The Molecular Genetics of Language

Dr. Sonja C Vernes
Language & Genetics Department
LSA Summer School, Ann Arbor, 2013

Overview

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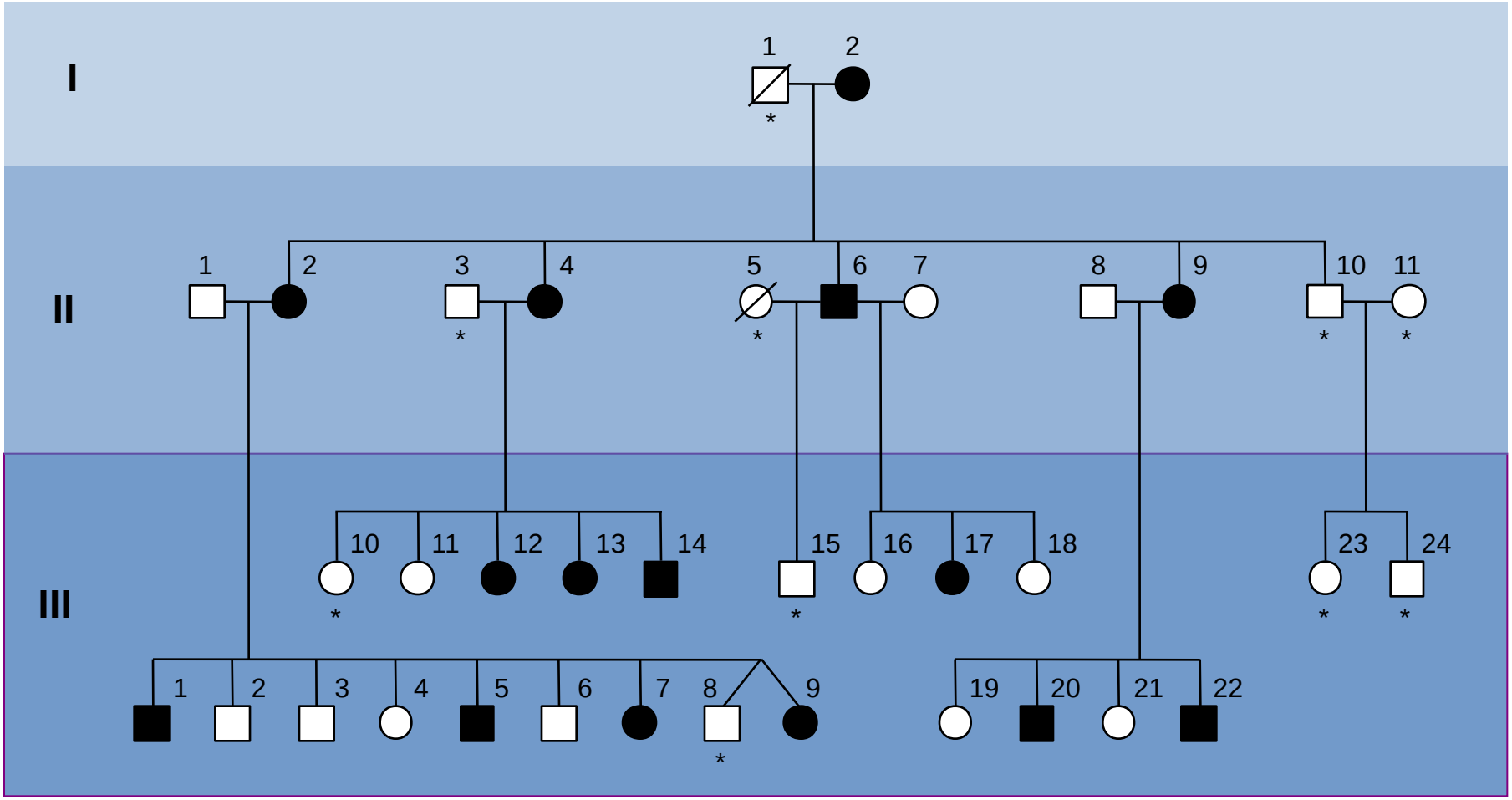
Part I – The genetics of language – finding the genes

Part II – FOXP2: a case study

Part III – Finding new genes involved in language

The KE family



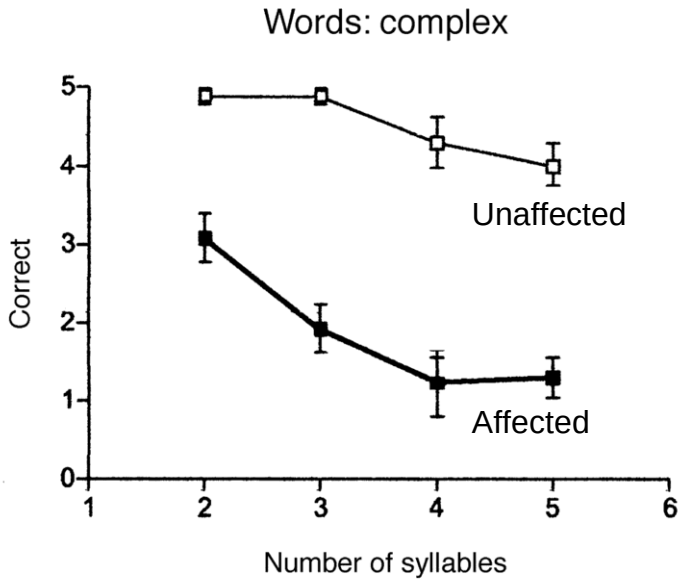
● ■ = speech and language disorder

Lai, Fisher, et al,. Nature, 2001

KE Family phenotype

Verbal Language

Orofacial dyspraxia – deficits in motor control during articulation



Watkins et al. Brain, 2002

KE Family phenotype

Deficits in Verbal Language

Orofacial dyspraxia – deficits in motor control during articulation

KE Family phenotype

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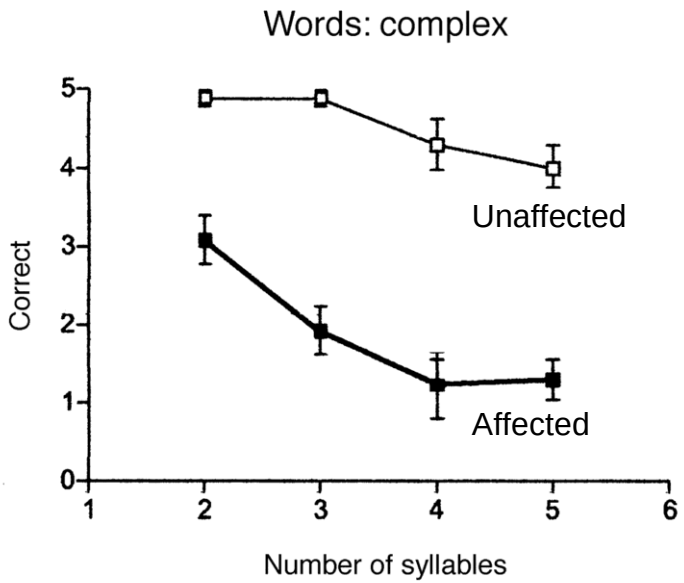
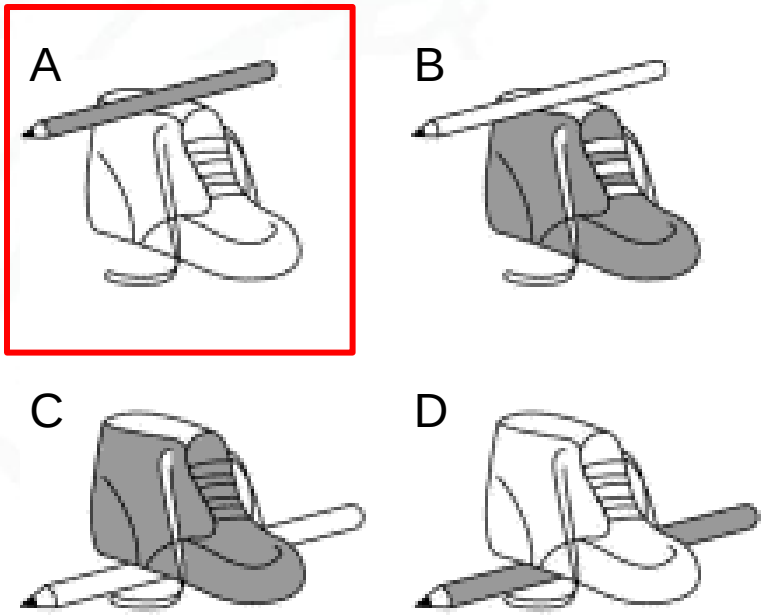
Verbal Language

Orofacial dyspraxia – deficits in motor control during articulation



Deficit in receptive/expressive language

Impaired linguistic & grammatical processing



"The pencil on the shoe is grey"

Watkins et al. Brain, 2002

KE Family phenotype

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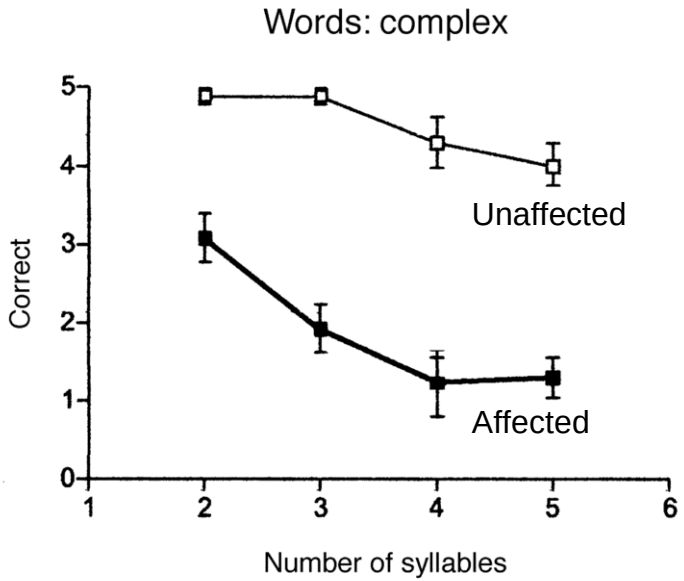
Verbal Language

Orofacial dyspraxia – deficits in motor control during articulation



Deficit in receptive/expressive language

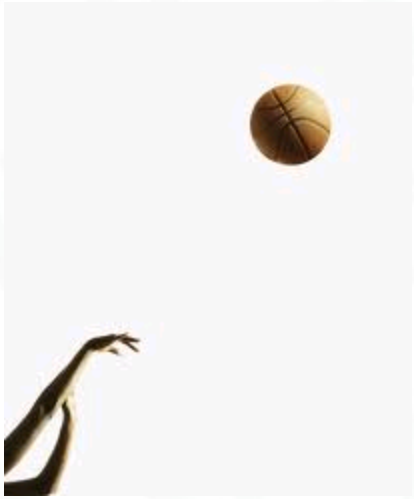
Impaired linguistic & grammatical processing

- Functional magnetic resonance imaging (fMRI)
- During language tasks

Covert Verb Generation Task

Ball

'non-vocal'



'throw'

'catch'

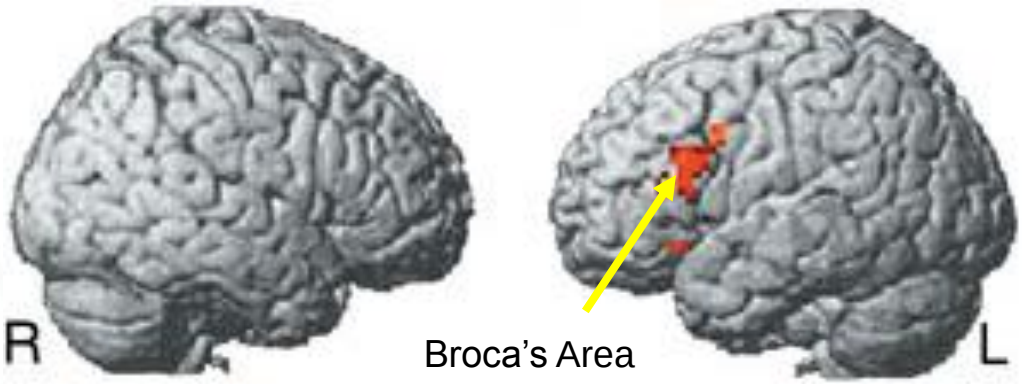
'bounce'

