Genes, brains and behavior. Lecture 8

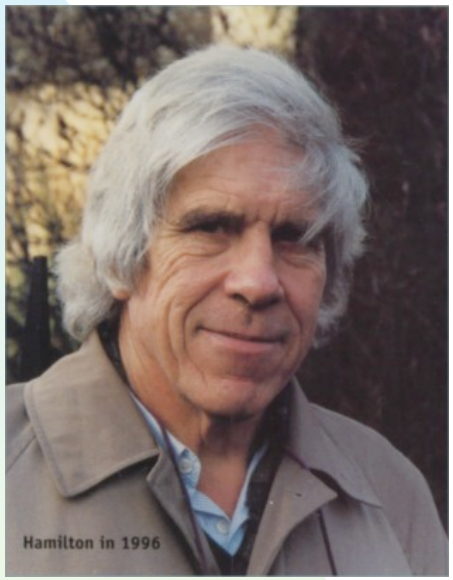
2 mammalian examples: FosB and FoxP2

Karl-Friedrich Fischbach, Neurogenetics, Freiburg

Altruistic behaviour and the concept of inclusive fitness

William D. Hamilton

1 August 1936 – 7 March 2000



Hamilton‘s rule:

$C < R \times B$

Where C is the cost in fitness to the actor, R the genetic relatedness between the actor and the recipient and B is the fitness benefit to the recipient. Fitness costs and benefits are measured in fecundity (number of offsprings)

In own words:

We invest more when the recipient of our help is related.

How is relatedness measured in real life by our brains?

Surely not by gene sequences

Imprinting

adoption in the animal kingdom by imprinting

adoption in the animal kingdom by imprinting

Today´s topics

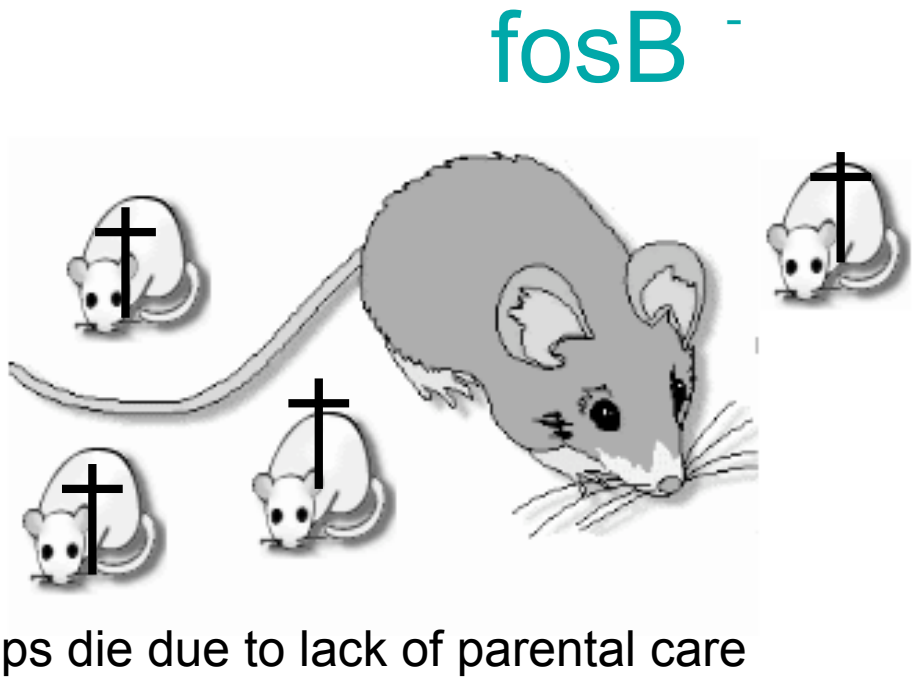
- 1. Imprinting and the FosB gene in mammals (revisited)

- 2. Evolution of speech and the FoxP2 gene in vertebrates

The FosB gene

nurturing behaviour in mammals

Gene mutations play an important role in brood care



pups die due to lack of parental care

Brood care behaviour

e. g.

- nest building
- retrieval behaviour
- grooming
- warming
- sniffing
- lactation
- protection

gene knock-out with fosB gene

- „immediate early genes“ (IEGs)
- transcription factor
- 4 family members
  - c-fos
  - fosB → expressed hypothalamus
  - fra-1
  - fra-2

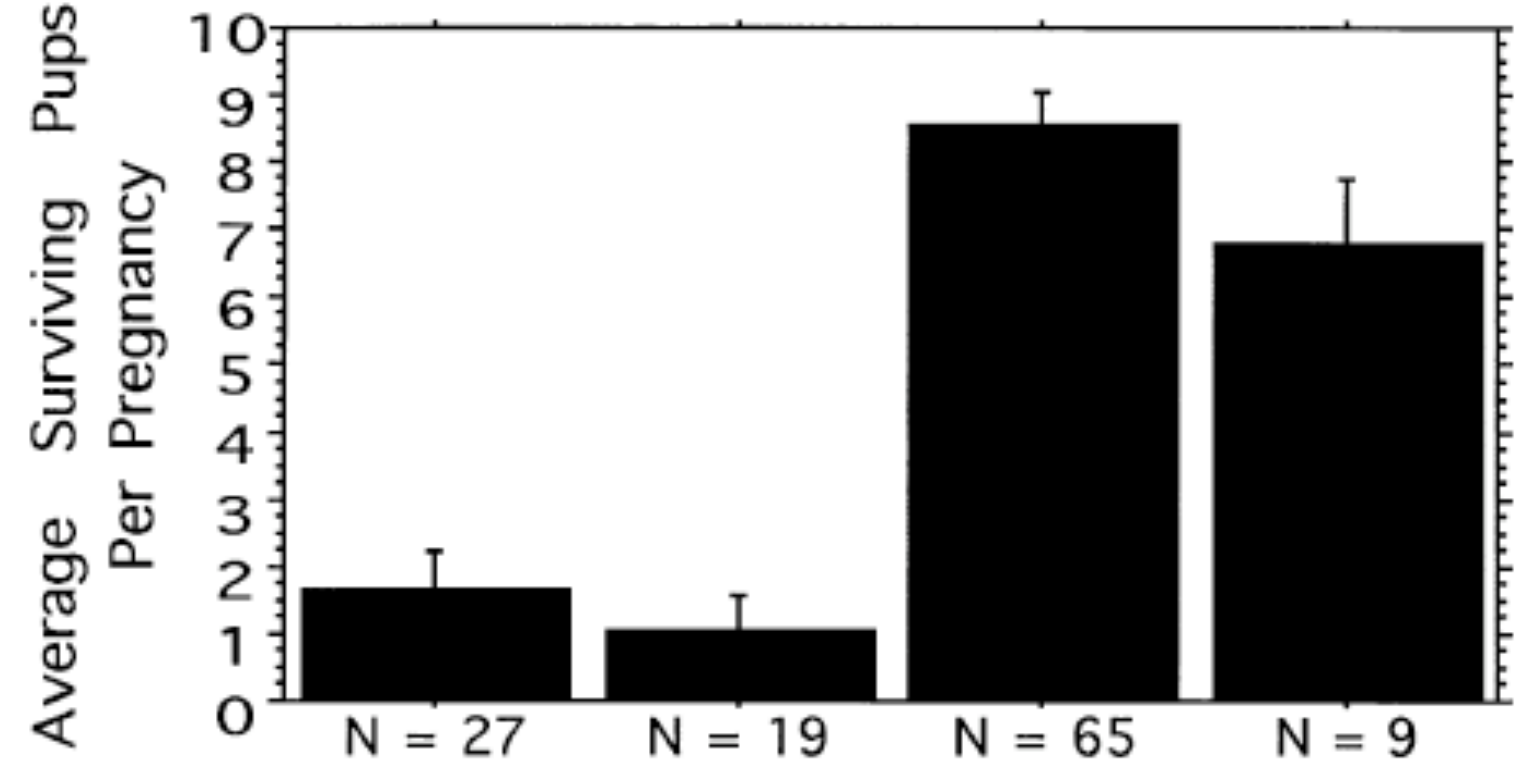
fos-proteins

- form heterodimers with Jun-family proteins → AP-1-complex
- DNA binding at AP-1 target site (TGACTCA)
- strong fosB mutant effects

