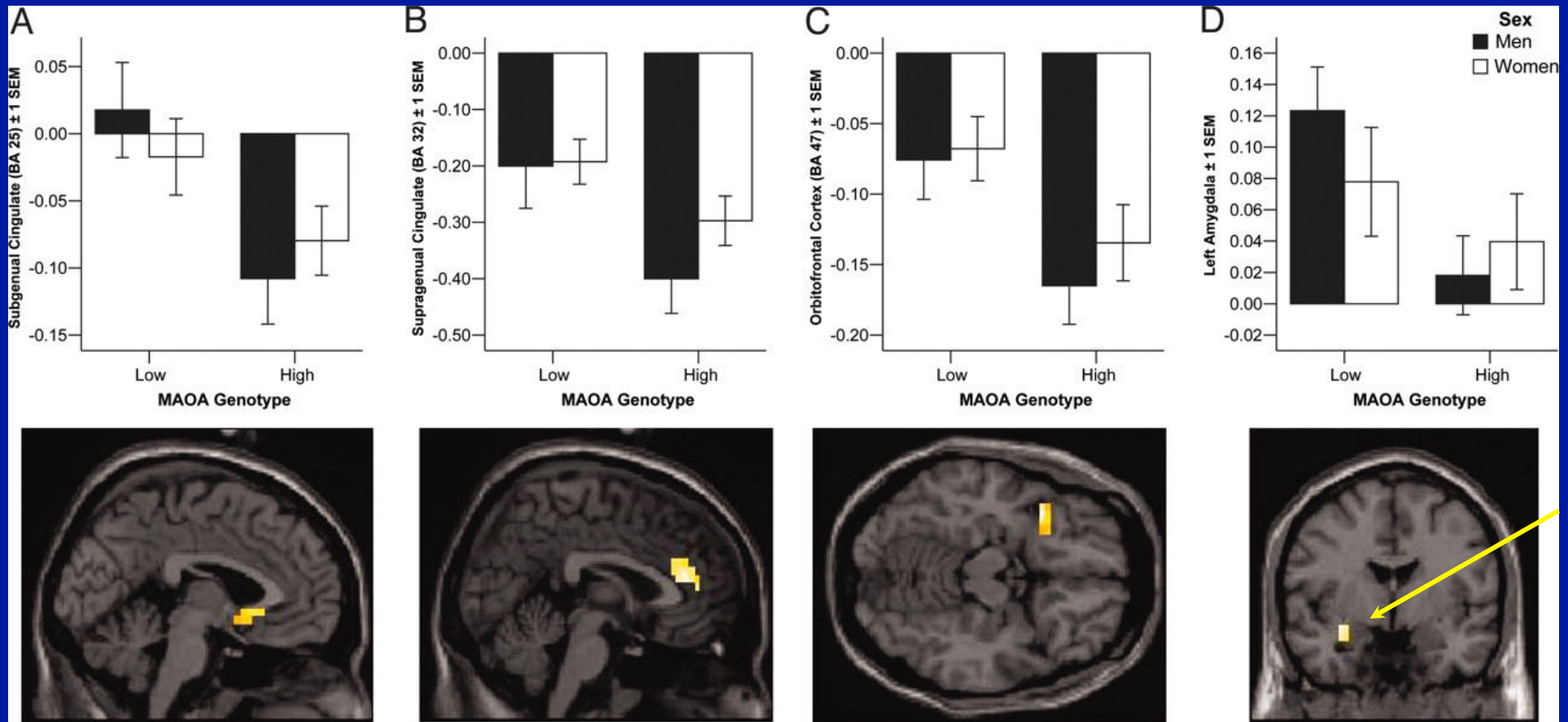


Alterazioni Strutturali Cerebrali negli Individui con Genotipo MAOA-L rispetto a Quelli con MAOA-H