KE Family phenotype

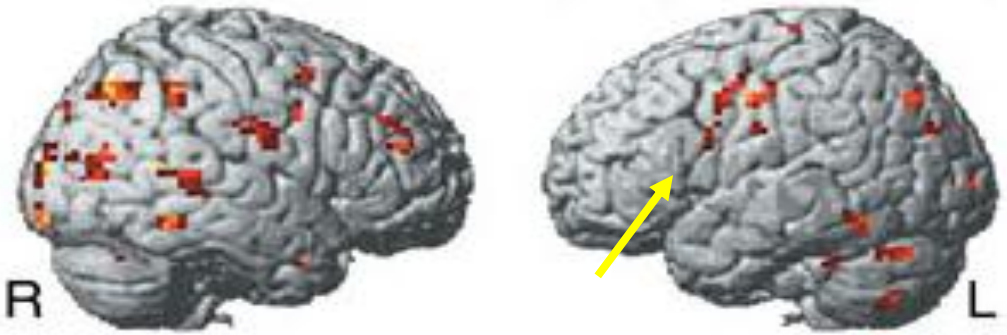
Deficit in receptive/expressive language

Covert verb generation task:

Unaffected group:

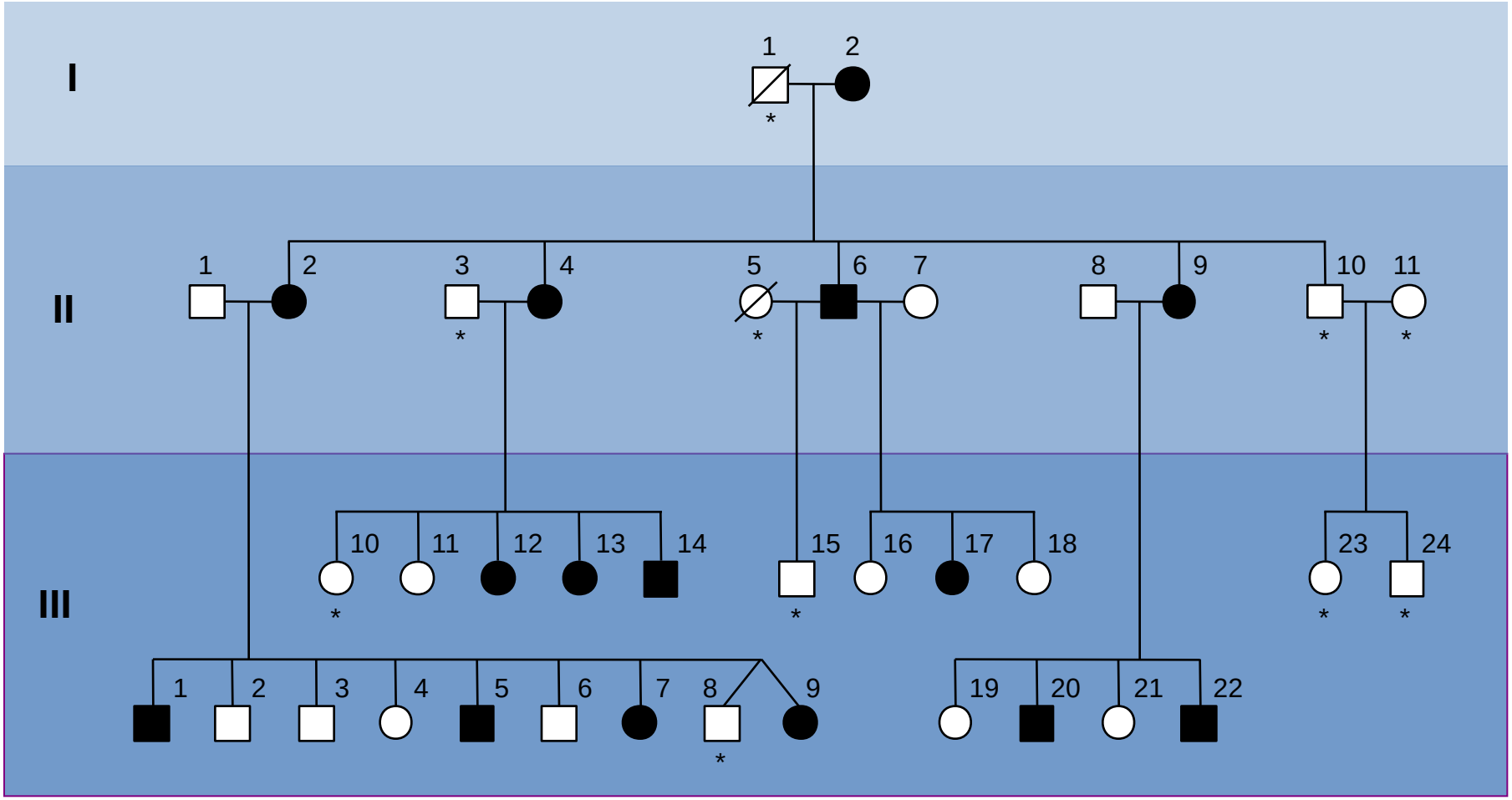


Affected group:



Liegeois et al, Nat Neurosci 2003

The KE family – mapping the gene

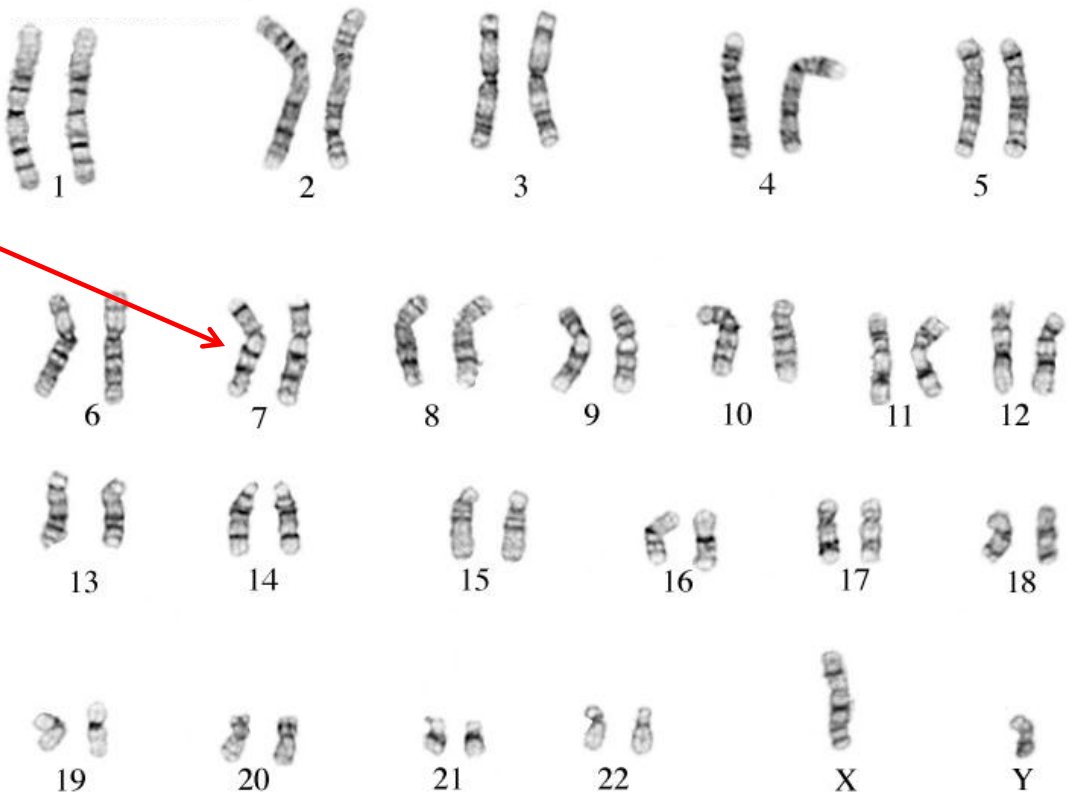


● ■ = speech/language disorder

Lai, Fisher, et al,. Nature, 2001

The KE family – mapping the gene

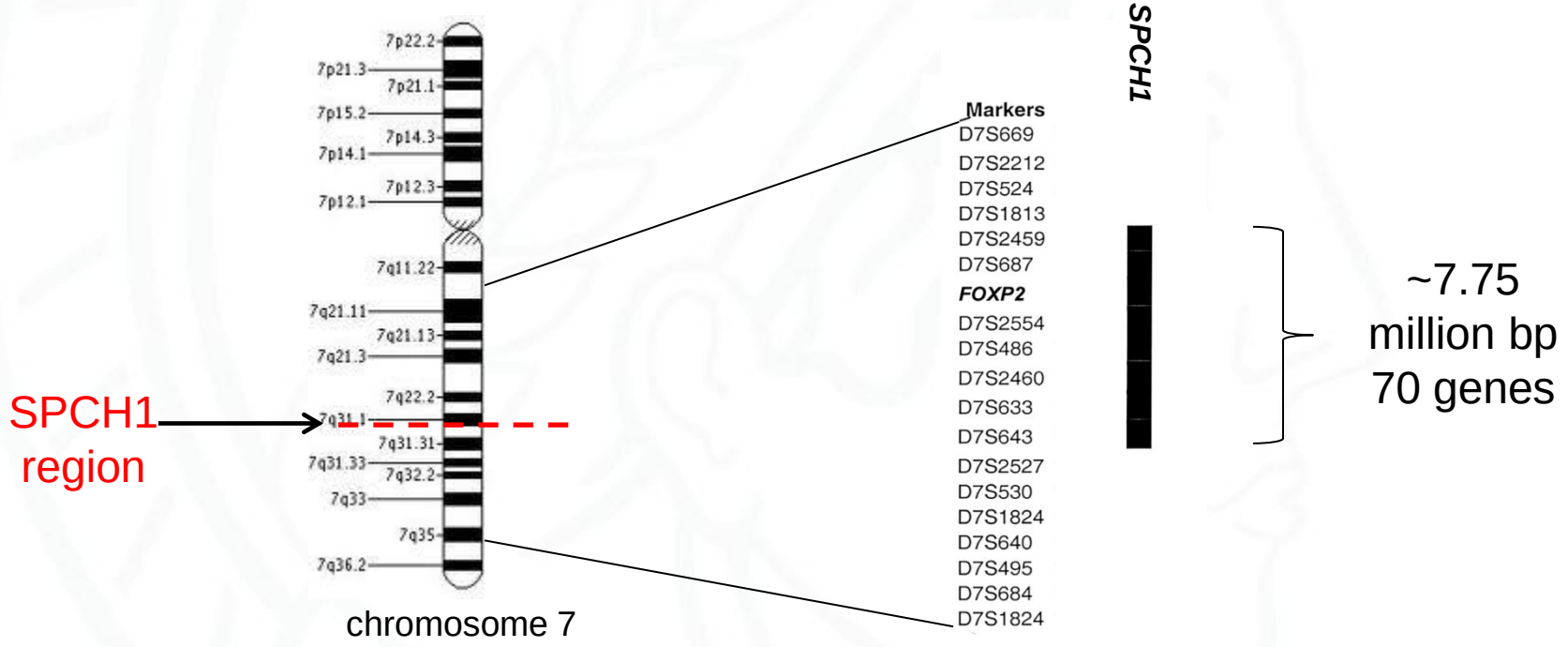
Mapped the disorder to Chr 7



Looking for one change amidst 3 billion base pairs!
Narrowed the search to *only* 159 million base pairs...