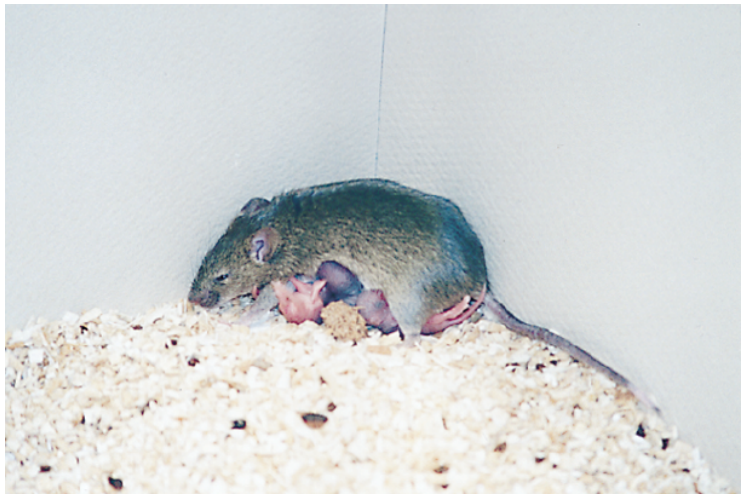
→no care for their offspring

→newborns die >50%

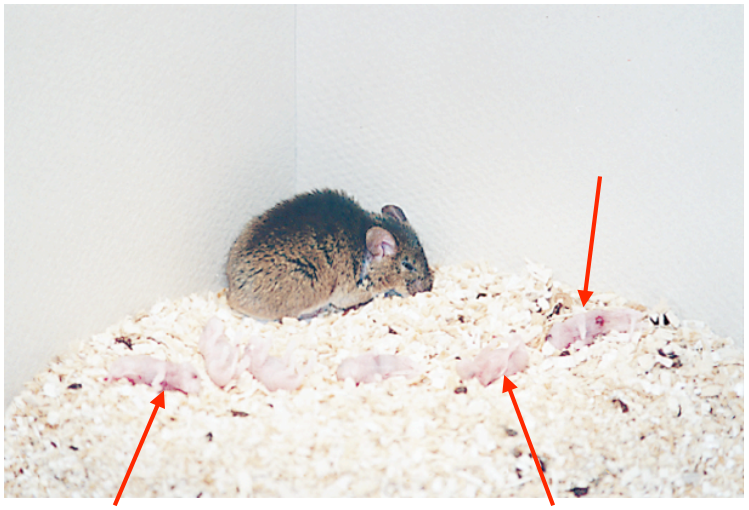
Genotype of the mother matters



behavioral observation

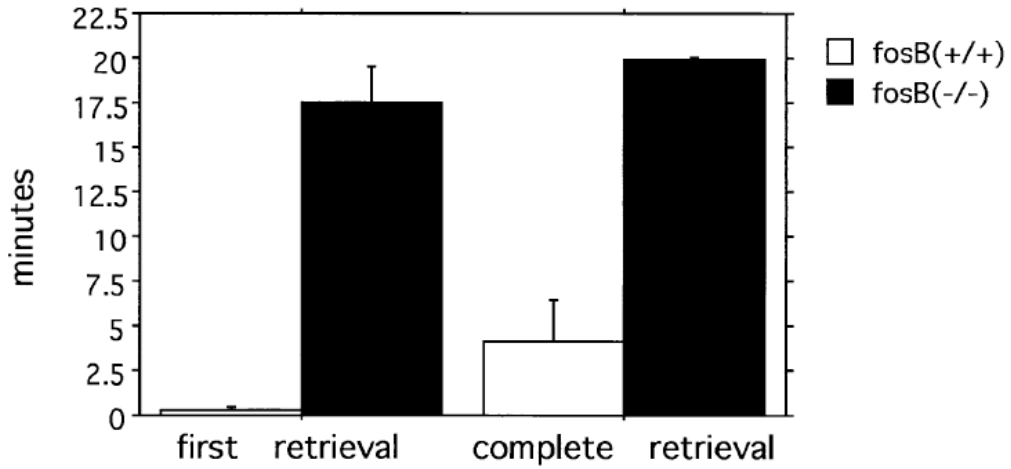


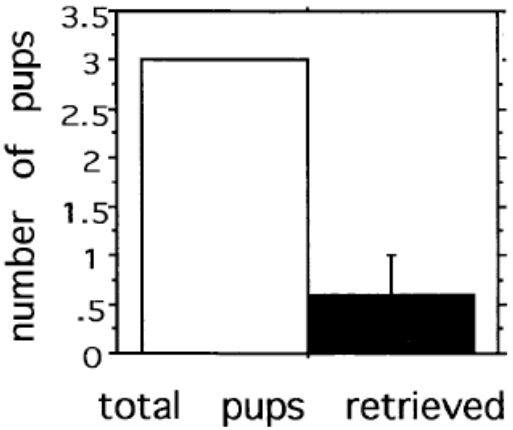
wildtyp



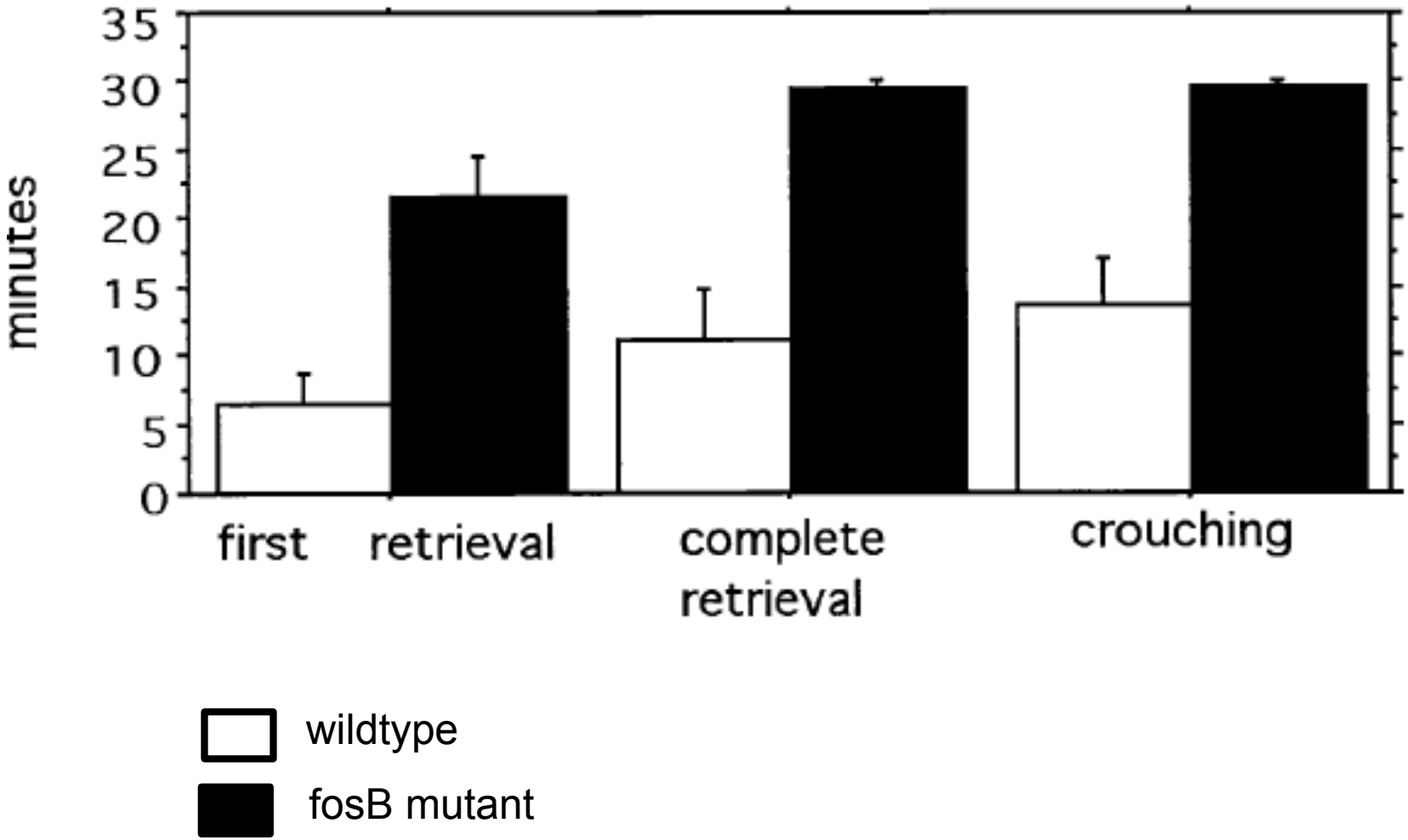
mutant

Retrieval behaviour

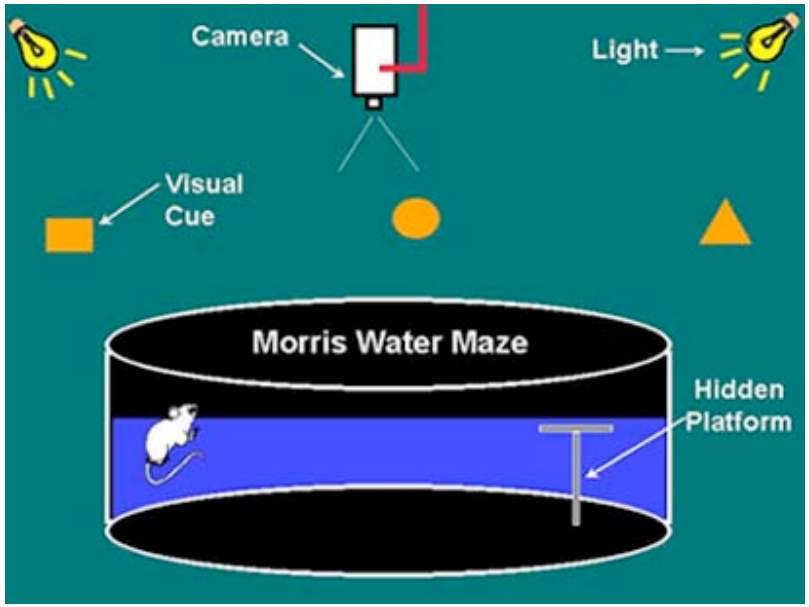


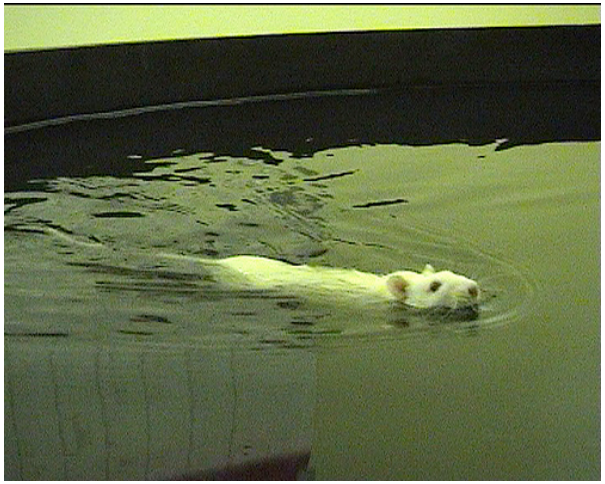


male mutants show also retrieval defect



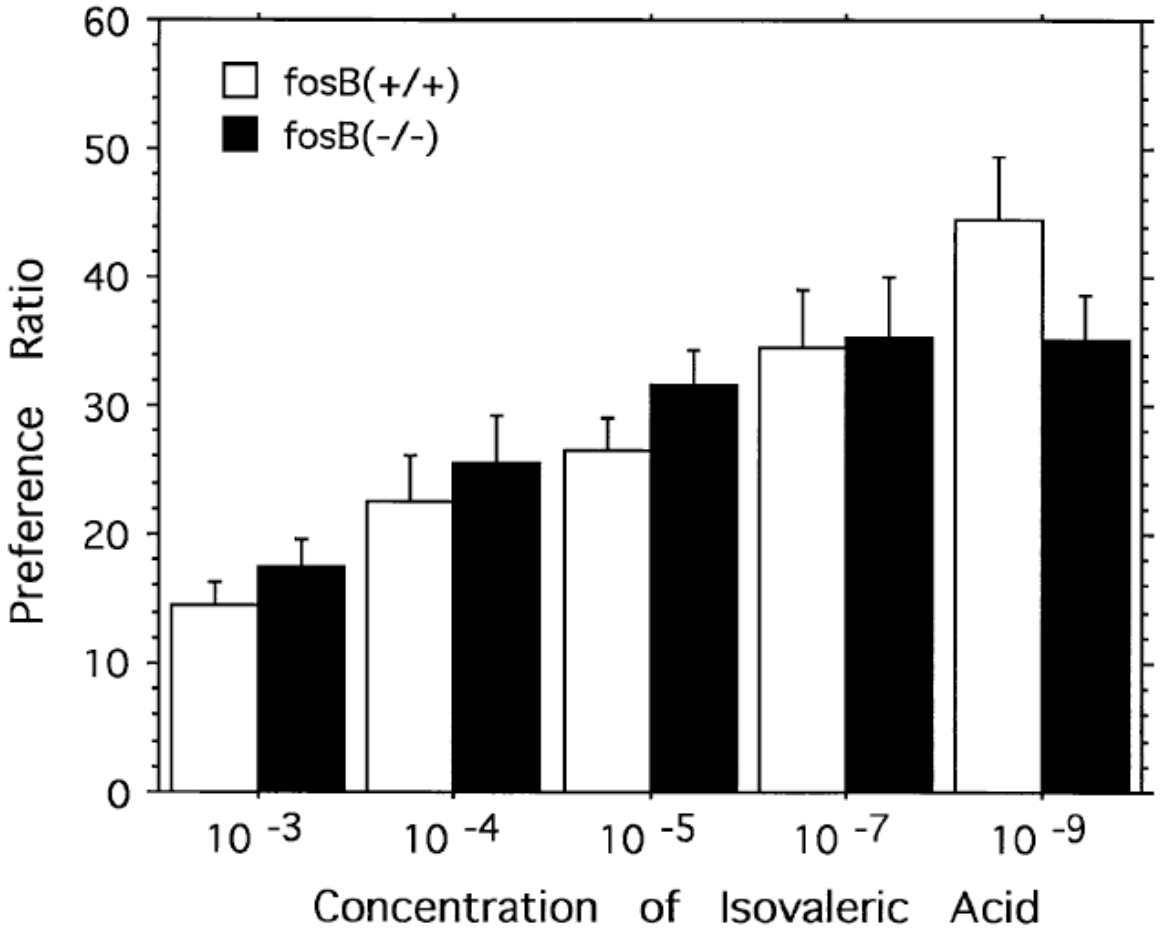
Morris‘ water-maze





→ no general cognitive dysfunction

Aversive Conditioning



summary for fosB part