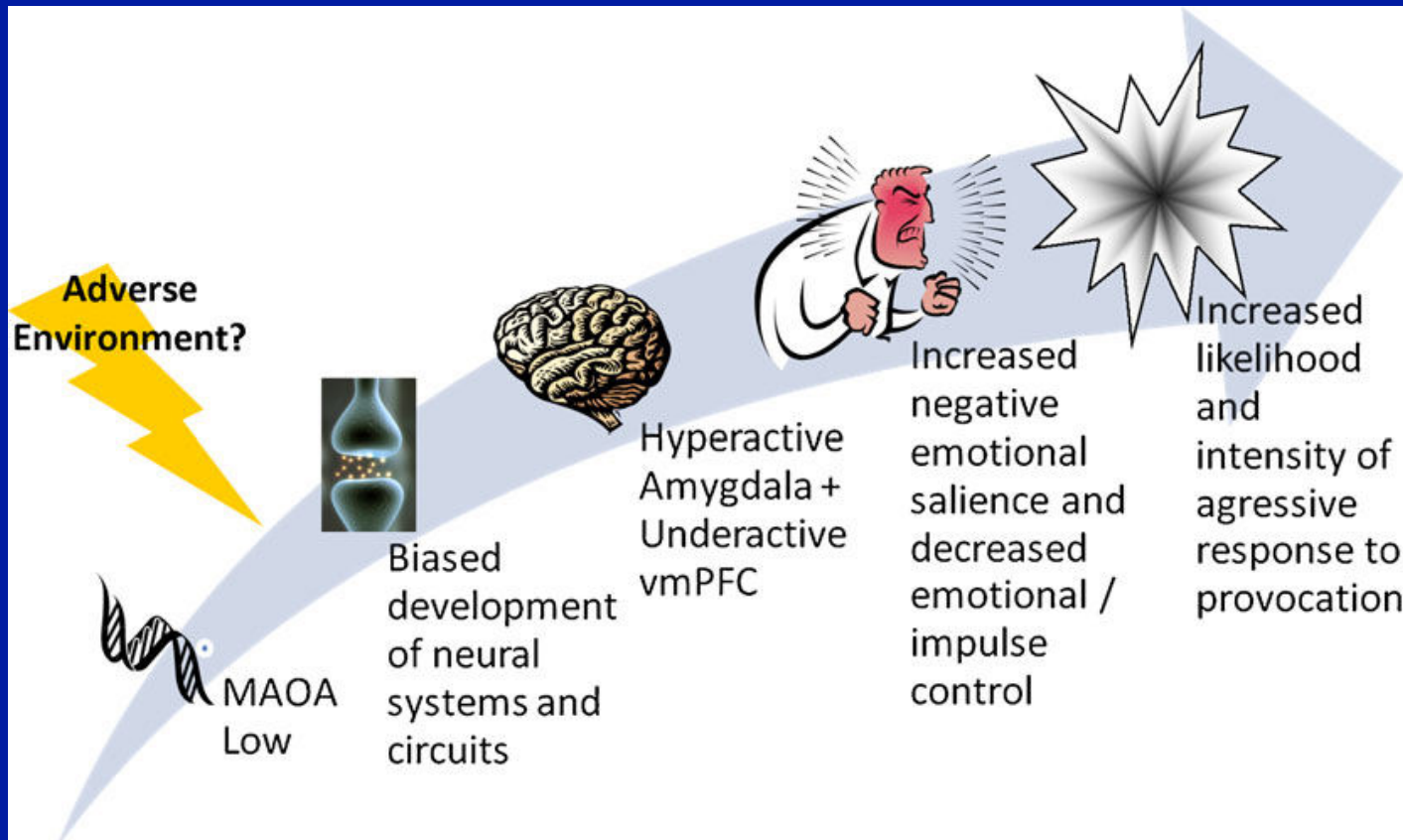
Meyer-Lindenberg, Andreas et al. (2006) Proc. Natl. Acad. Sci. USA 103, 6269-6274