…getting closer

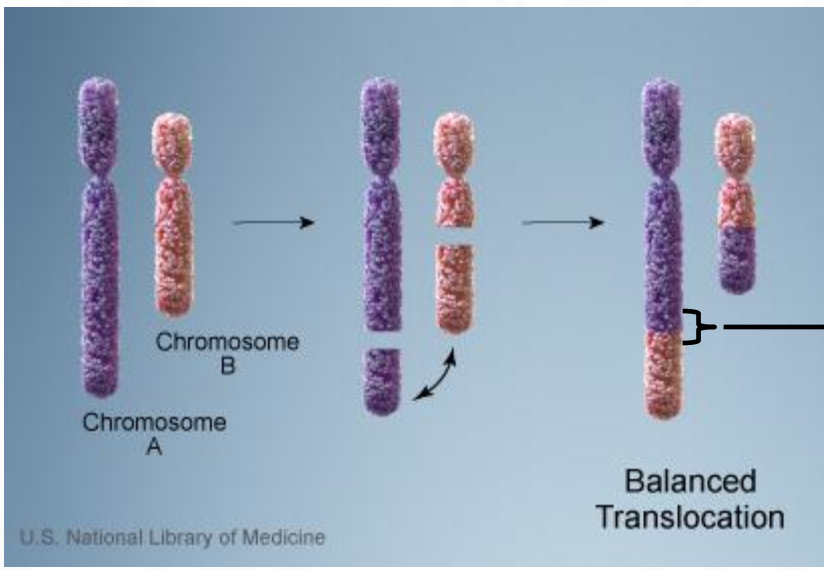
Linkage mapped the disorder to the ‘SPCH1’ region

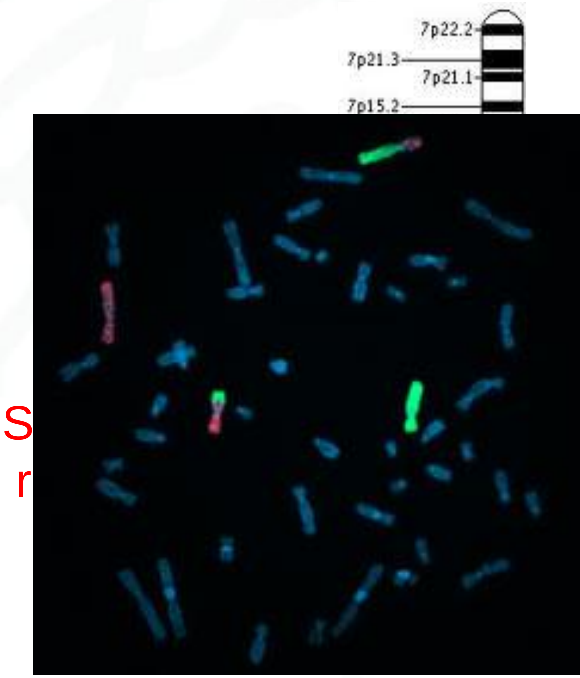


Sometimes science is about getting really, really lucky...

An unrelated individual ('patient CS') with the same speech and language disorder

...and a breakage of chromosome 7





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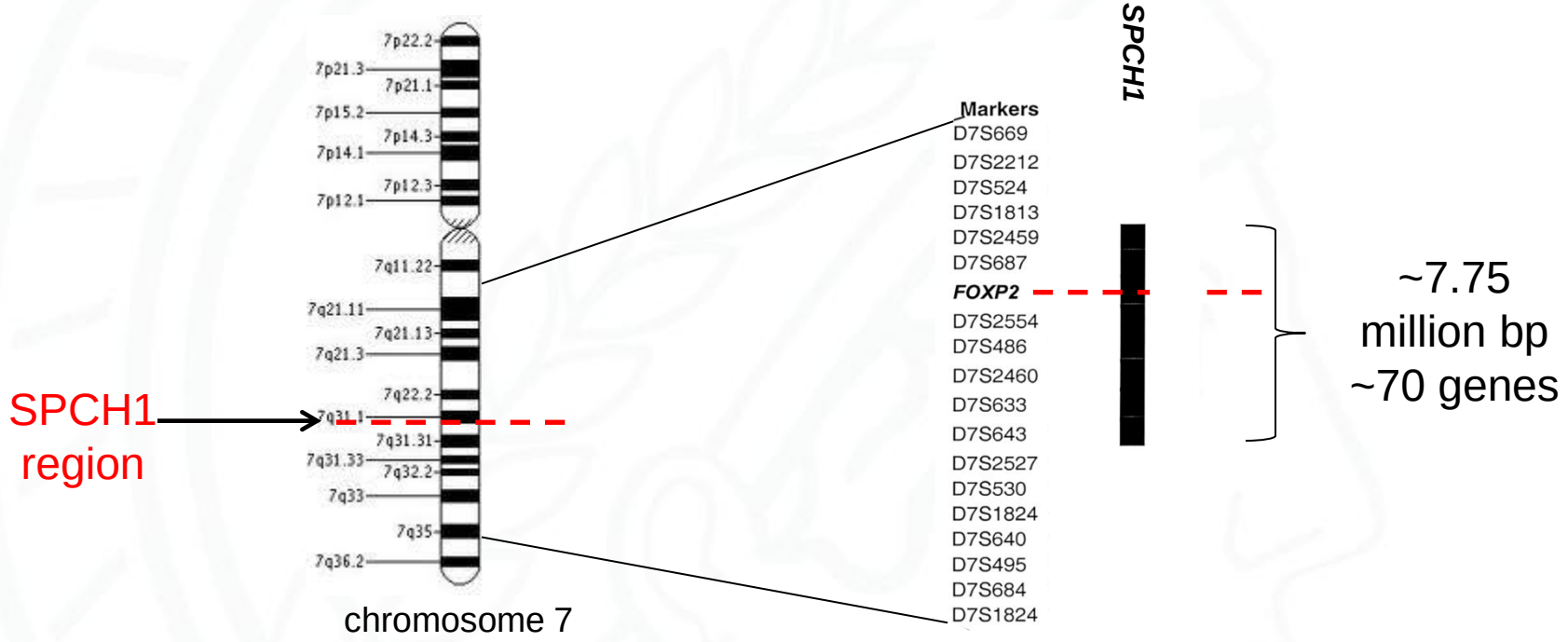
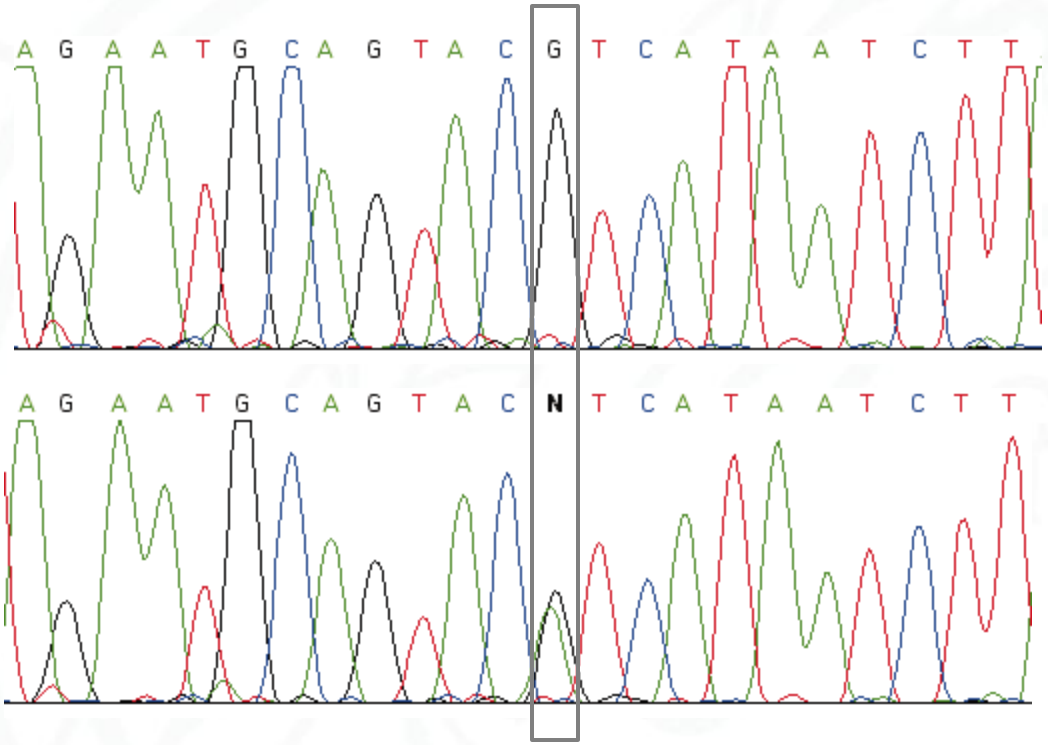
Finding the gene...



Looks like FOXP2 is the responsible gene. Now to prove it...

Finding the gene...and the mutation

DNA:



Normal

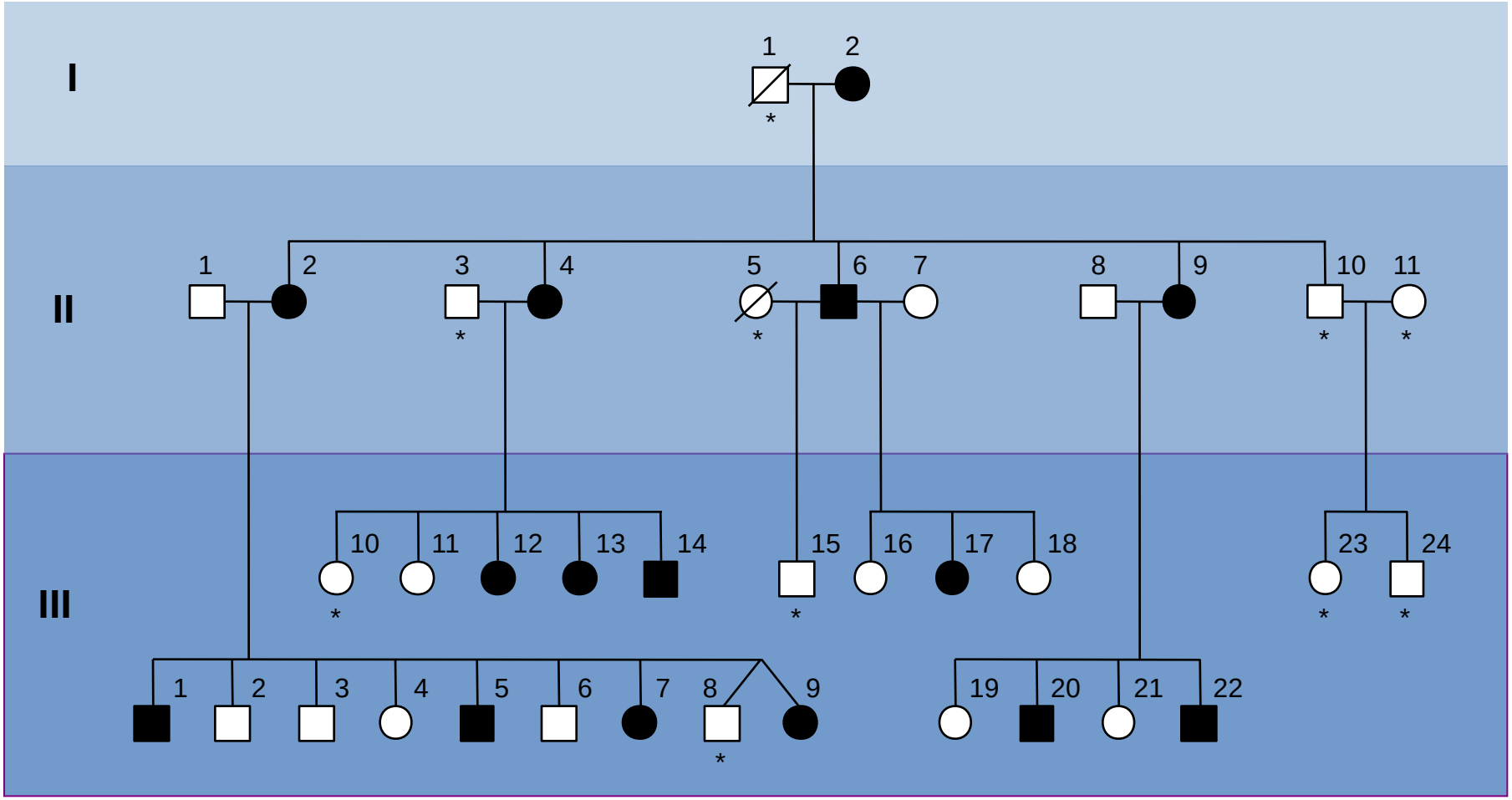
Affected

PROTEIN:

...NAVRHNLSL... Normal

...NAV**H**HNLSL... Affected

The KE family



● ■ = speech/language disorder & FOXP2 mutation

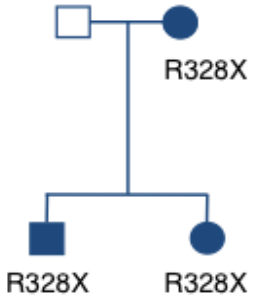
Lai, Fisher, et al,. Nature, 2001

FOXP2 mutations cause S&L disorders

•AD Pedigree

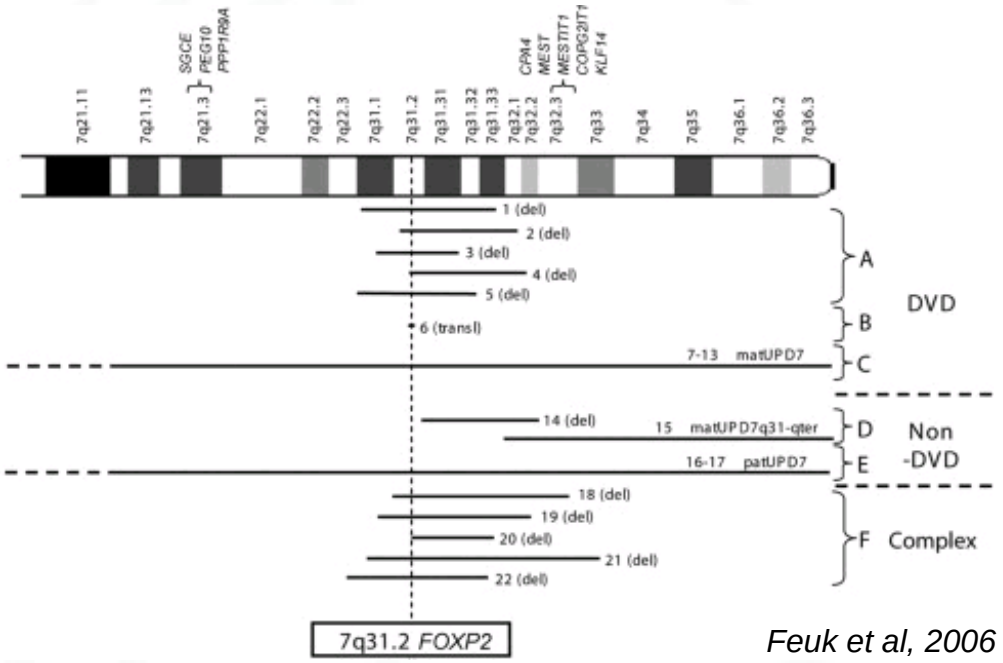
MacDermot et al, 2005

-Arginine →Stop (R328X)



•Deletions/rearrangements of FOXP2 locus

Feuk et al, 2006;
Shriberg et al, 2006;
Lennon et al, 2007;
Palka et al, 2011;
Zillina et al, 2011;
Rice et al, 2011 etc



Feuk et al, 2006

ALL patients have one normal copy of FOXP2

FOXP2 – the gene involved in language

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Scientists find gene for human language

By Andrew Moran
Nov 11, 2009 in Science

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Scientists have discovered a mutated gene for why humans have language and chimpanzees, our closest relative, do not. Only one gene is involved in the important barrier.

Chimpanzees do not speak but humans certainly do (maybe too much sometimes) and scientists

TOP NEW

Home / News / Foxp2 – the 'language protein' which makes women talk more

Foxp2 – the 'language protein' which makes women talk more

0

Feb 21, 2013 at 8:02 AM
Author : India.com Health

Tags: Foxp2, Mice, Psychology, Talking, Women, Women tlaking

Like 23 Tweet 6 +1 0

A recent study finally reveals why women talk more, much more than men! Turns out they've higher levels of a language protein called Foxp2 which plays an important role in language development in human beings. This might explain why women on average speak 13,000 more words than men in day!

Researchers also did tests on baby rats where the sex difference in Foxp2 levels is reversed, with young male rates normally having more. Separated from their mothers the males made more noise and were retrieved first.

theguardian

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The Twitter gene

Communication on Twitter – or indeed anywhere – would be impossible without FOXP2

*This is the first in a series of posts by **Anna Perman** in which she sifts through the alphabetic spaghetti of genetics to identify her favourite genes*

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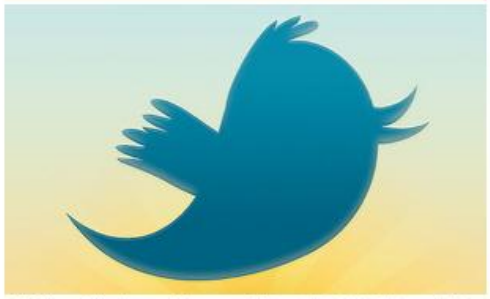


FOXP2 is crucial for language in humans and for tweeting in birds. Photograph: Alamy

Posted by
Anna Perman
Monday 17 October 2011
12.25 BST
guardian.co.uk
Jump to comments (16)

Article history

Science
Genetics · Language · Biology

Technology
Twitter

End of Part I

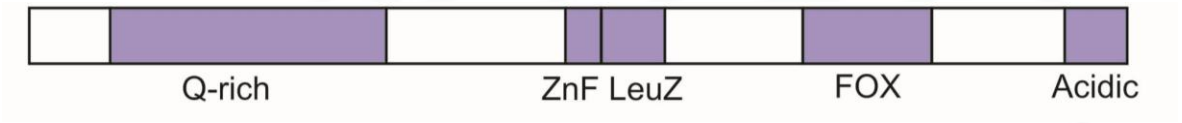
Questions??

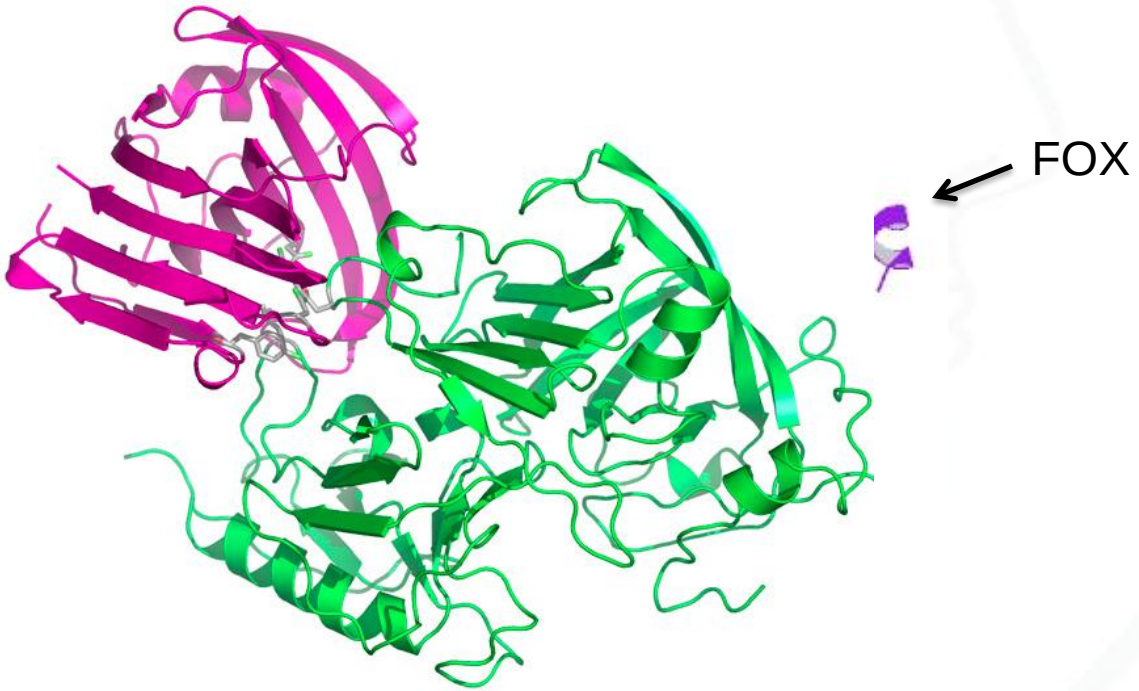
What is a FOXP2?

FOXP2 mutations are found in speech and language disorder patients

What does FOXP2 encode?

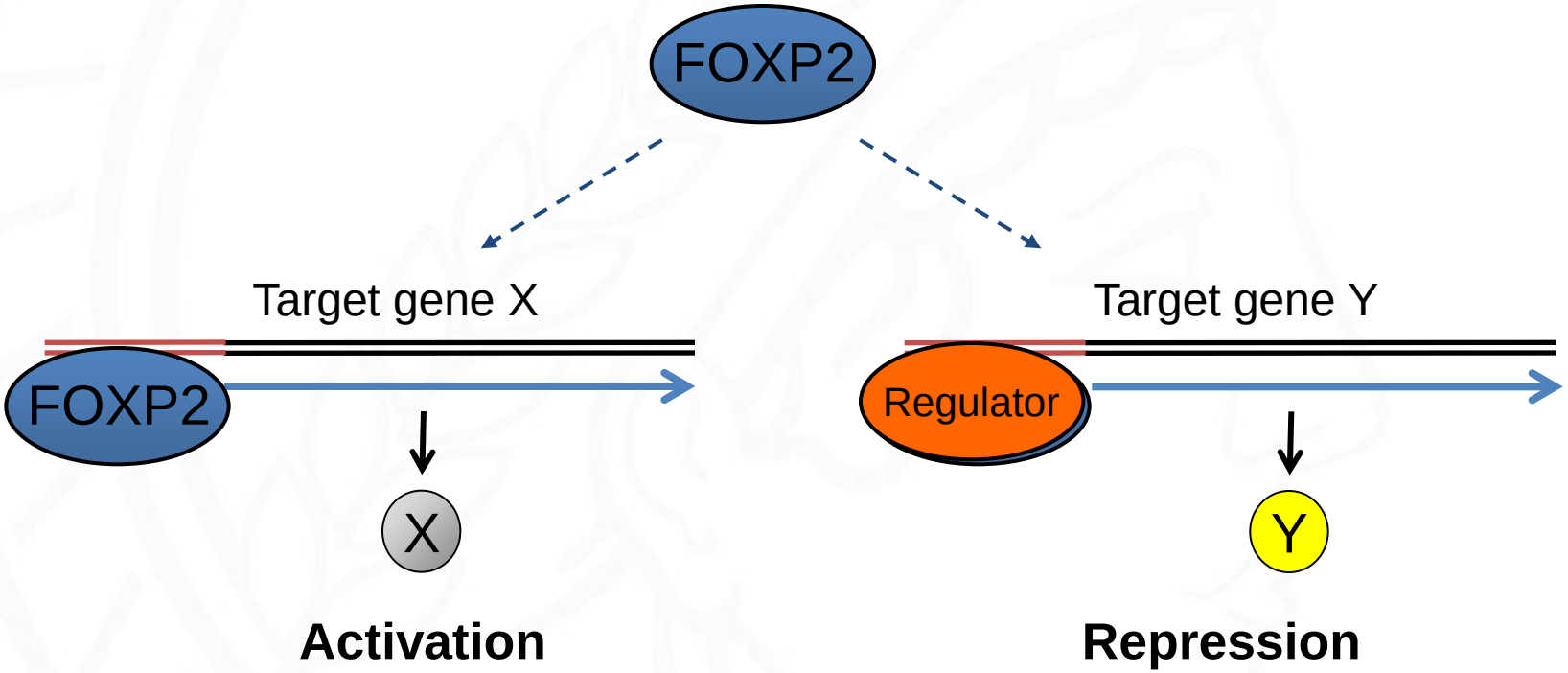
Normal FOXP2





What does FOXP2 do?