- Mutation in fosB → nurturing defect in mice, caused by maternal genotype
- defect is not sex-specific, males also do not care
- no gross physiological or anatomical defects, however smaller body size
- fosB is expressed in the hypothalamus
- no cognitive or olfactory defect, no general defect of the hypothalamus

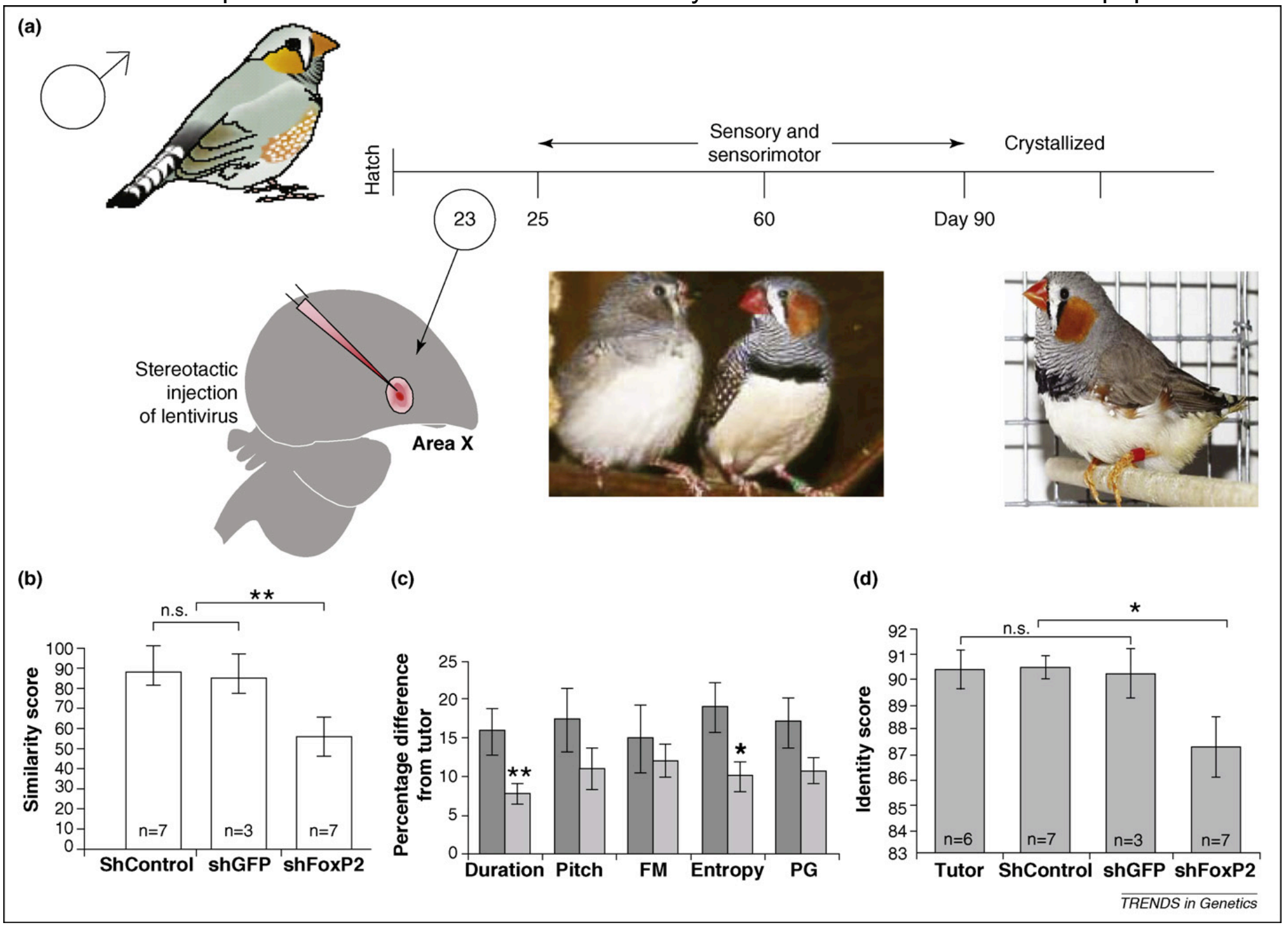
- **fosB is believed to play a role in the multisensory imprinting process by which parents build affective bonds to their offspring**.

The FoxP2 gene

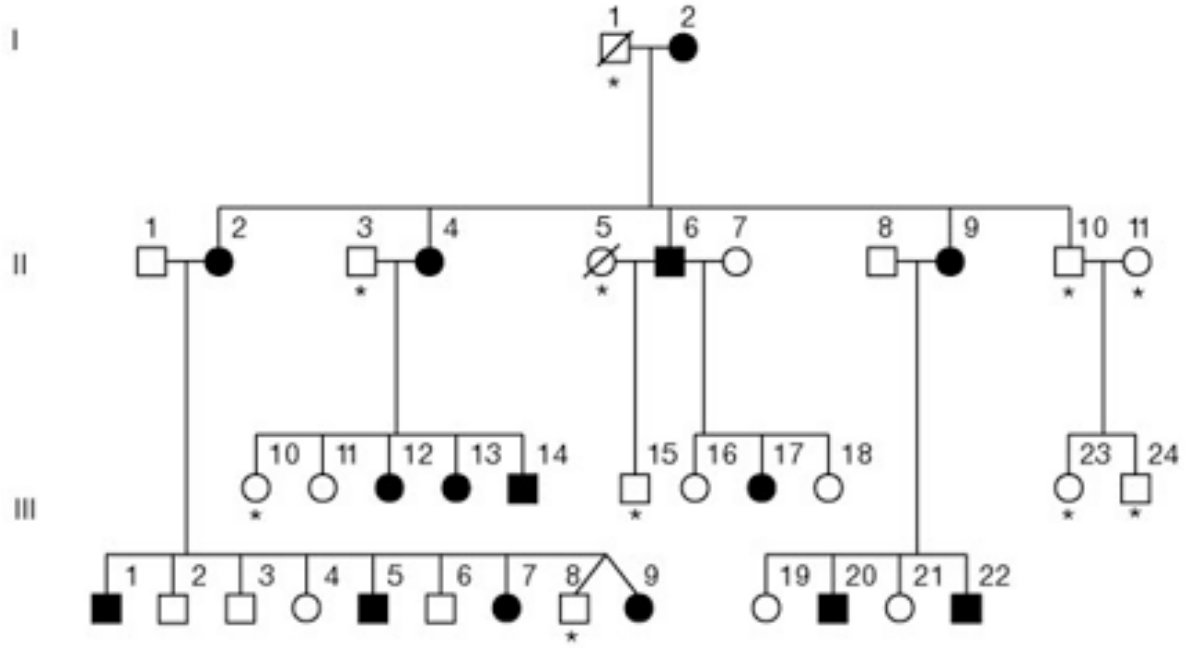
A transcription factor gene of importance for vocalization in vertebrates

Do not confuse FoxP2 with FosB!