Risposta Cerebrale Funzionale a Volti con Espressioni di Rabbia o di Paura negli Individui con Genotipo MAOA-L rispetto a Quelli con MAOA-H



Meyer-Lindenberg, Andreas et al. (2006) Proc. Natl. Acad. Sci. USA 103, 6269-6274

L'ipotesi biologica riguardo all'influenza del genotipo MAOA sul comportamento



Nature vs Nurture: l'interazione gene ambiente a livello molecolare

MAOA genotype	Developmental 5-HT	Circuit-level effects	Early-life experience	Behavioral outcome
 ACCGGCACCGGCACCACTAACCGGCACCT MAOA-H				
 ACCGGCACCGGCACCACTAACCGGCACCT MAOA-L				
 ACCGGCACCGGCACCACTAACCGGCACCT MAOA-H				
 ACCGGCACCGGCACCACTAACCGGCACCT MAOA-L				

TRENDS in Neurosciences

Nature vs Nurture: l'interazione gene ambiente a livello molecolare

MAOA genotype	Developmental 5-HT	Circuit-level effects	Early-life experience	Behavioral outcome
 ACCGGCACCGGCACCAAGTACCGGACCAAGT MAOA-H				
 ACCGGCACCGGCACCAAGTACCGGACCAAGT MAOA-L				
 ACCGGCACCGGCACCAAGTACCGGACCAAGT MAOA-H				
 ACCGGCACCGGCACCAAGTACCGGACCAAGT MAOA-L				

TRENDS in Neurosciences

Buckholtz and Meyer-Lindenberg (2008) Trends in Neurosciences Vol.31 No.3

Nature vs Nurture: l'interazione gene ambiente a livello molecolare

MAOA genotype	Developmental 5-HT	Circuit-level effects	Early-life experience	Behavioral outcome
 AGCGGCACCGGCACCGAGTAACCGGACCGAGT MAOA-H				
 AC08GCACCGGCACCGAGTACCGGACCGAGT MAOA-L				
 AC08GCACCGGCACCGAGTACCGGACCGAGT MAOA-H				
 AC08GCACCGGCACCGAGTACCGGACCGAGT MAOA-L				