FOXP2 regulates other genes



Understanding FOXP2 function

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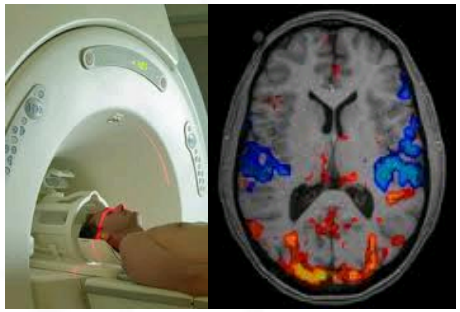
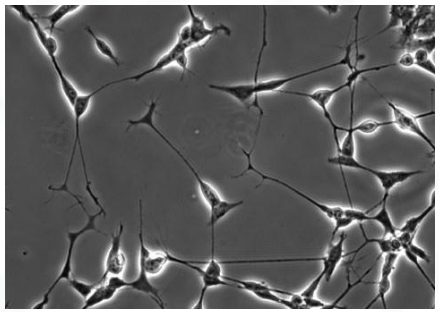
Experimenting in human systems

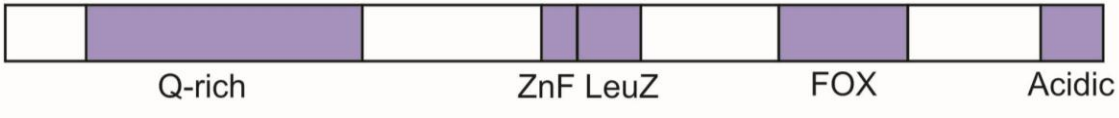




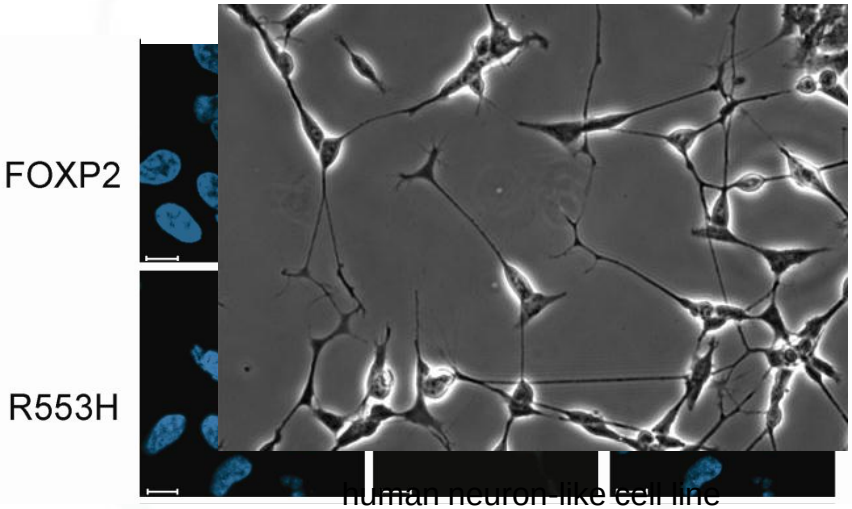
human neuron-like cell line

Understanding FOXP2 function

Normal FOXP2



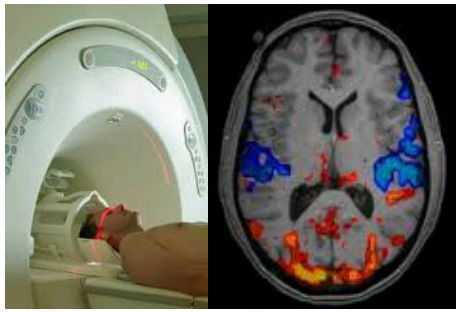
KE Affected

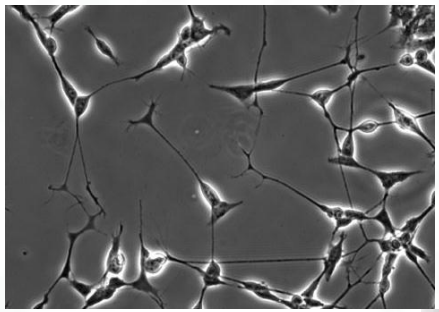


Vernes et al, HMG, 2006

Understanding FOXP2 function

Experimenting in human systems





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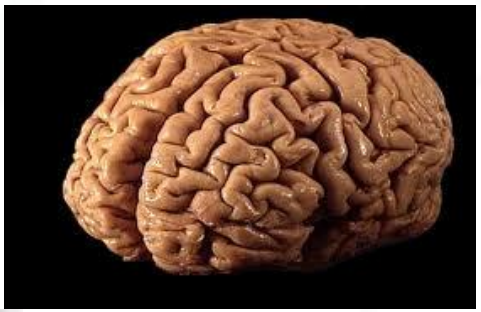


Using mice to study language

Mice squeak, but they are no good at grammar

Model Foxp2 function in the mouse brain

- complex developmental program
- heterogenous cellular/signalling environment
- language likely evolved by adapting existing brain structures

Human/mouse FOXP2:

- proteins are almost identical
- found in the same brain regions

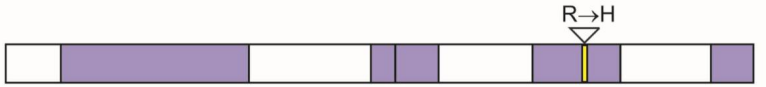
Modelling Foxp2 in the mouse

- Foxp2 knockout mouse
- Foxp2.R552H ('KE mouse;)

  -carries the same mutation found in the KE family

Normal mouse:

R552H (KE) mouse:



Foxp2 knockout mouse

No Foxp2 at all during development

- Post-natal lethality
- Impaired vocalisations
- Severe generalized motor impairment

The ‘KE’ mouse

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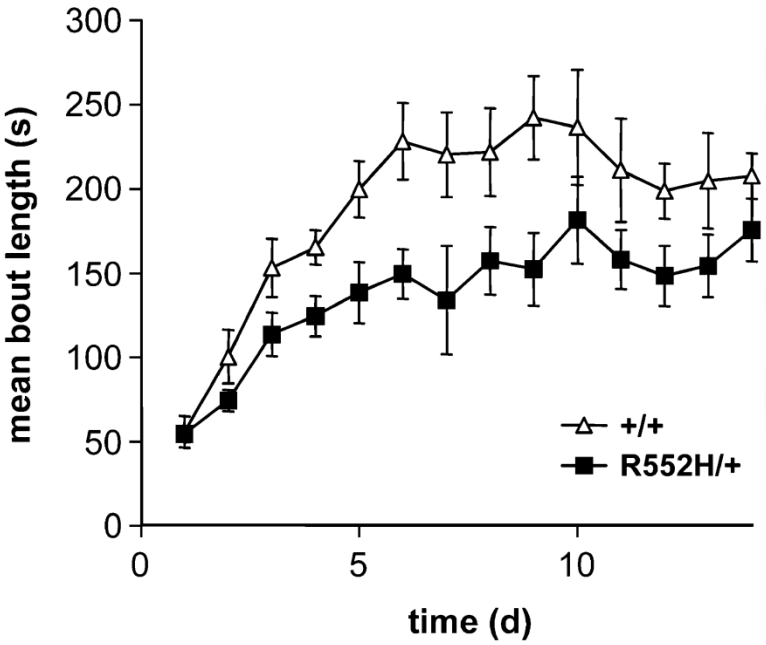
- One normal copy of Foxp2 and one ‘KE’ copy
- Mostly phenotypically normal, including normal vocalisations

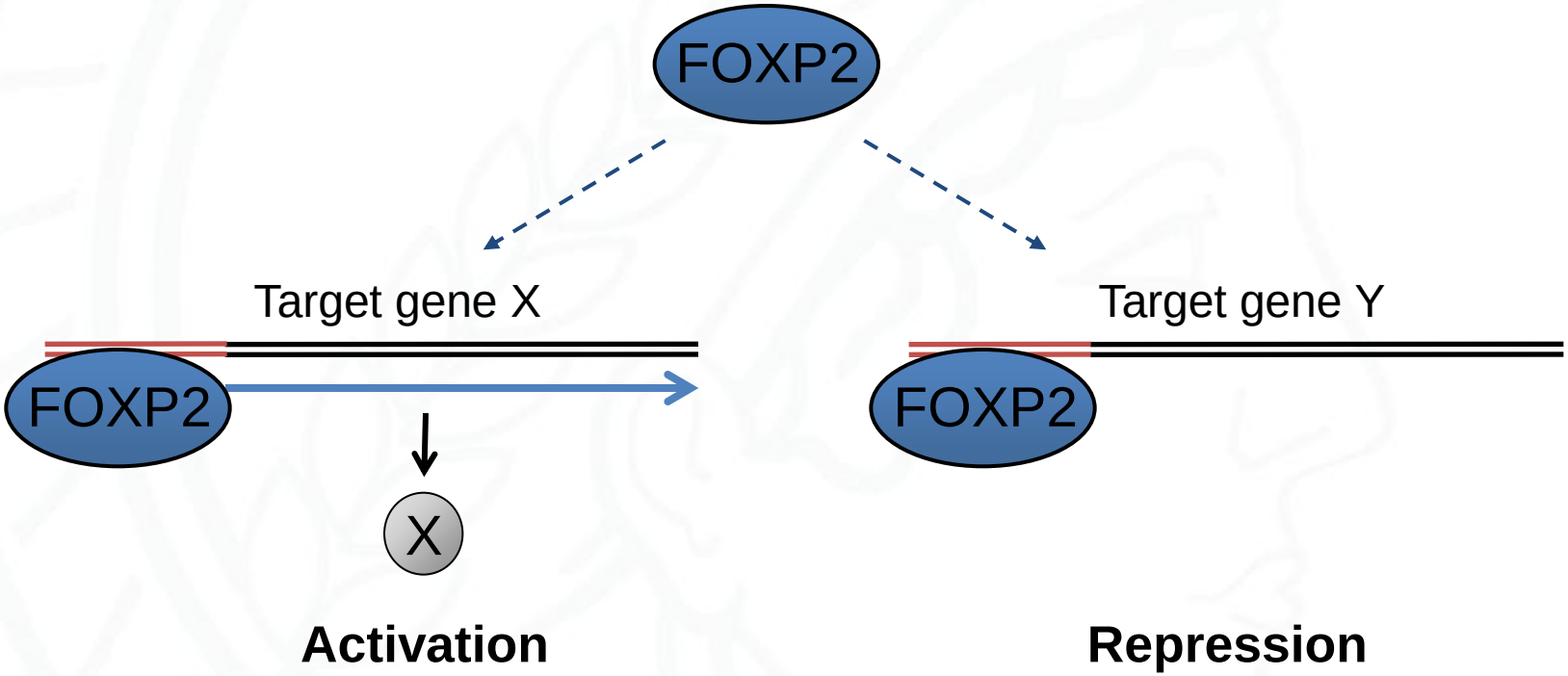
Impaired motor learning (rotarod)



Groszer et al., Curr Biol, 2008

What does FOXP2 do in the brain?

FOXP2 regulates other genes



What genes/pathways does it regulate?

Does Foxp2 help neurons connect?

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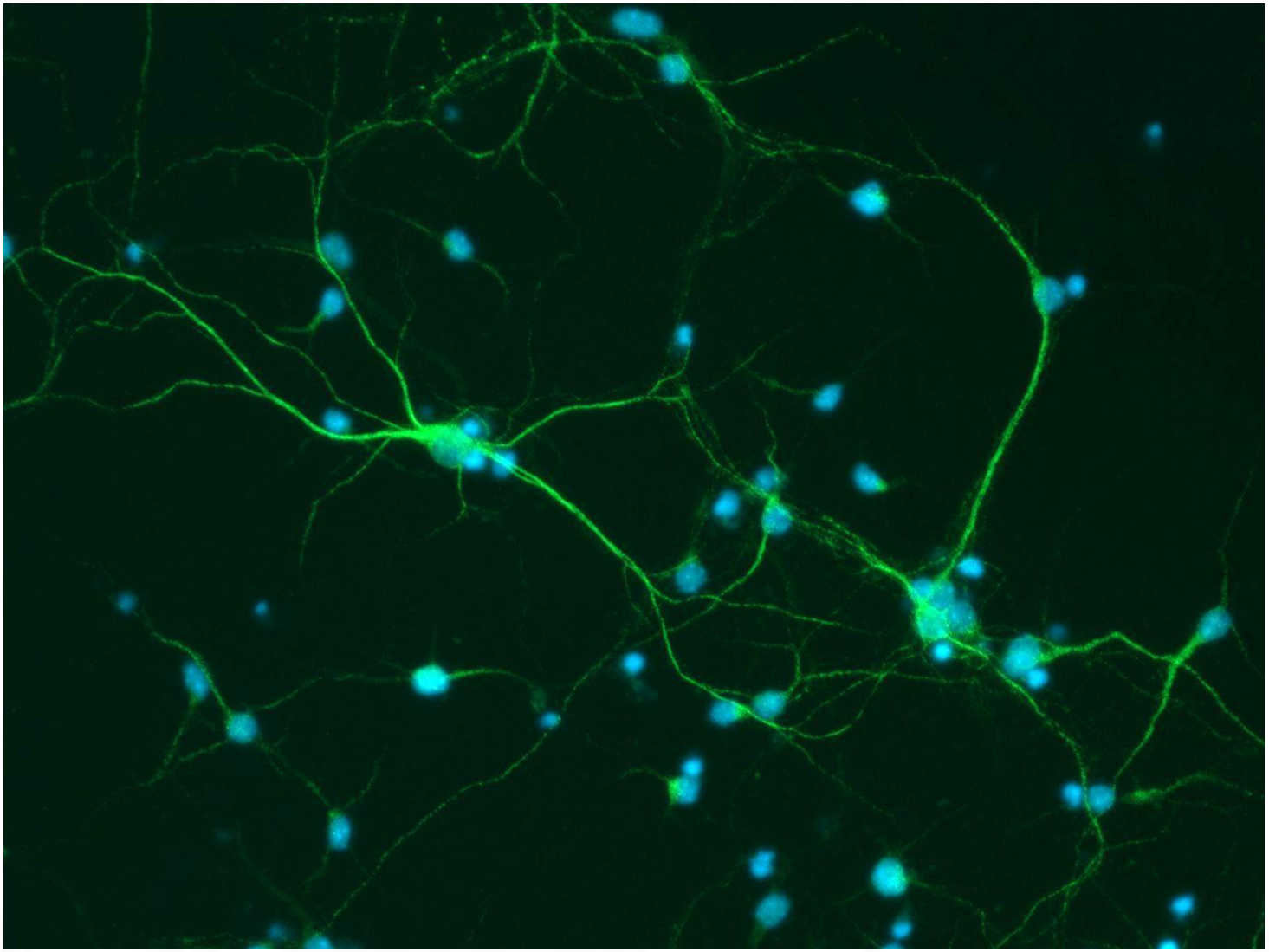
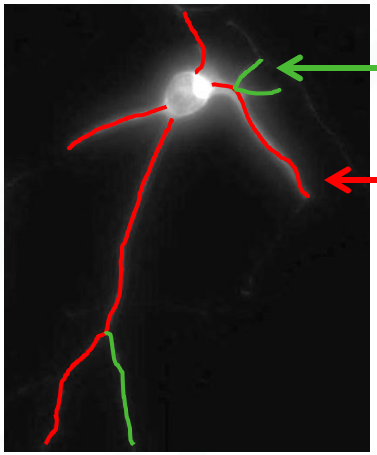