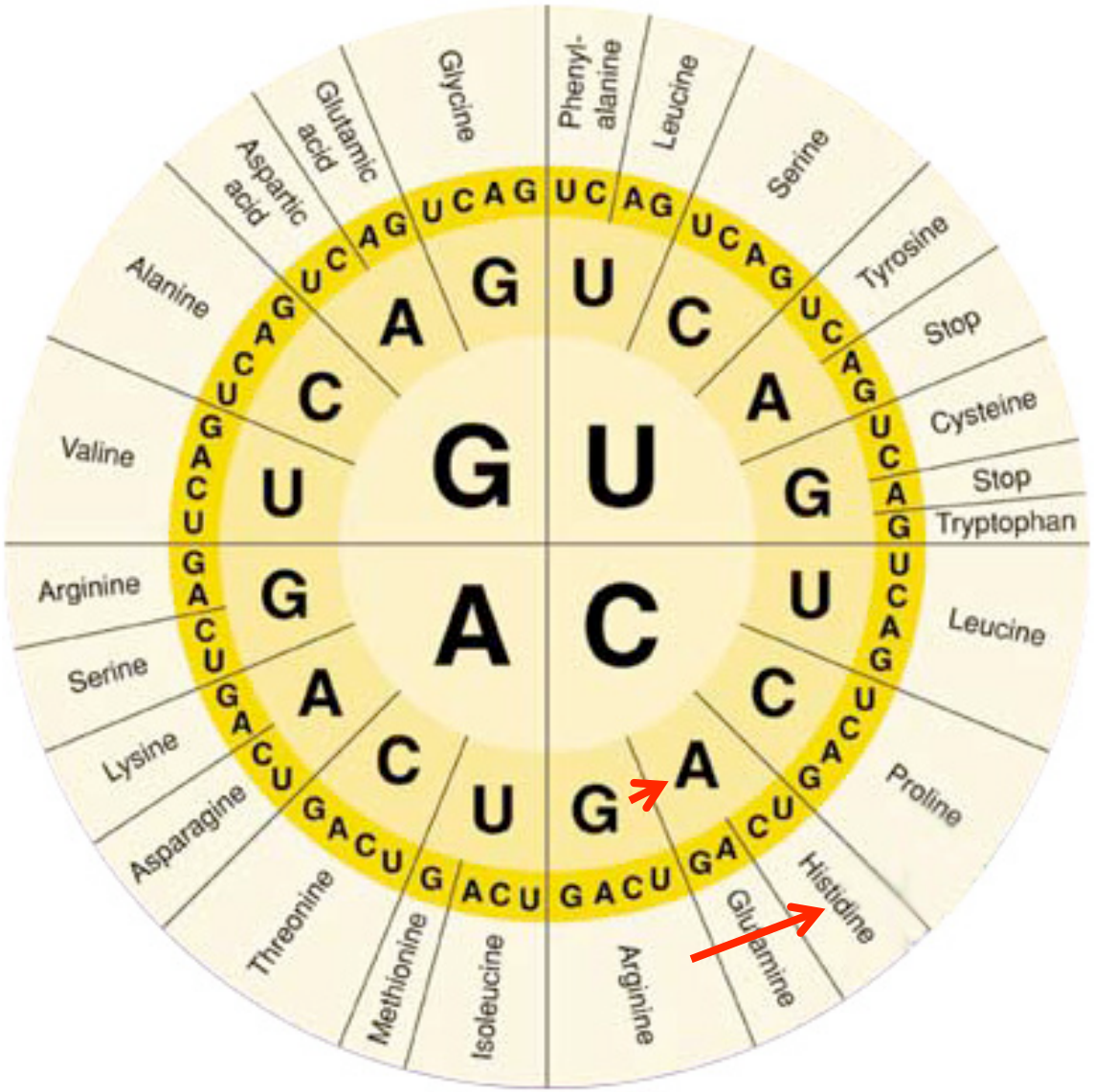
Incomplete and inaccurate vocal imitation by FoxP2 knockdown zebra-finch pupils



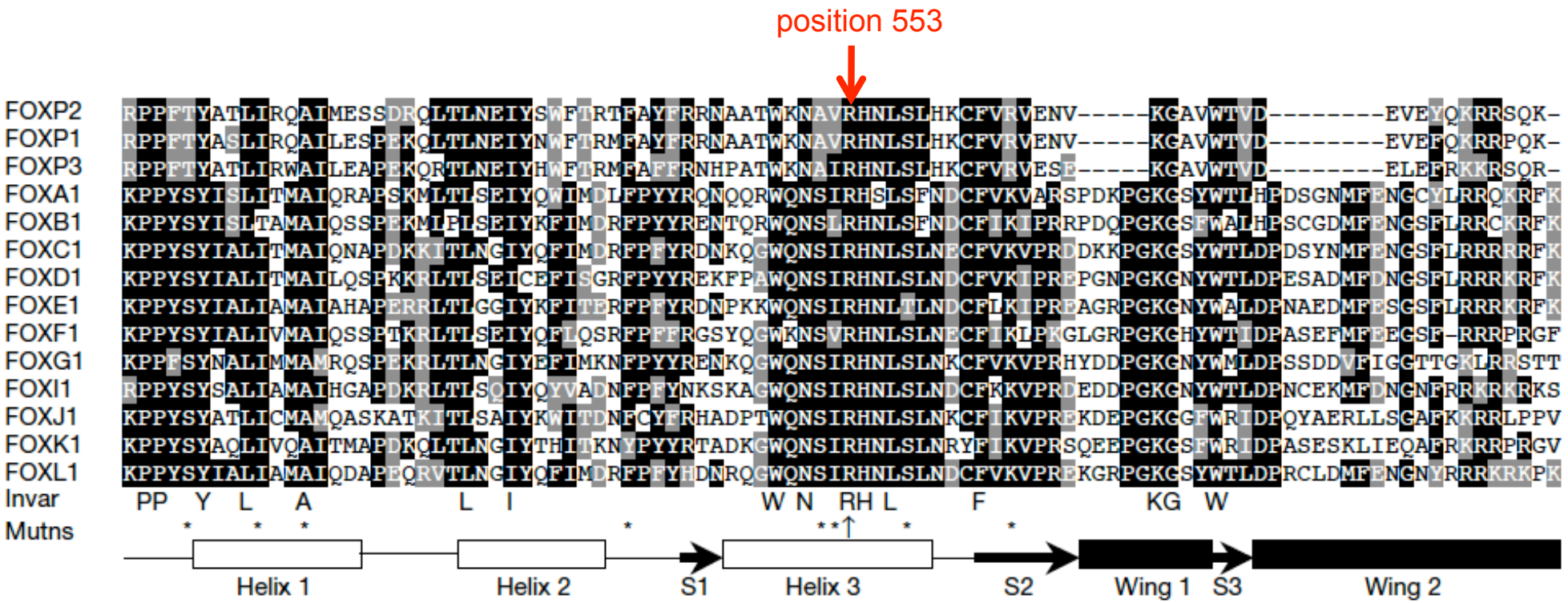
The FoxP2 gene is mutated in a severe speech and language disorder in humans



Pedigree of the KE family. Affected individuals are indicated by filled symbols. Asterisks indicate those individuals who were unavailable for genetic analyses. Squares are males, circles are females, and a line through a symbol indicates that the person is deceased.


G U C A
Glycine
Glutamic acid
Aspartic acid
Alanine
Phenyl-alanine
Leucine
Serine
Tyrosine
Stop
Cysteine
Stop
Tryptophan
Valine
Arginine
Serine
Lysine
Asparagine
Leucine
Proline
Histidine
Glutamine
Arginine
Threonine
Methionine
Isoleucine

The mutation is in the highly conserved DNA-binding FOX domain of the FOXP2 gene



This mutation and its severe effects on speech in humans draw the attention of scientists interested in evolution to this gene.

The FoxP2 gene

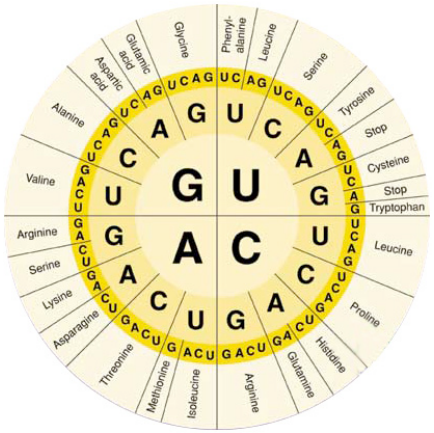
Letters to Nature

Nature **418**, 869-872 (22 August 2002) | doi:10.1038/nature01025; Received 11 November 2001; Accepted 29 July 2002; Published online 14 August 2002

Molecular evolution of *FOXP2*, a gene involved in speech and language

Wolfgang Enard[1], Molly Przeworski[1], Simon E. Fisher[2], Cecilia S. L. Lai[2], Victor Wiebe[1], Takashi Kitano[1], Anthony P. Monaco[2] & Svante Pääbo[1]

Silent and replacement nucleotide substitutions mapped on a phylogeny of primates. Bars represent nucleotide changes. Grey bars indicate amino-acid changes.



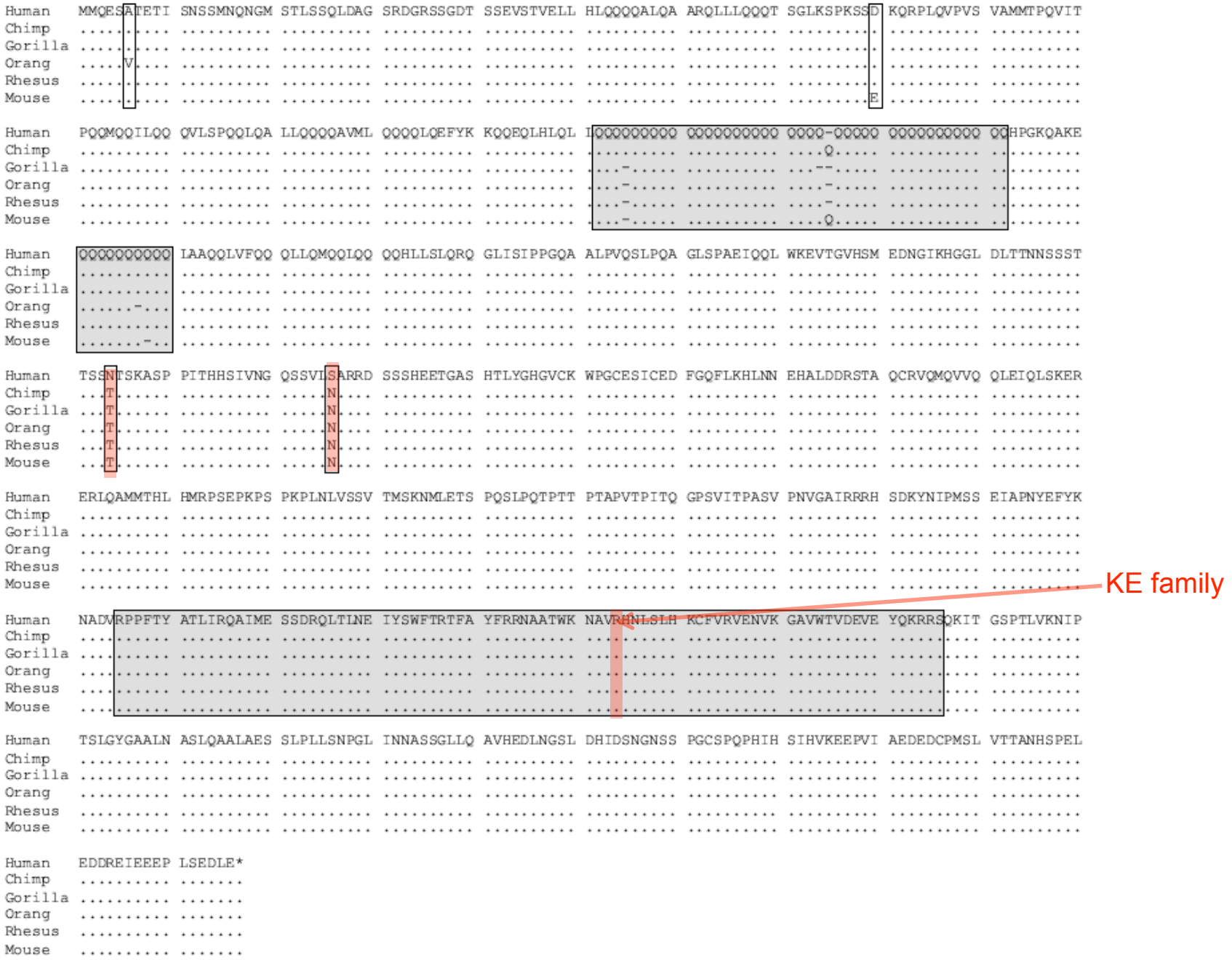
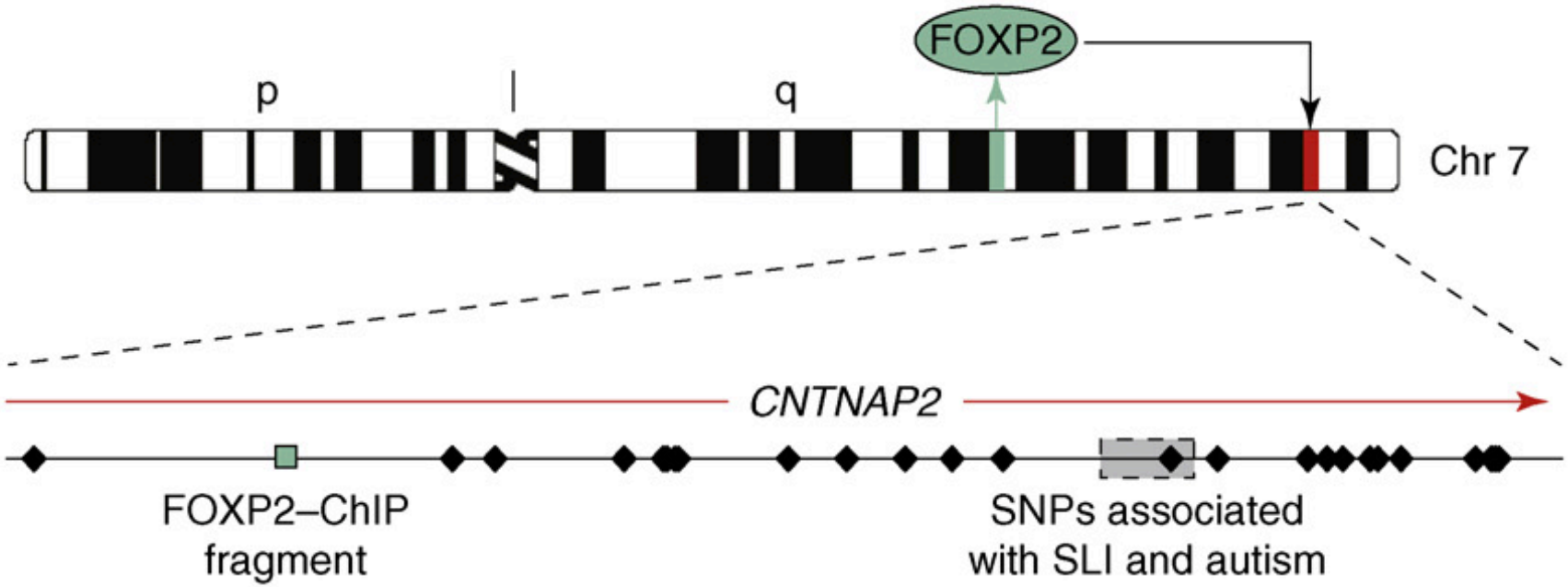