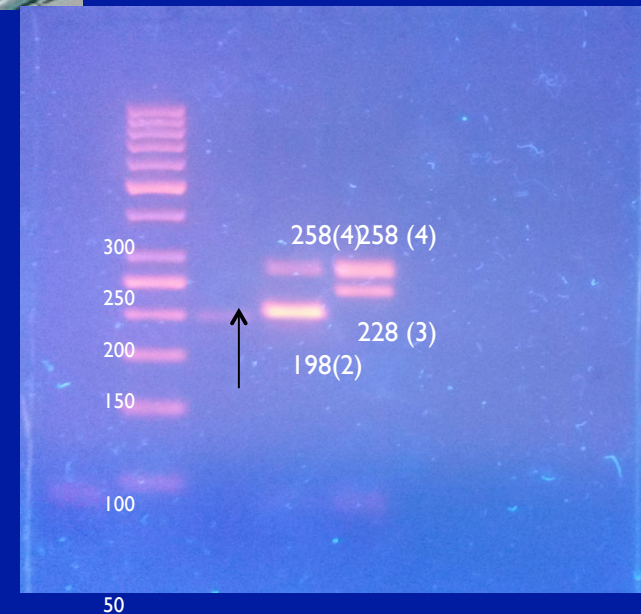
TRENDS in Neurosciences

Buckholtz and Meyer-Lindenberg (2008) Trends in Neurosciences Vol.31 No.3

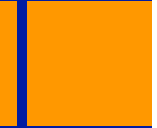
Giovanni Dalle Bande Nere



MAOA-uVNTR
2ripetizioni



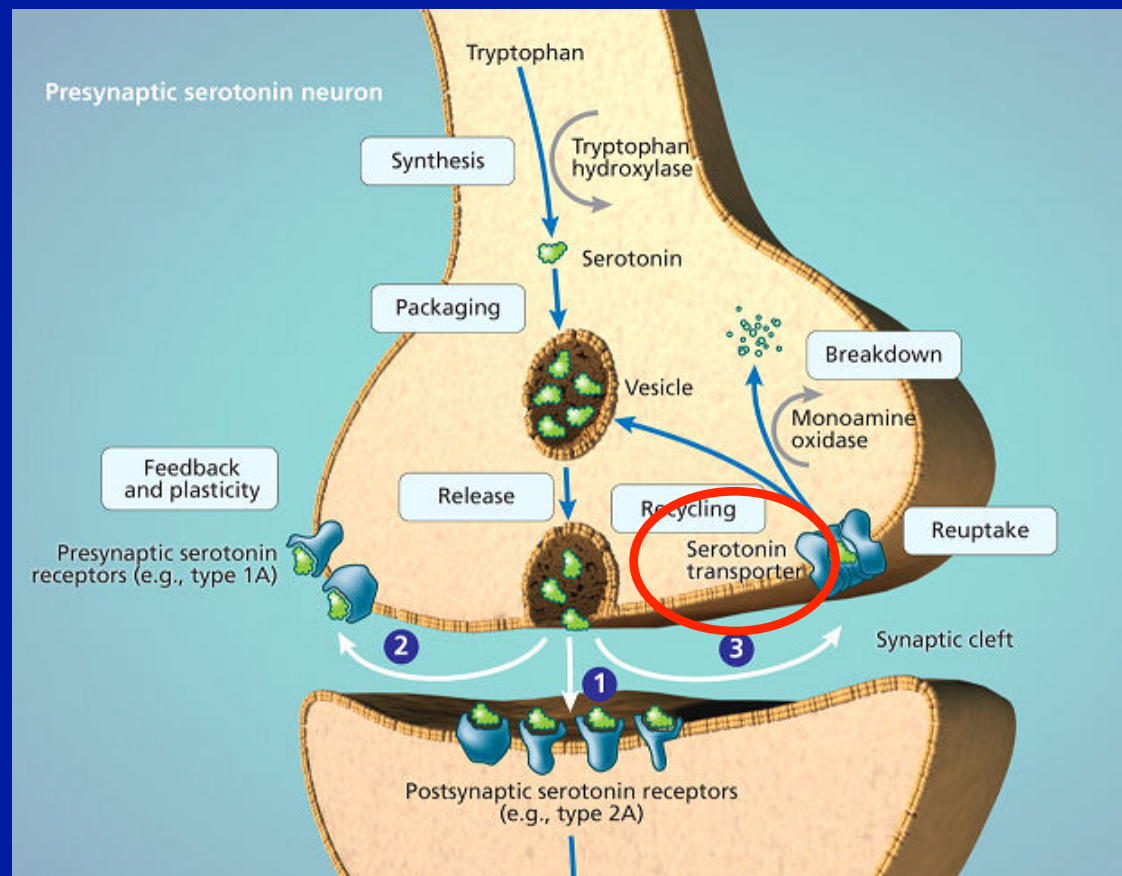
... ma altre varianti genetiche si associano al comportamento antisociale



- *SLC6A4* 5HTTLPR
- *DRD4* VNTR I-II
- *DRD4* rs_1800955
- *COMT* rs 4680 (Val/Met)

SLC6A4 (solute carrier family 6 (neurotransmitter transporter), member 4)