Does Foxp2 help neurons connect?



number branches

number of neurites

Neurite length

Foxp2 is quantitatively affecting the growth of neurites

- may be important for connectivity of language networks in the developing brain

Vernes et al., PLoS Genetics, 2011

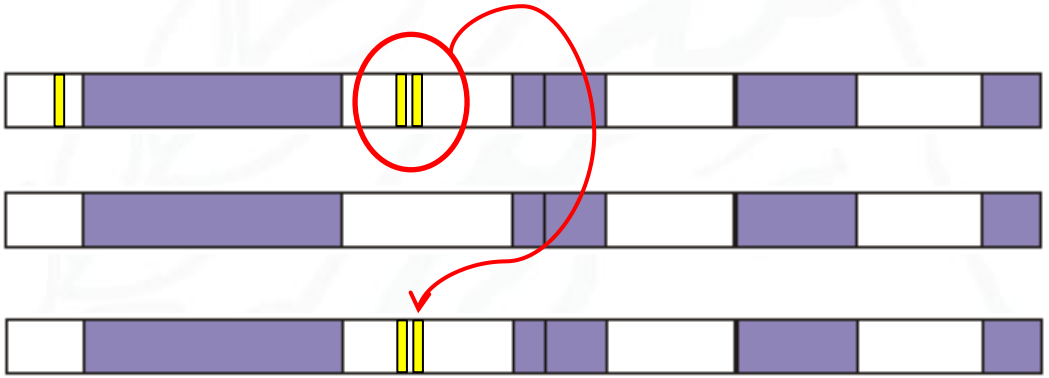
A ‘humanized’ mouse

If FOXP2 is so important for human language, what happens when you put human FOXP2 into a mouse?

Human

Mouse

‘Humanized’ mouse



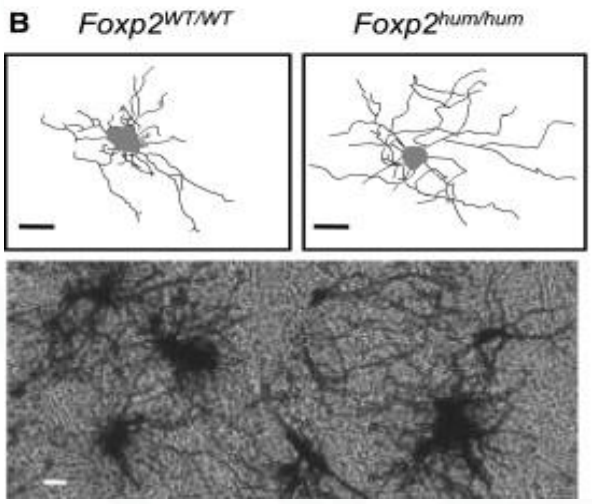
Spoiler: the mice dont start speaking...

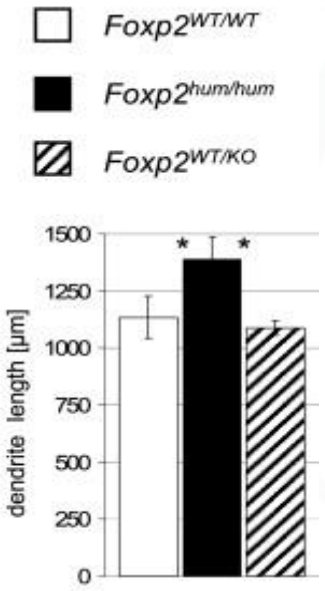
A ‘humanized’ mouse

Battery of ~300 tests, most showed no phenotype at all

- Less exploratory behaviour
- Vocalisation differences (frequency)
- Altered synaptic plasticity
- High dopamine levels in brain
- Connectivity differences

Neurite growth:





Neurites

No Foxp2

Mouse Foxp2

Human FOXP2

Enard et al, Cell, 2009

Models for learned vocalisation

-Songbirds (Zebrafinch) are vocal learners

-only males sing (courtship song)

-song varies amongst birds

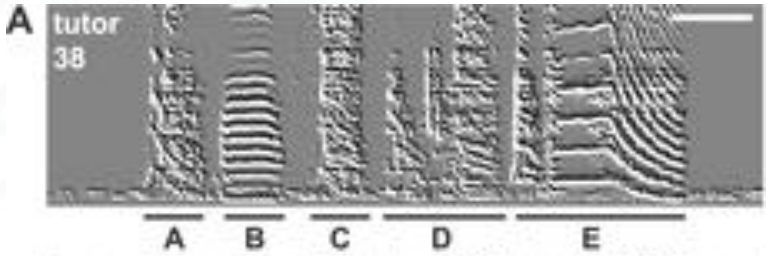
-the individual has a stereotyped song

FoxP2 and learned vocalisations

Zebrafinch courtship song:

-song is learned from a tutor

-pupil matches tutor song VERY closely

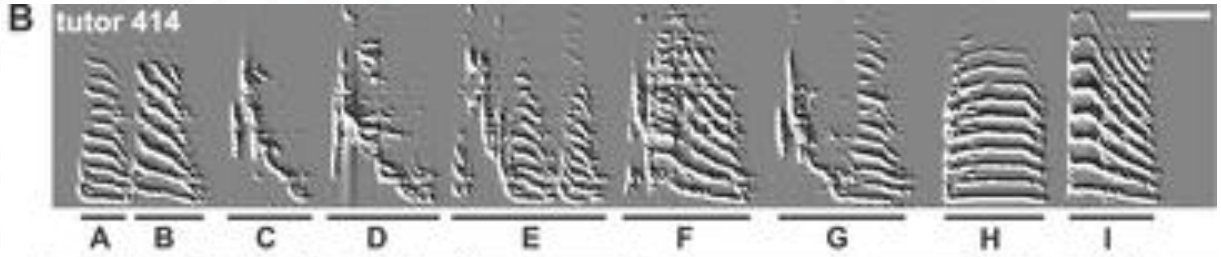


Is FoxP2 involved in learned vocalisations in the songbird?

-Foxp2 knockout in songbird brain

-loss of FoxP2 affects song learning

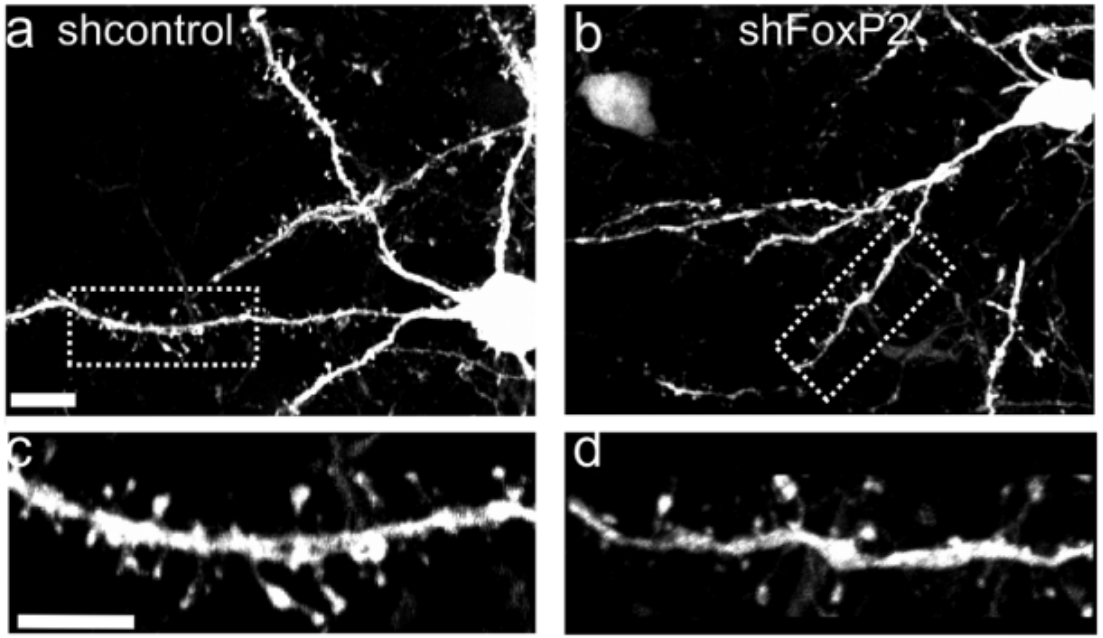
Tutor

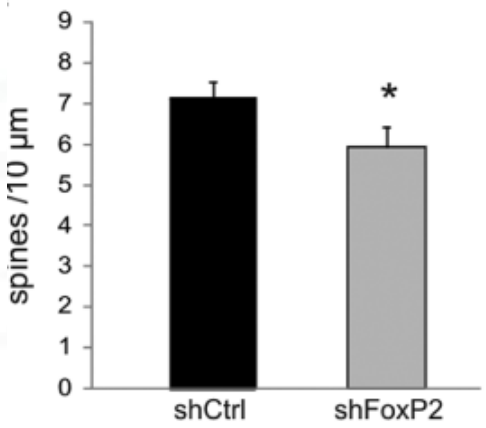


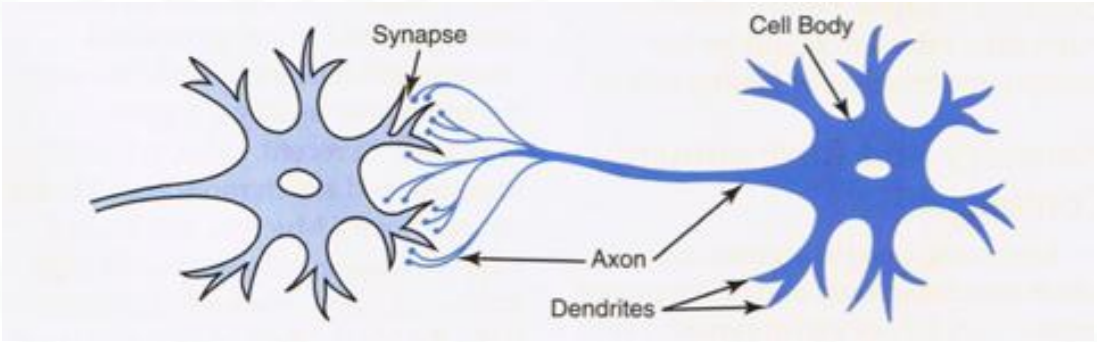
FOXP2 knockout

Haesler et al, PLoS Biol, 2007

Connectivity in the songbird brain







Schultz et al, Genes, Brain, Behav., 2010

Modelling FOXP2

FOXP2:

- Affects connectivity of neural circuits
- Affects plasticity in these circuits

Suggests developmental role in establishing neural circuitry and adult role in modulating the output of circuits

- Is involved in motor control and motor learning
- Is necessary for learned vocalisations

Suggests ancestral role in features that may represent precursors to human speech and language