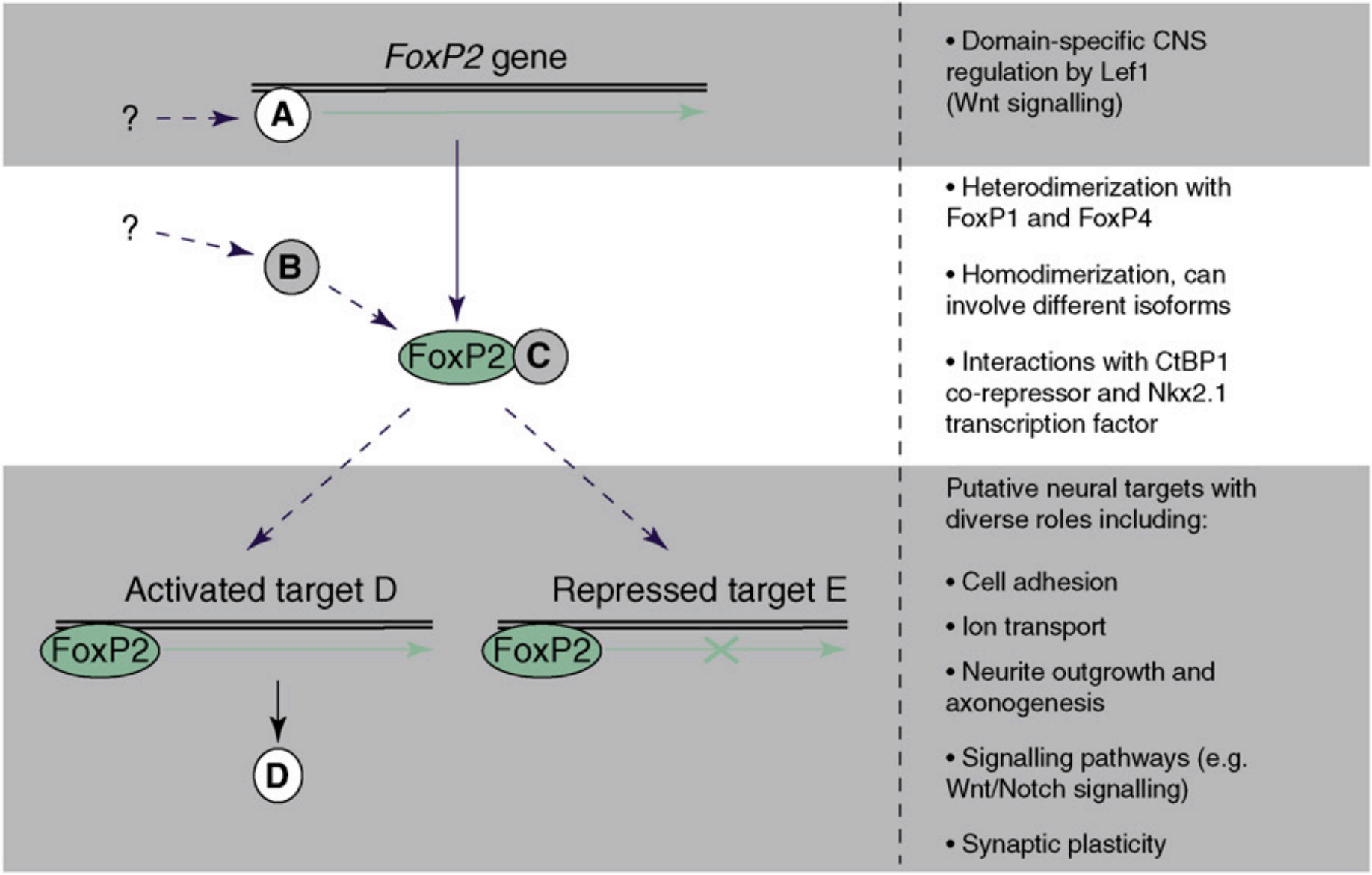
Figure 1 Alignment of the amino-acid sequences inferred from the *FOXP2* cDNA sequences. The polyglutamine stretches and the forkhead domain are shaded. Sites that differ from the human sequence are boxed.

Chromosome 7



The *CNTNAP2* gene codes for a member of the neurexin superfamily
and is regulated by FOXP2