Trasportatore della serotonina



L (long) → 16 ripetizioni
S (short) → 14 ripetizioni

Attività ridotta

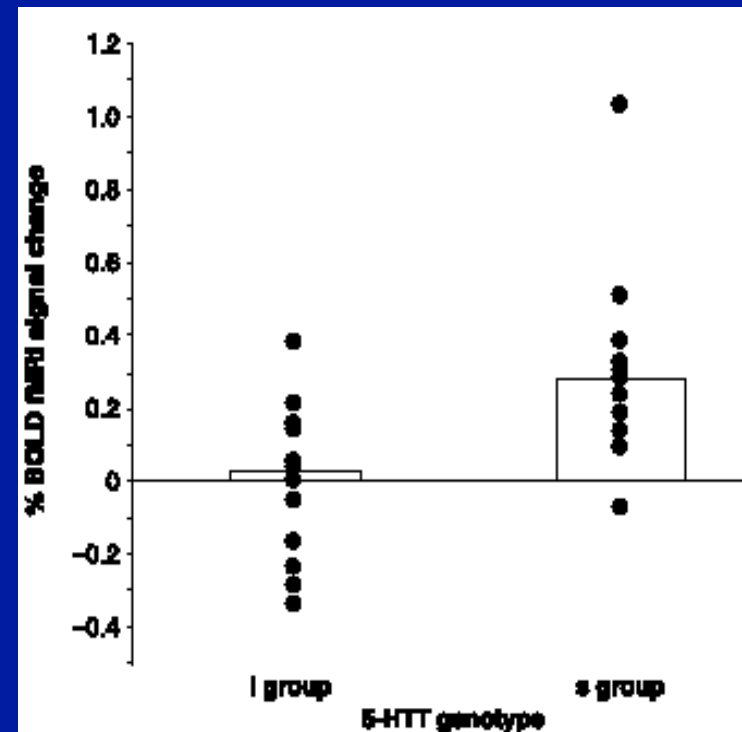
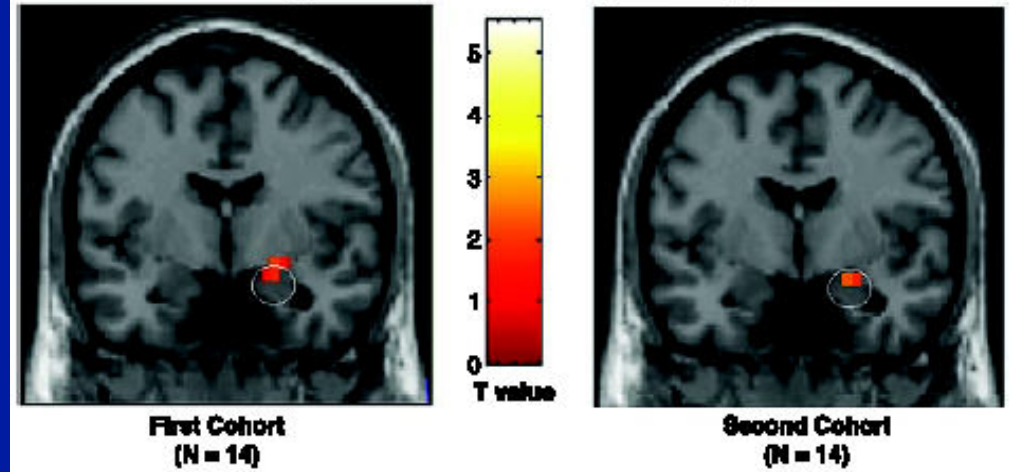
(Heils et al., 1996, Hu et al., 2006)

Serotonin Transporter Genetic Variation and the Response of the Human Amygdala

Ahmad R. Hariri,¹ Venkata S. Mattay,¹ Alessandro Tessitore,¹
 Bhaskar Kolachana,¹ Francesco Fera,¹ David Goldman,²
 Michael F. Egan,¹ Daniel R. Weinberger^{1*}