End of Part II

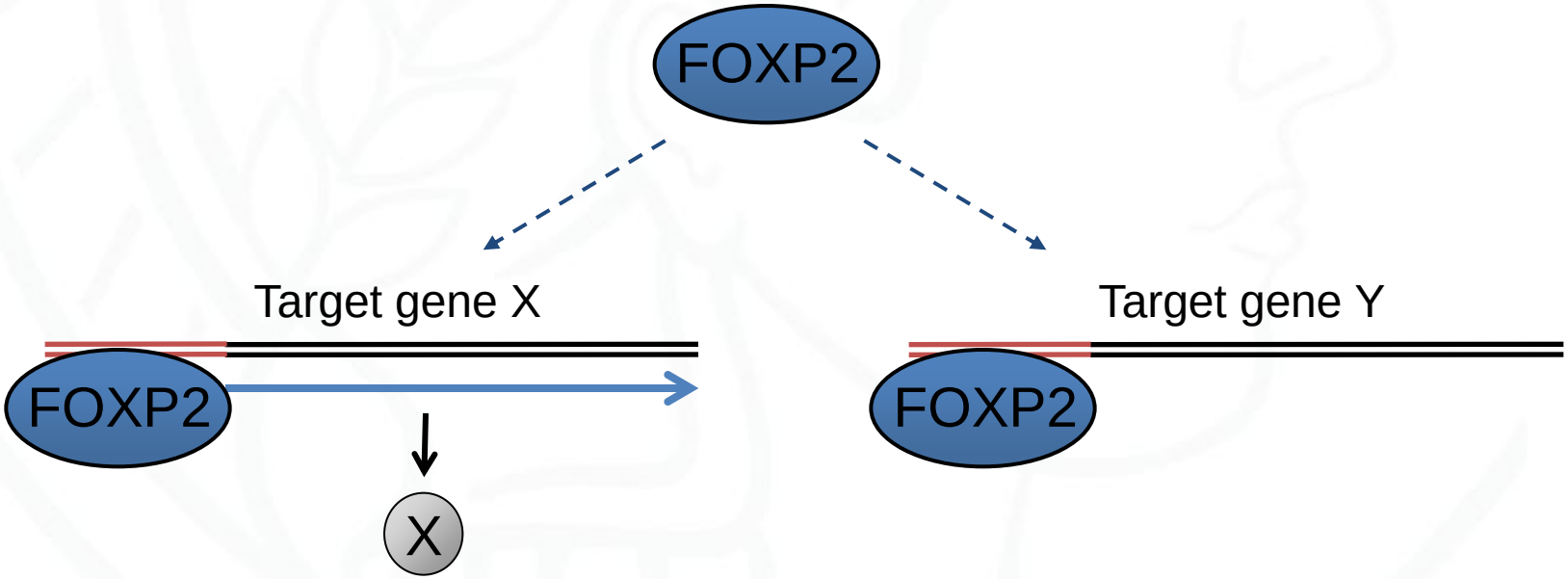
Questions??

FOXP2 as a molecular window into language

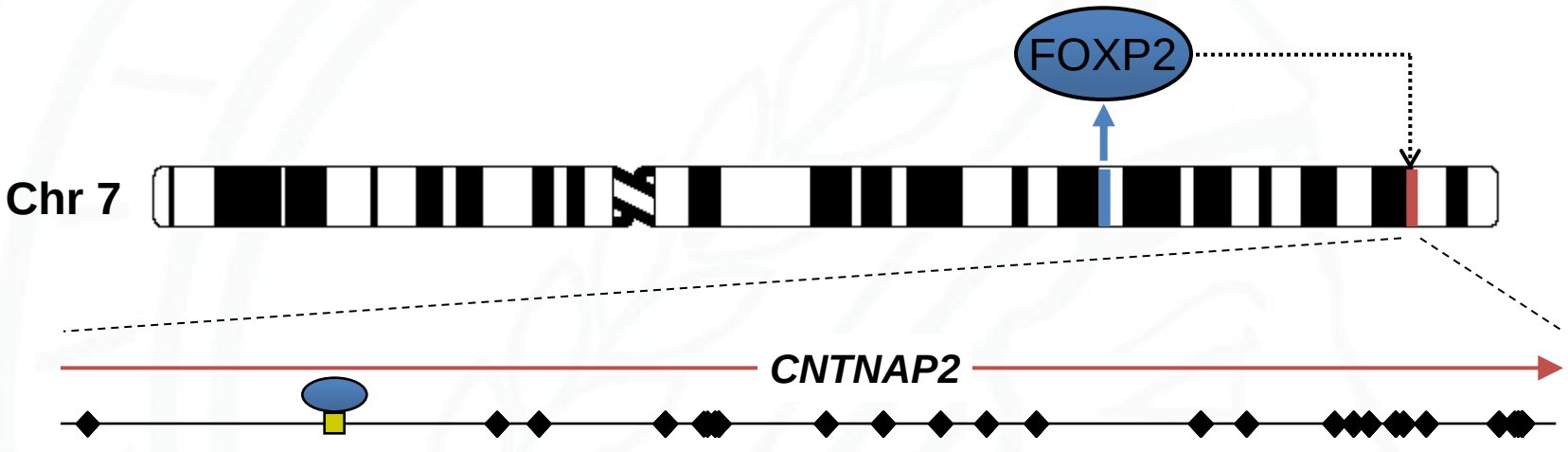
FOXP2 mutations cause rare disorder.

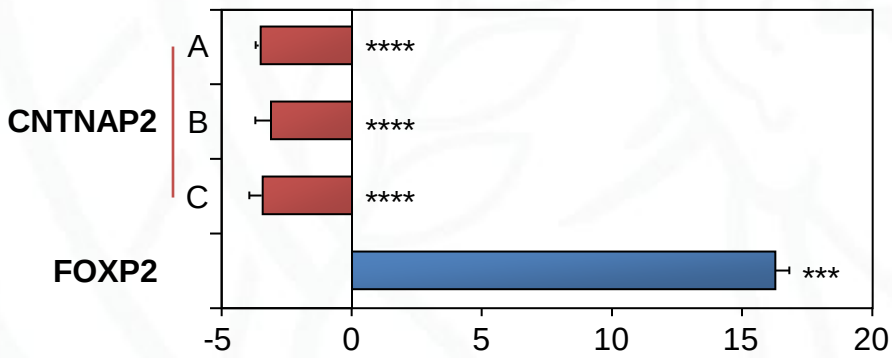
Language is a complex trait & language disorders generally multifactorial genetic causes

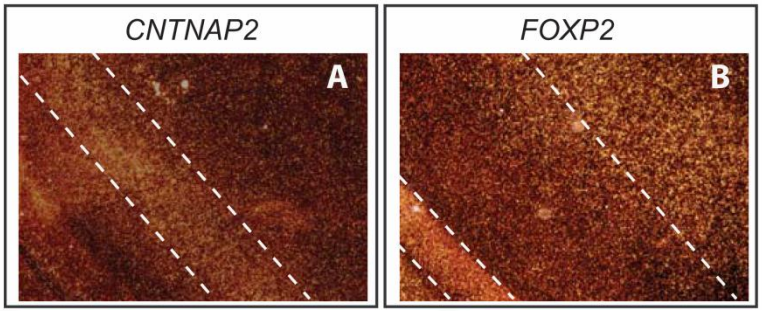
We can use FOXP2 networks to identify new candidate genes for complex language disorder



FOXP2 as a molecular window

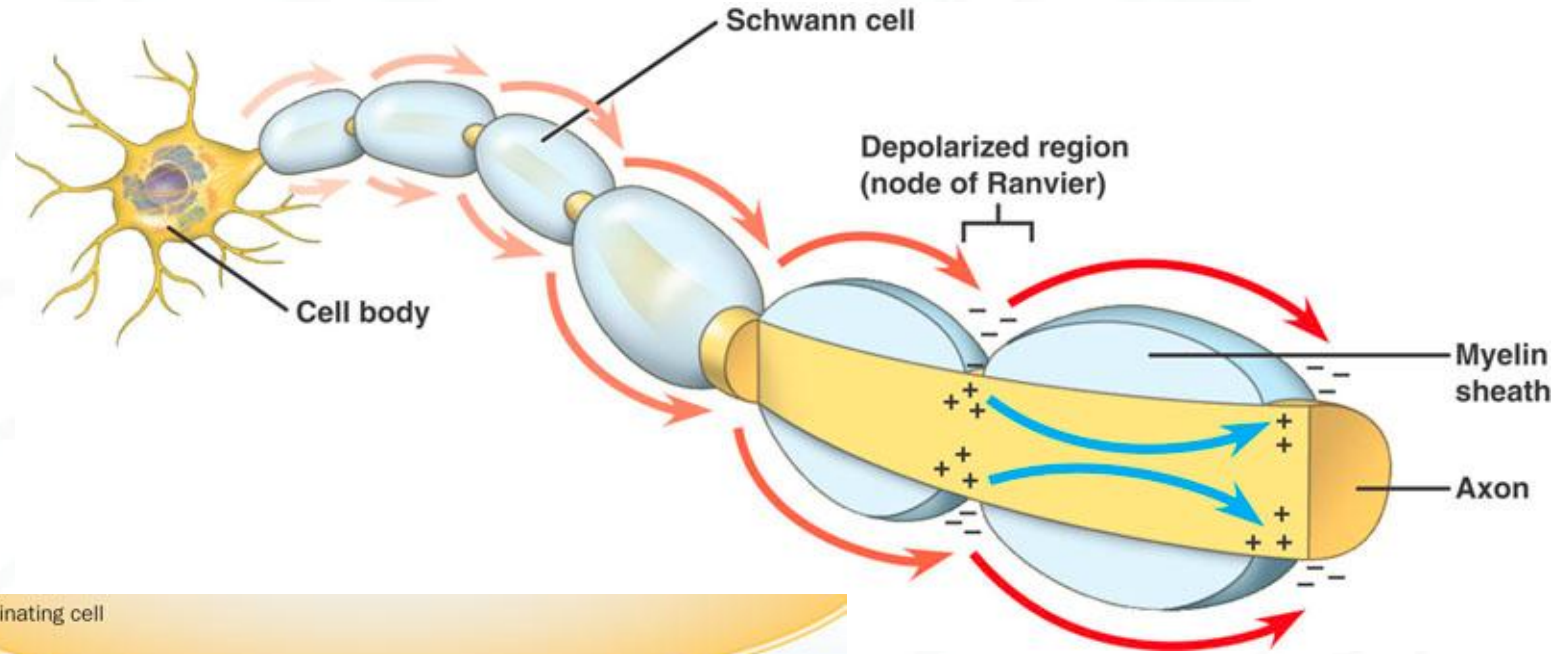


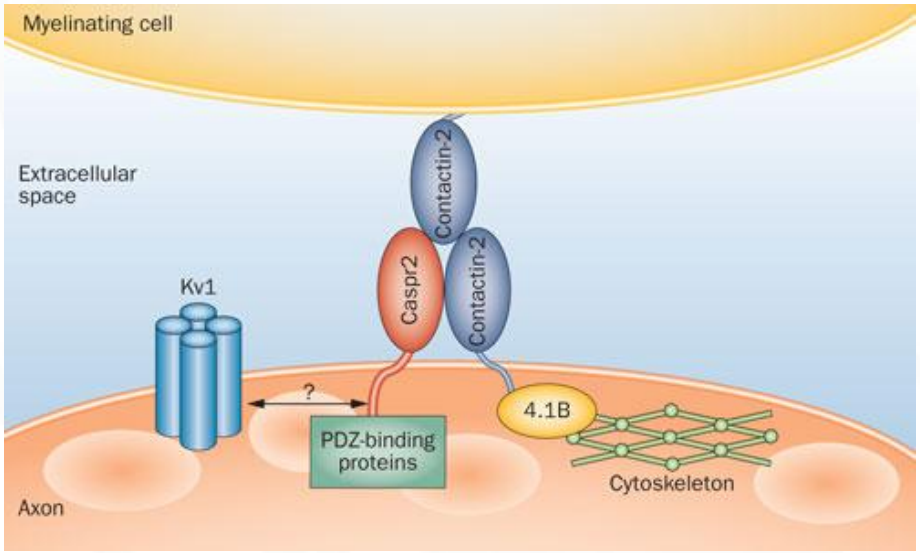




Vernes et al. NEJM, 2008

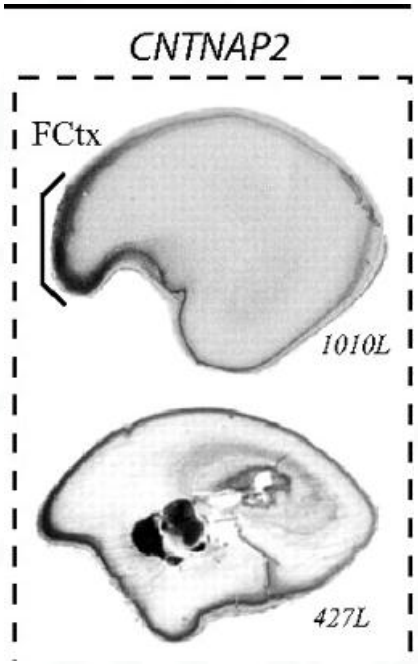
What is CNTNAP2 (Caspr2)?