Functional genomics of FOXP2

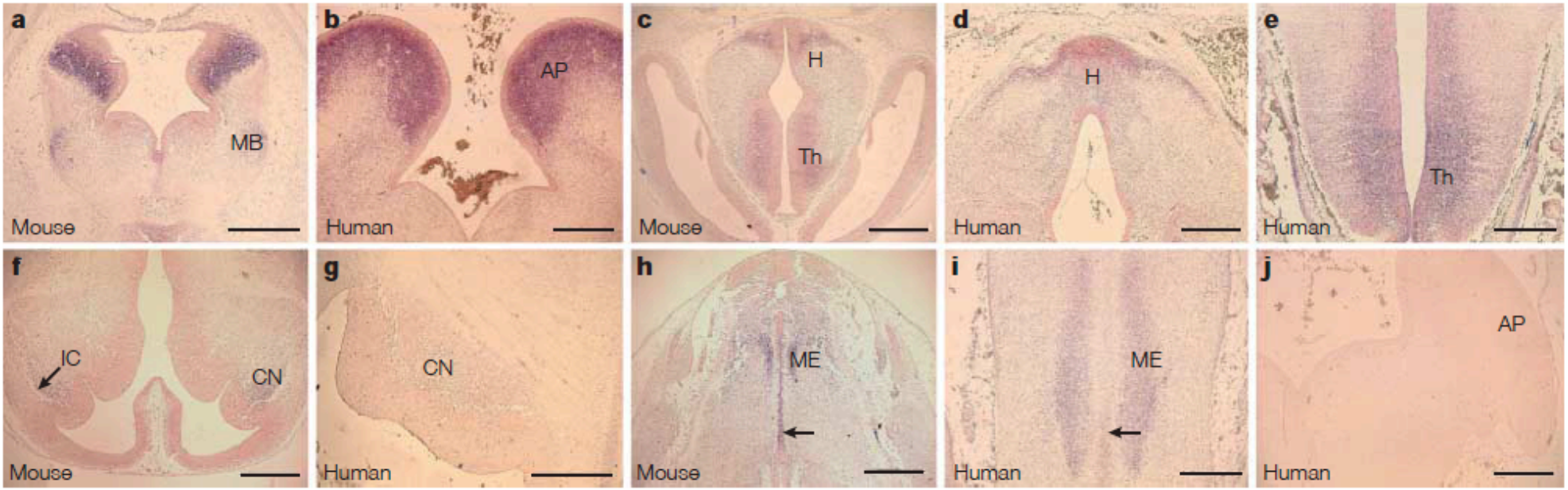


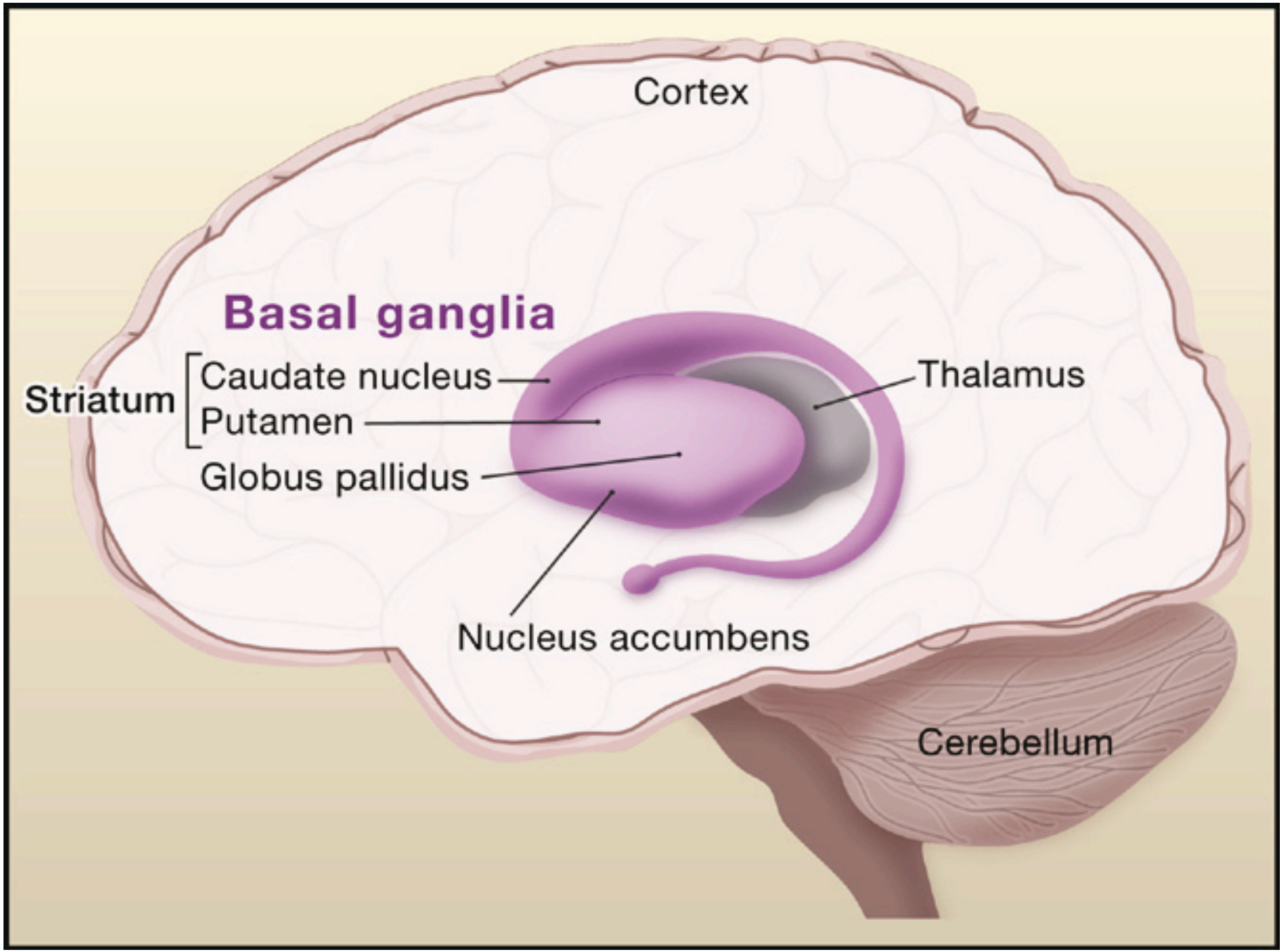
TRENDS in Genetics

Expression of FOXP2 is highly conserved in vertebrate brains

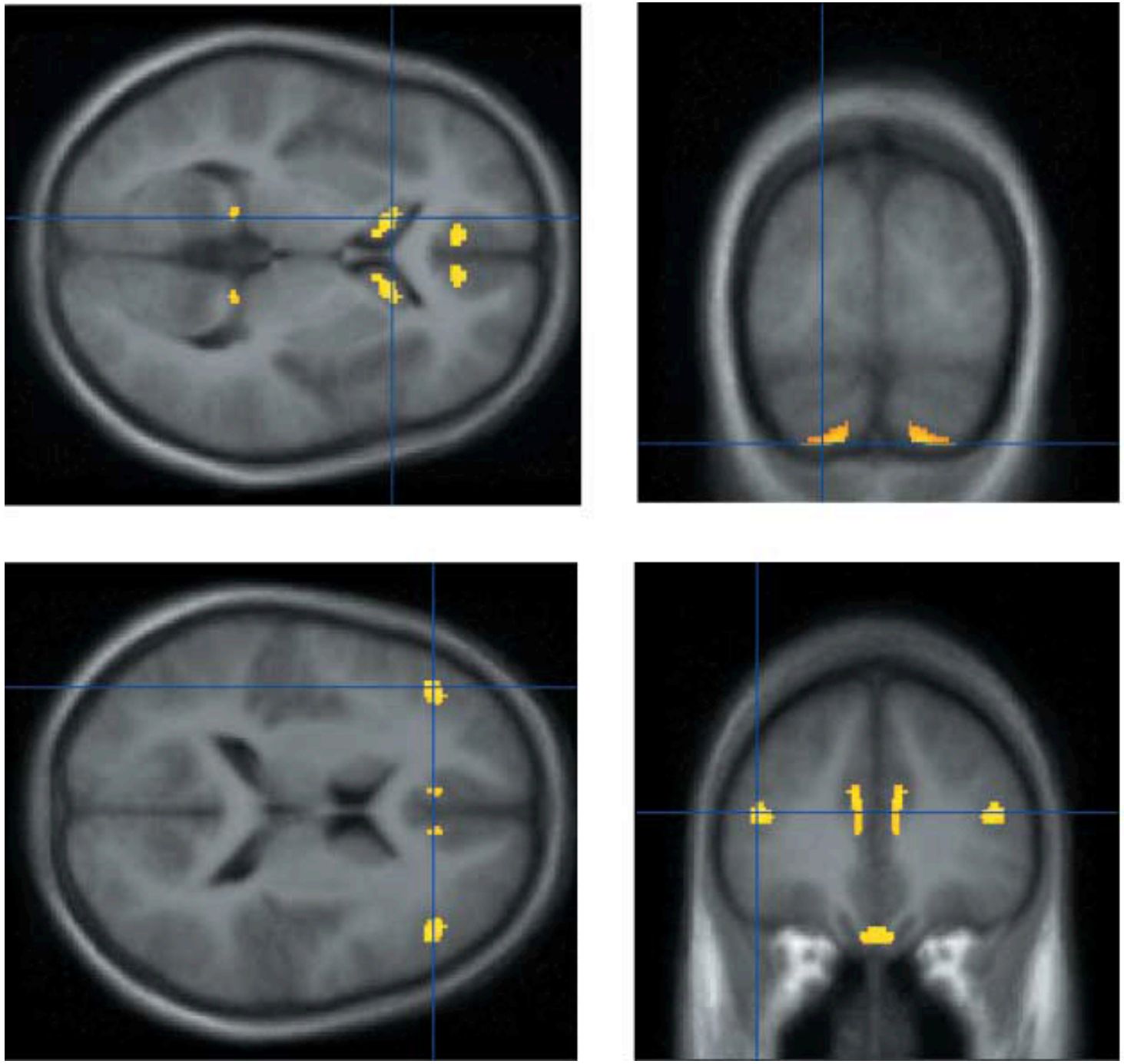
FoxP2 orthologues exist in highly similar forms in many Vertebrates, showing comparable neural expression patterns; In humans, monkeys, mice, rats, birds, crocodiles and Zebrafish, FoxP2 is consistently expressed in distributed circuits involving (among others) the cortex, basal ganglia (BG), thalamus and cerebellum

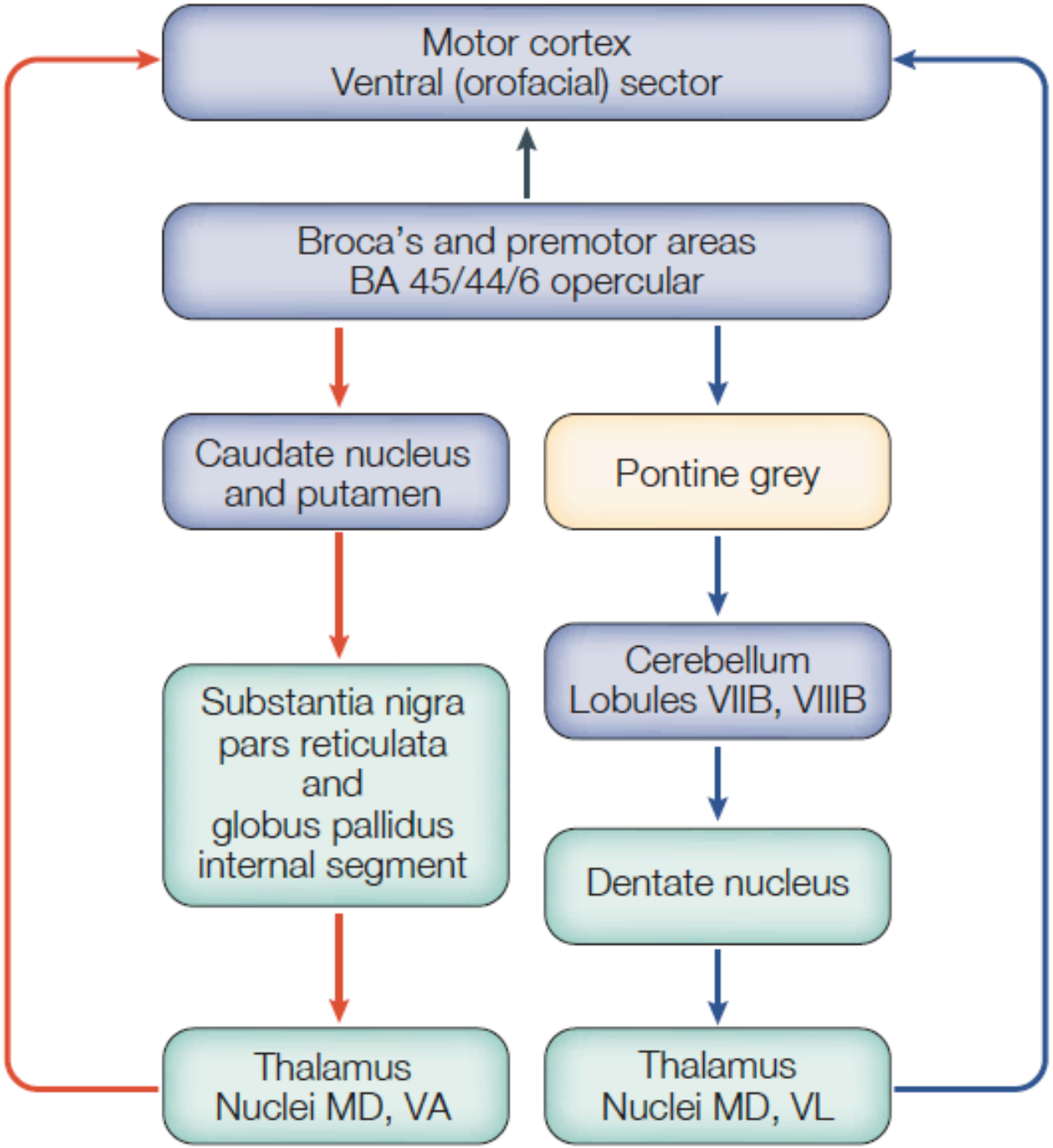
Mouse and human expression of FOXP2 is similar