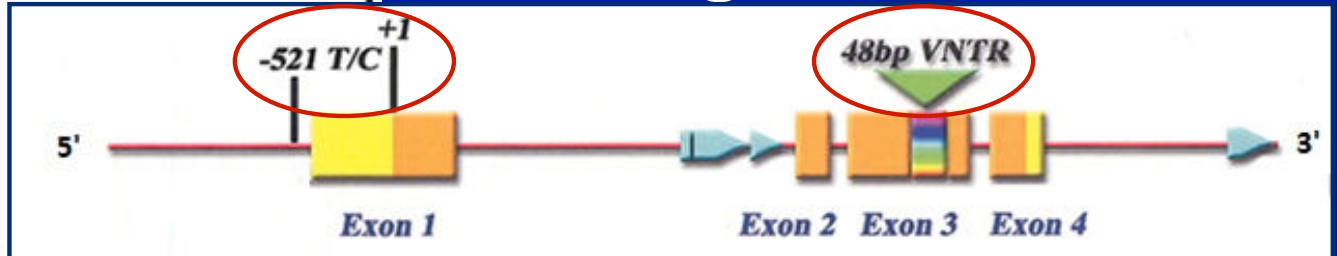
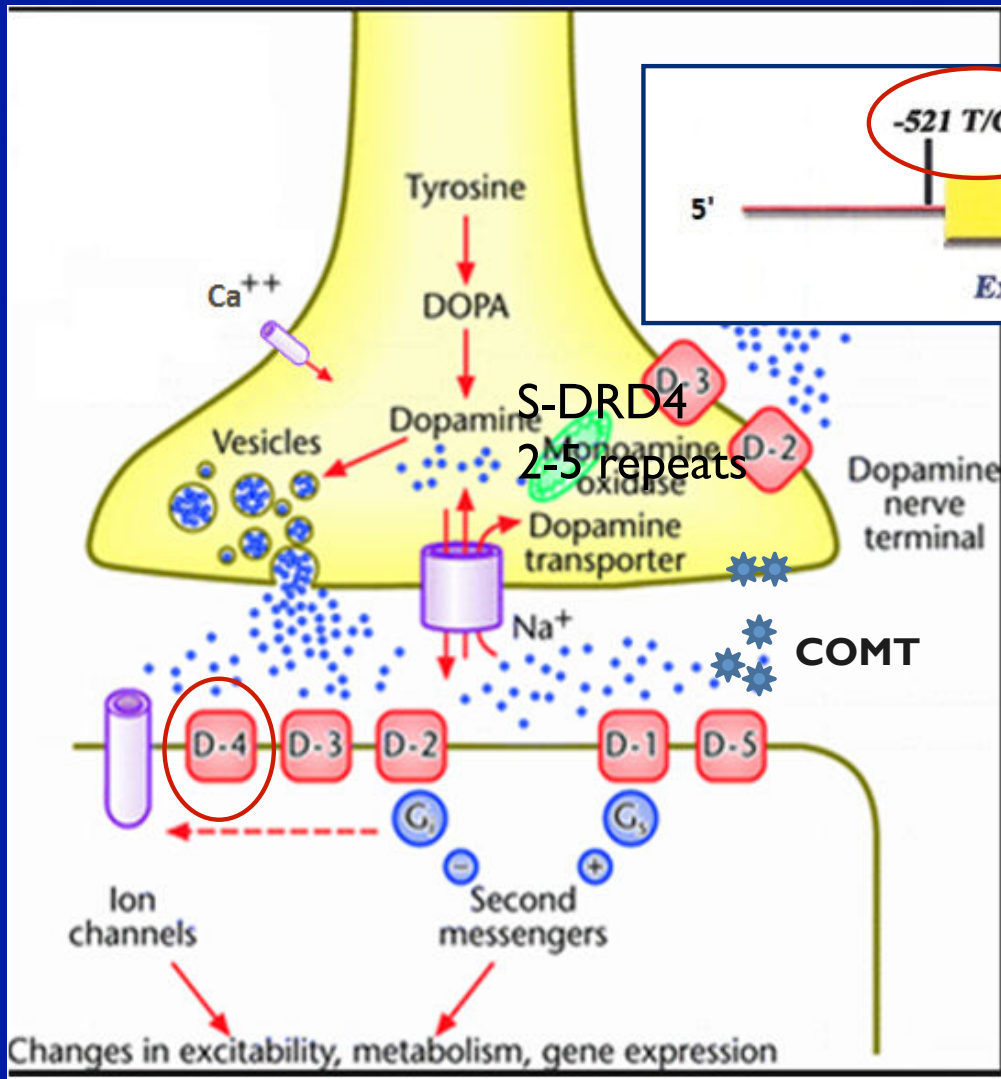
Individui con una o due copie dell'allele corto del promotore del trasportatore della serotonina (5-HTT), che è stato associato con una ridotta espressione e funzione di 5-HTT e un aumento di comportamenti ansiosi, mostravano una maggiore attività dell'amigdala in risposta a stimoli di paura rispetto ad individui omozigoti per l'allele lungo

Amygdala Response: s Group > l Group

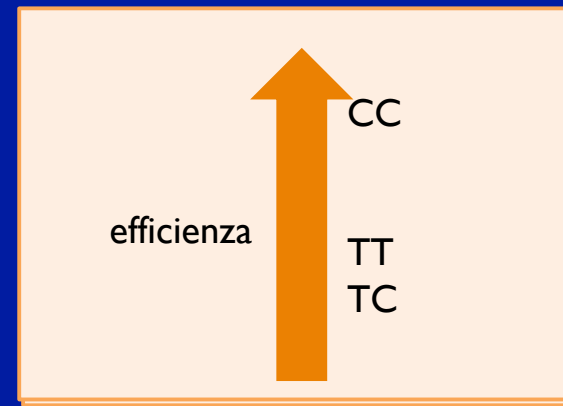


Dopamine Receptor D4

DRD4 gene



rs1800955 -> C/T



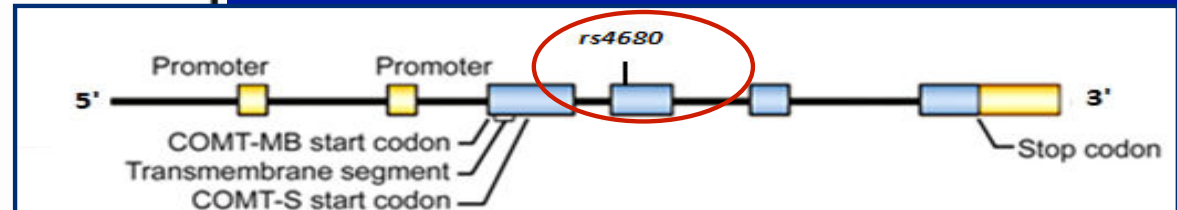
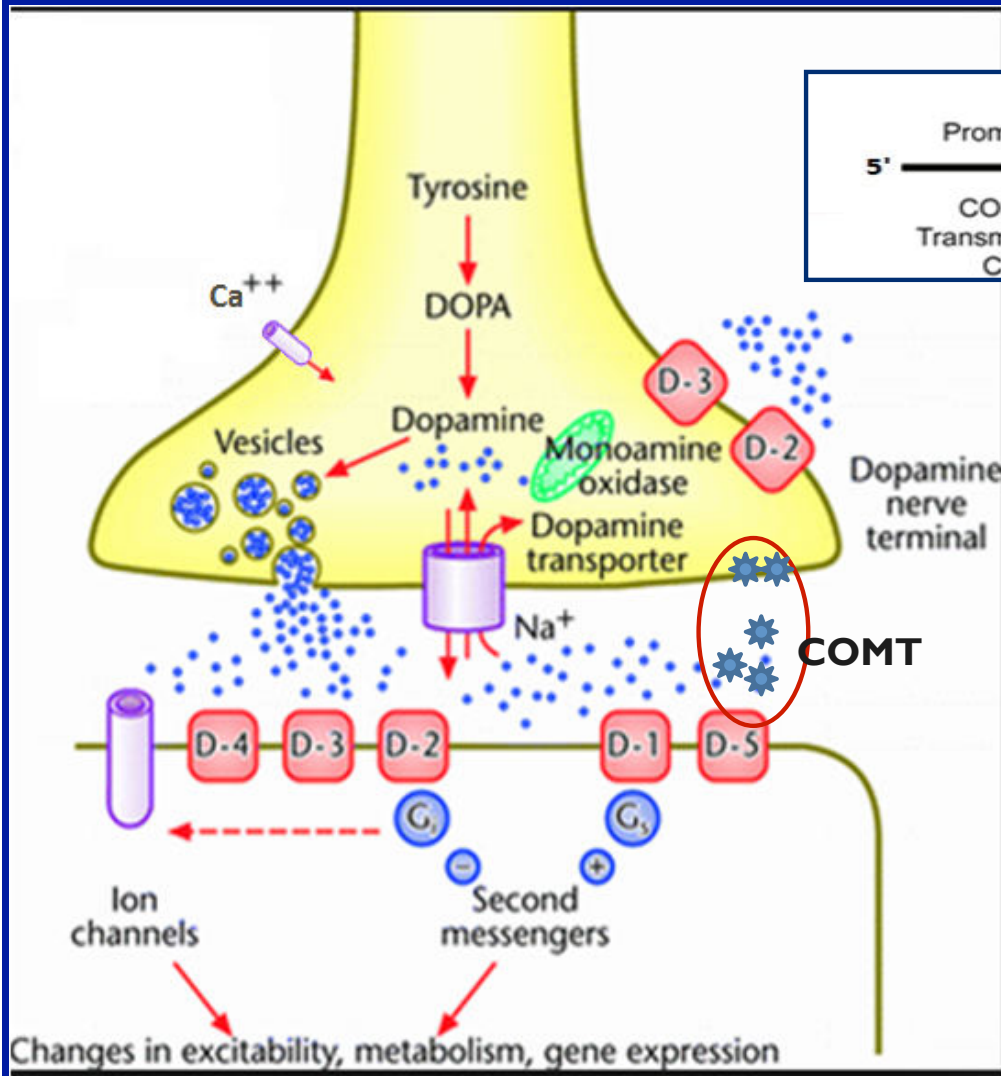
DRD4 and Novelty and reward seeking

- **DRD4-2r e 7r and CC genotype** associati con tratti di personalità “nevelty seeking” (Becker et al., 2005; Okuyama et al, 1999; Munafò et al, 2008)
- **DRD4-7r** associati con abuso di fumo e di alcool (Skowronek er al., 2006; Laucht et al., 2005; Laucht et al., 2007)



Catechol O-methyltransferase

COMT gene



COMT rs4680 →
 G>A
GTG → Val-158
ATG → Met-158

Attività enzimatica ↑
 Val/Val (G/G)
 Val/Met (G/A)
 Met/Met (A/A)

COMT Val/58Met

A Functional Single Nucleotide Polymorphism (V158M) in the COMT Gene Is Associated with Aggressive Personality Traits

Dan Rujescu, Ina Giegling, Anton Gietl, Annette M. Hartmann, and Hans-Jürgen Möller

Association Between Catechol O-Methyltransferase Genotype and Violence in Schizophrenia and Schizoaffective Disorder

Herbert M. Lachman, M.D., Karen A. Nolan, Ph.D., Pavel Mohr, M.D., Takuya Saito, M.D., and Jan Volavka, M.D., Ph.D.

Aggressive Behavior in Schizophrenia Is Associated With the Low Enzyme Activity COMT Polymorphism: A Replication Study

Rael D. Strous,¹ Karen A. Nolan,² Raya Lapidus,¹ Libna Diaz,³ Takuya Saito,³ and Herbert M. Lachman^{3*}