Cortex
Basal ganglia
Striatum
Caudate nucleus
Putamen
Globus pallidus
Thalamus
Nucleus accumbens
Cerebellum

Bilateral voxel-based morphometry (VBM) analyses showing (in colour) some of the regions in which affected KE family members have significantly reduced grey matter





Blue and green areas express FOXP2

The FoxP2 gene

Cell, Volume 137, Issue 5, 961-971, 29 May 2009

doi:10.1016/j.cell.2009.03.041

Article

A Humanized Version of Foxp2 Affects Cortico-Basal Ganglia Circuits in Mice

Wolfgang Enard[1], Sabine Gehre[1], Kurt Hammerschmidt[2], Sabine M. Hölter[3], Torsten Blass[1], Mehmet Somel[1, 25], Martina K. Brückner[4], Christiane Schreiweis[1], Christine Winter[5], Reinhard Sohr[6], Lore Becker[7, 8], Victor Wiebe[1], Birgit Nickel[1], Thomas Giger[1], Uwe Müller[9], Matthias Groszer[10, 26], Thure Adler[8, 11], Antonio Aguilar[12], Ines Bolle[13], Julia Calzada-Wack[14], Claudia Dalke[3], Nicole Ehrhardt[8, 15], Jack Favor[16], Helmut Fuchs[8], Valérie Gailus-Durner[8], Wolfgang Hans[8], Gabriele Hölzlwimmer[14], Anahita Javaheri[8, 12], Svetoslav Kalaydjiev[11, 27], Magdalena Kallnik[3], Eva Kling[7, 8], Sandra Kunder[14, 28], Ilona Moßbrugger[14], Beatrix Naton[8], Ildikó Racz[17], Birgit Rathkolb[8, 18], Jan Rozman[8, 20], Anja Schrewe[8, 19], Dirk H. Busch[11], Jochen Graw[3], Boris Ivandic[19], Martin Klingenspor[20], Thomas Klopstock[7], Markus Ollert[12], Leticia Quintanilla-Martinez[14, 29], Holger Schulz[13], Eckhard Wolf[18], Wolfgang Wurst[3, 21], Andreas Zimmer[17], Simon E. Fisher[10], Rudolf Morgenstern[6], Thomas Arendt[4], Martin Hrabé de Angelis[8, 22], Julia Fischer[2], Johannes Schwarz[23, 24] and Svante Pääbo[1]

A Humanized Version of Foxp2 Affects Cortico-Basal Ganglia Circuits in Mice

It has been proposed that two amino acid substitutions in the transcription factor FOXP2 have been positively selected during human evolution due to effects on aspects of speech and language. Here, we introduce these substitutions into the endogenous Foxp2 gene of mice.

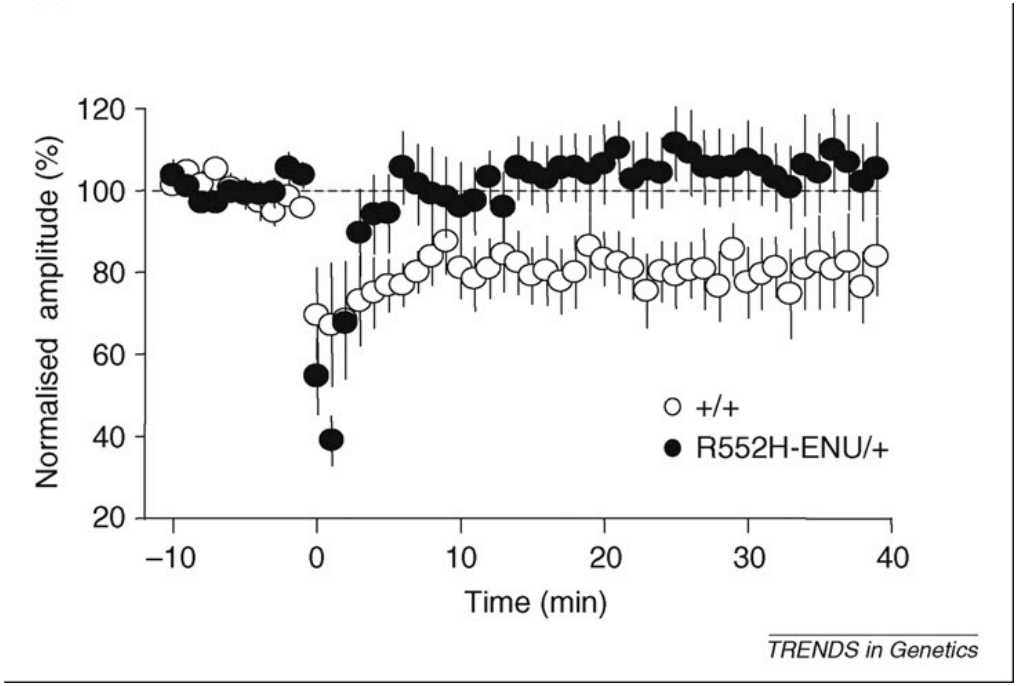
Although these mice are generally healthy, they have qualitatively different ultrasonic vocalizations, decreased exploratory behavior and decreased dopamine concentrations in the brain suggesting that the humanized Foxp2 allele affects basal ganglia.

In the striatum, a part of the basal ganglia affected in humans with a speech deficit due to a nonfunctional FOXP2 allele, we find that medium spiny neurons have increased dendrite lengths and increased synaptic plasticity.

Since mice carrying one nonfunctional Foxp2 allele show opposite effects, this suggests that alterations in cortico-basal ganglia circuits might have been important for the evolution of speech and language in humans.

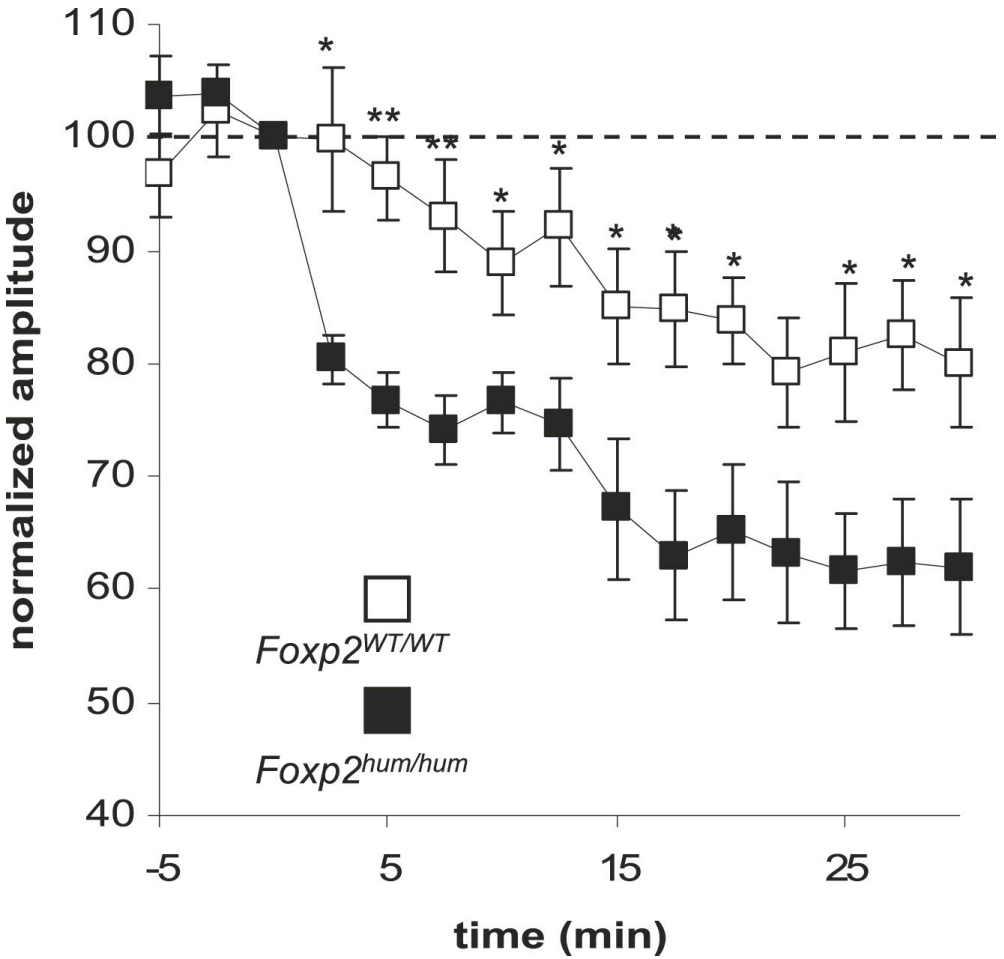
Mouse models: heterozygous null mutation

summary long-term depression data in medium spiny neurons in the striatum



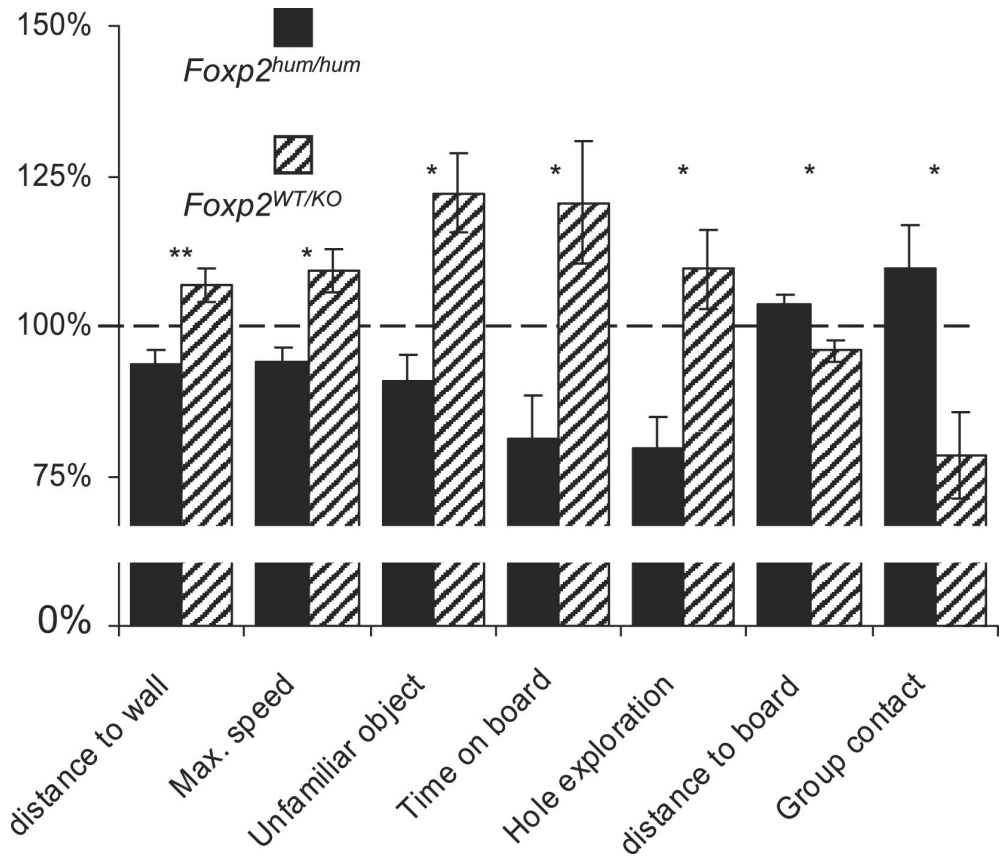
Foxp2^{hum} carries the two aminoacid substitutions characteristic of humans:

It increases Long-Term Depression in Medium Spiny Neurons of the striatum

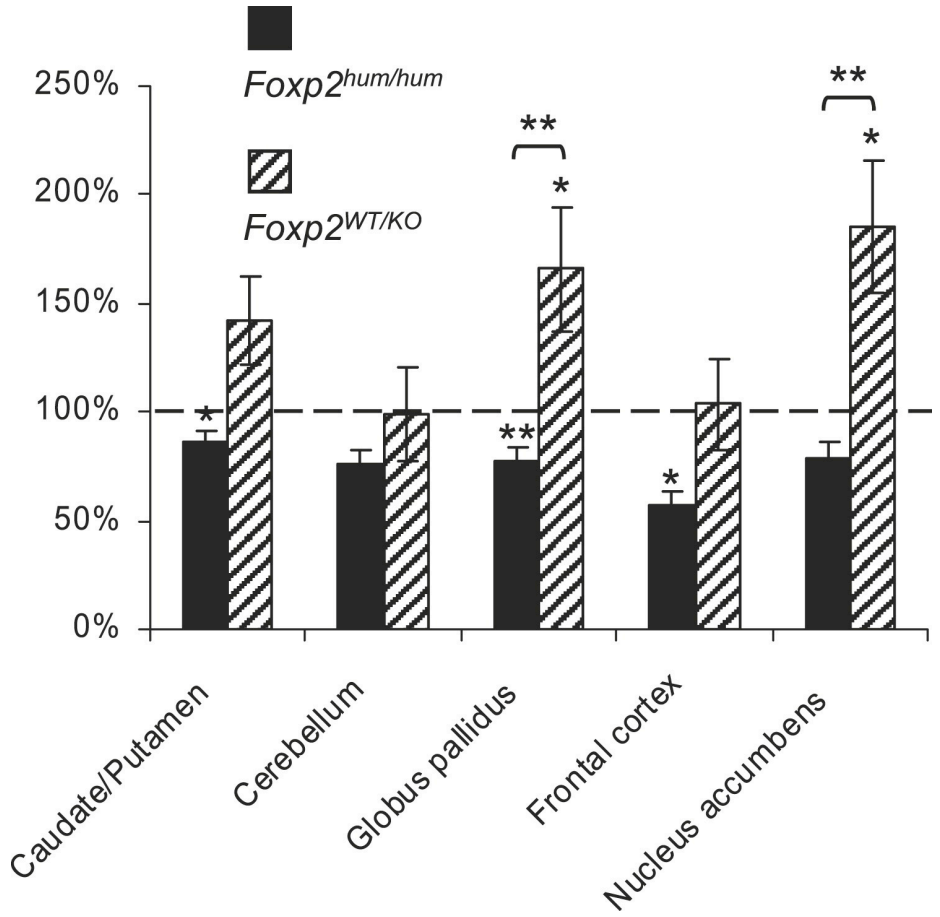


This is the opposite effect of the heterozygous null mutation!

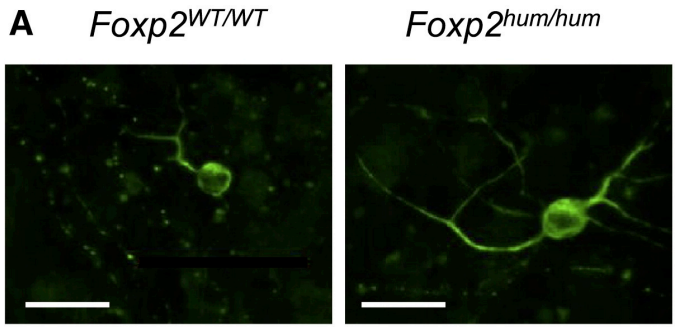
Different Exploratory Behavior of *Foxp2$^{hum/hum}$ and Foxp2$^{wt/ko}$ Mice*

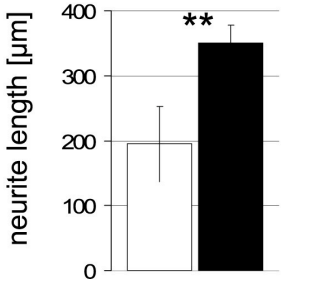


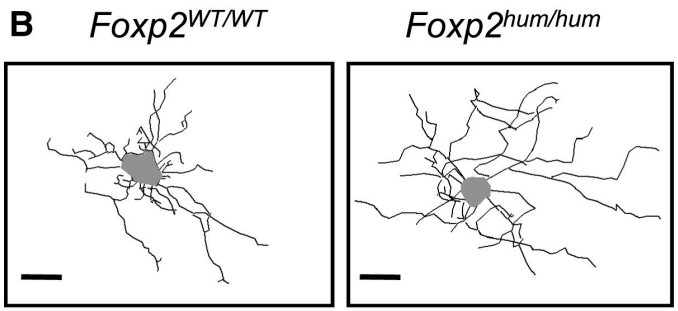
Brain Dopamine Concentrations in *Foxp2$^{hum/hum}$* and *Foxp2$^{wt/ko}$* Mice

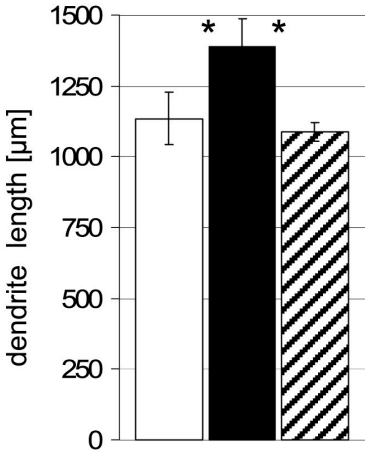


Foxp2^{hum} Increases the Length of Dendritic Trees

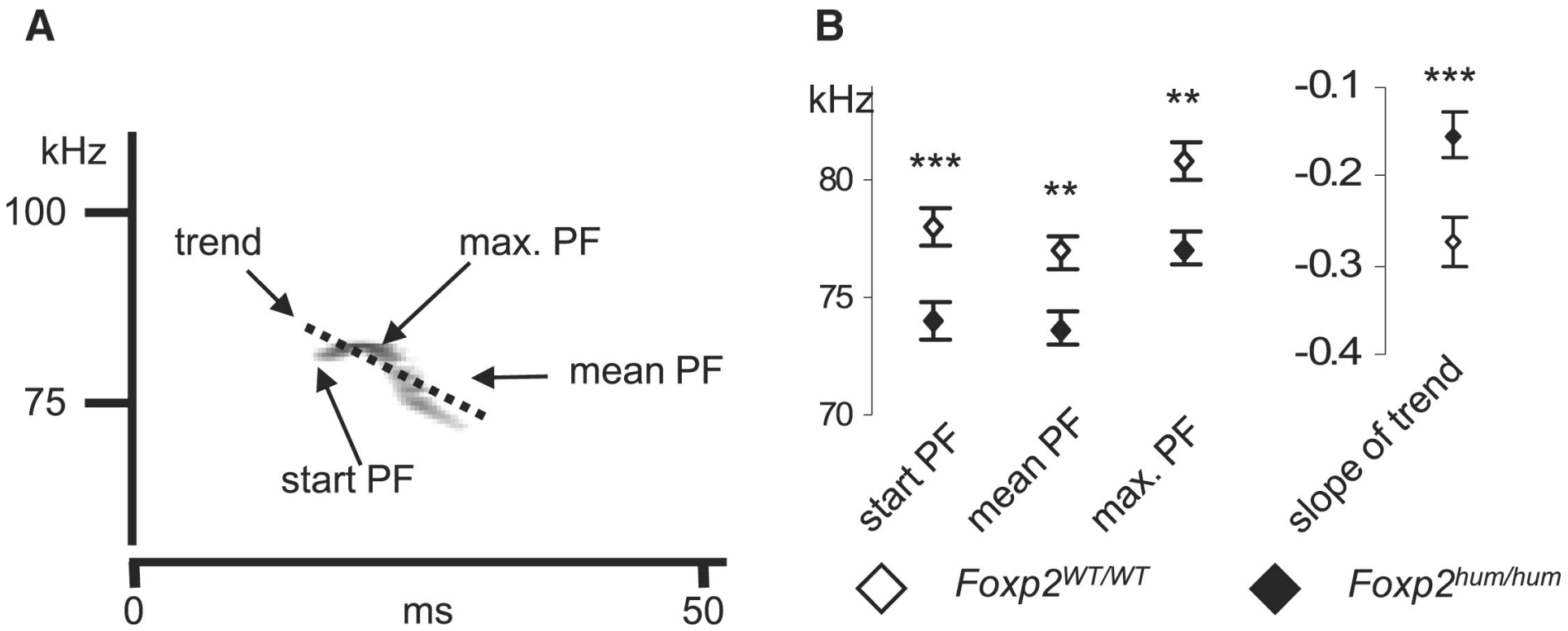








Foxp2^{hum} Affects the Structure of Pup Isolation Calls



Dr. Wolfgang Enard Video

http://www.youtube.com/watch?v=k27DfgKGVp8

Thank you for your attention!

End of lecture II