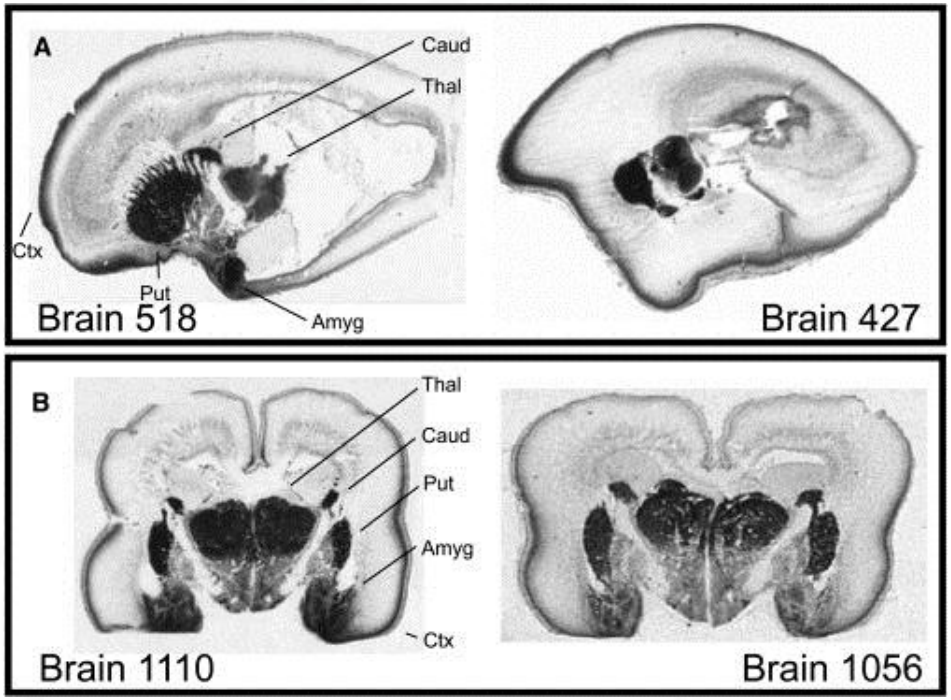




Rapid conduction of nerve impulses

CNTNAP2 (Caspr2)





Abrahams et al, PNAS, 2007

Alarcón et al AJHG, 2008

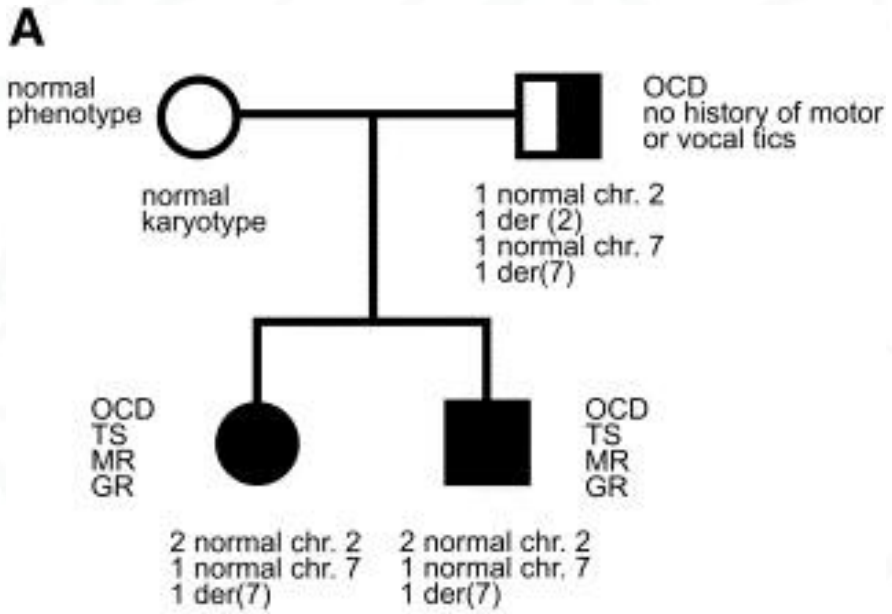
CNTNAP2 expression is enriched in frontal and perisylvian brain regions in humans (but not in mouse)

These regions implicated in higher order cognitive function, including language

CNTNAP2 mutations found in speech and language related disorders

Tourette's syndrome

- involuntary motor and vocal tics
- Intellectual disability
- speech abnormalities

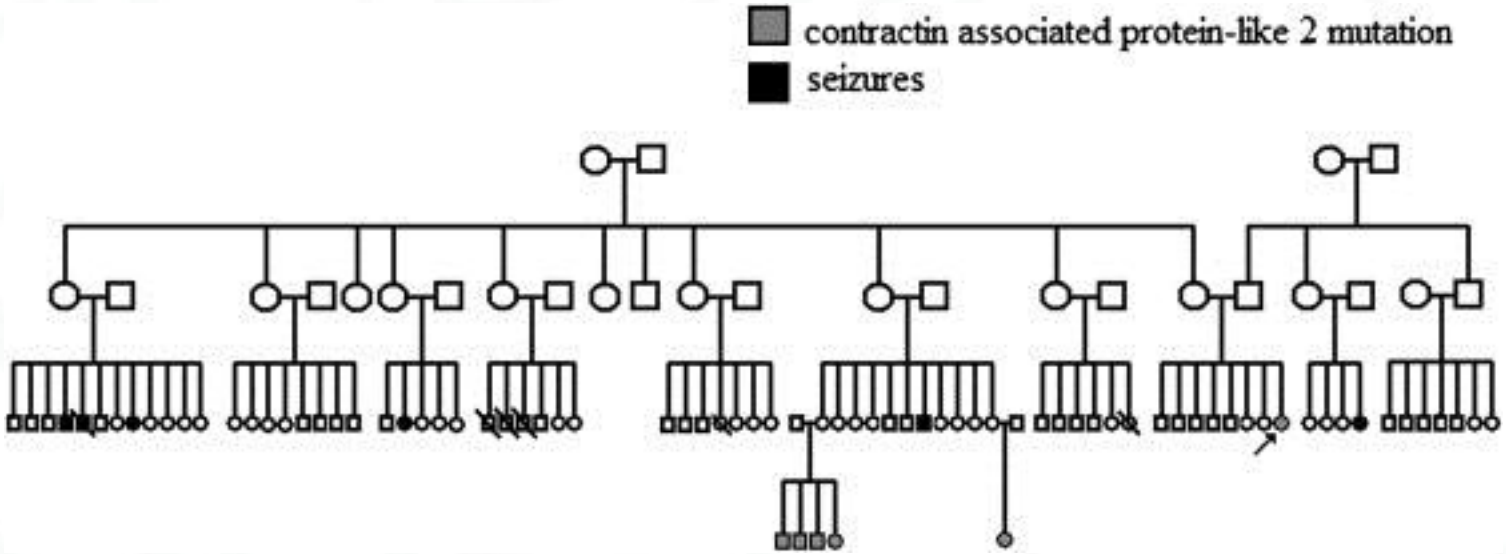


Verkerk et al, Genomics, 2003

CNTNAP2 mutations found in speech and language related disorders

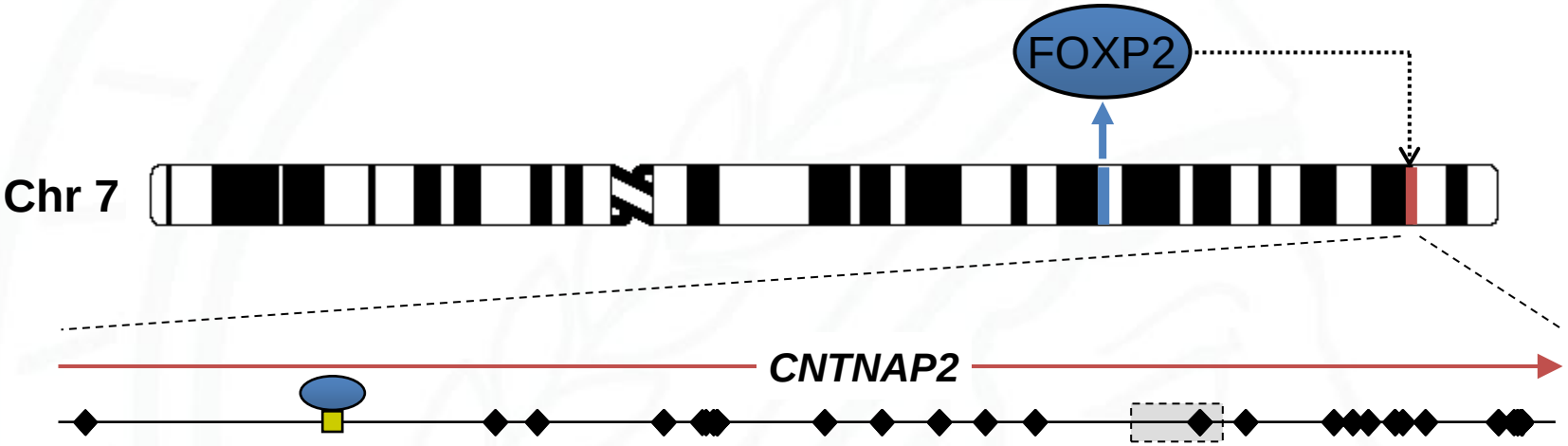
Cortical dysplasia focal epilepsy (CDFE)

- Seizures
- Intellectual disability
- Language regression
- ADHD & ASD characteristics



Jackman et al, Ped Neurol, 2009

A new candidate for language disorder?



FOXP2 regulates CNTNAP2

↓

CNTNAP2 ‘gene-of-interest’ for language related disorders

↓

Are CNTNAP2 variants associated with common language impairment?

Specific Language Impairment (SLI)

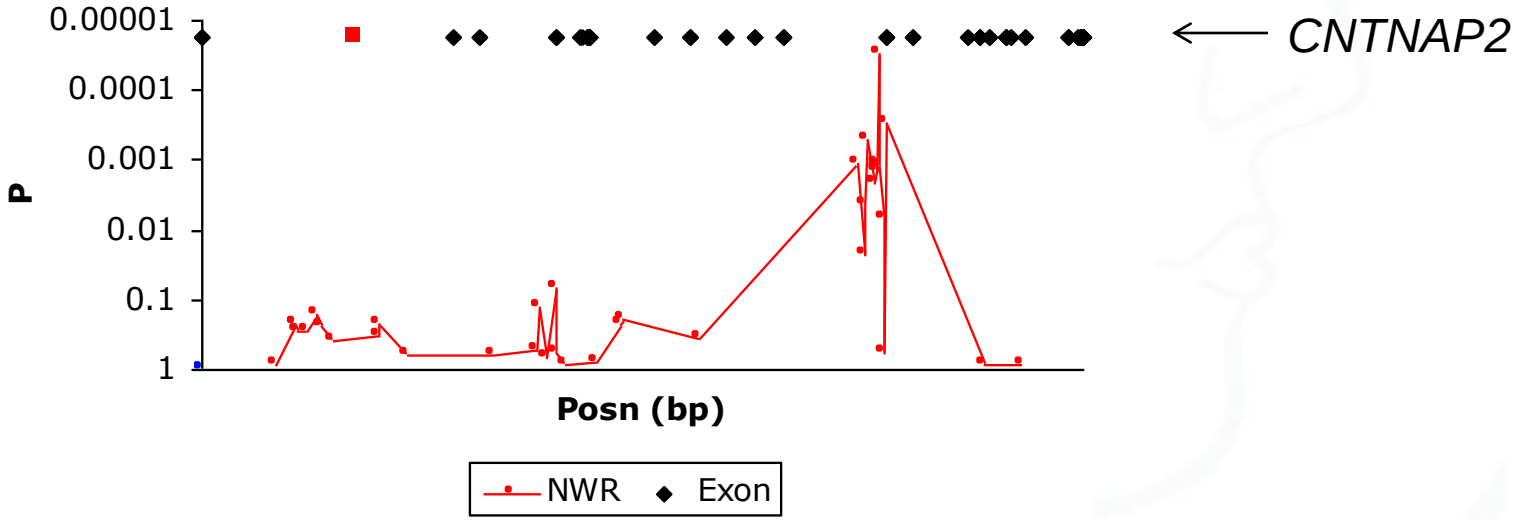
- Affects ~7% of school age children

- Deficit in language acquisition without other explanatory medical causes (e.g. hearing loss, mental retardation, other neurological damage)

- SLI consortium collects phenotypic data and DNA samples from hundreds of affected UK families

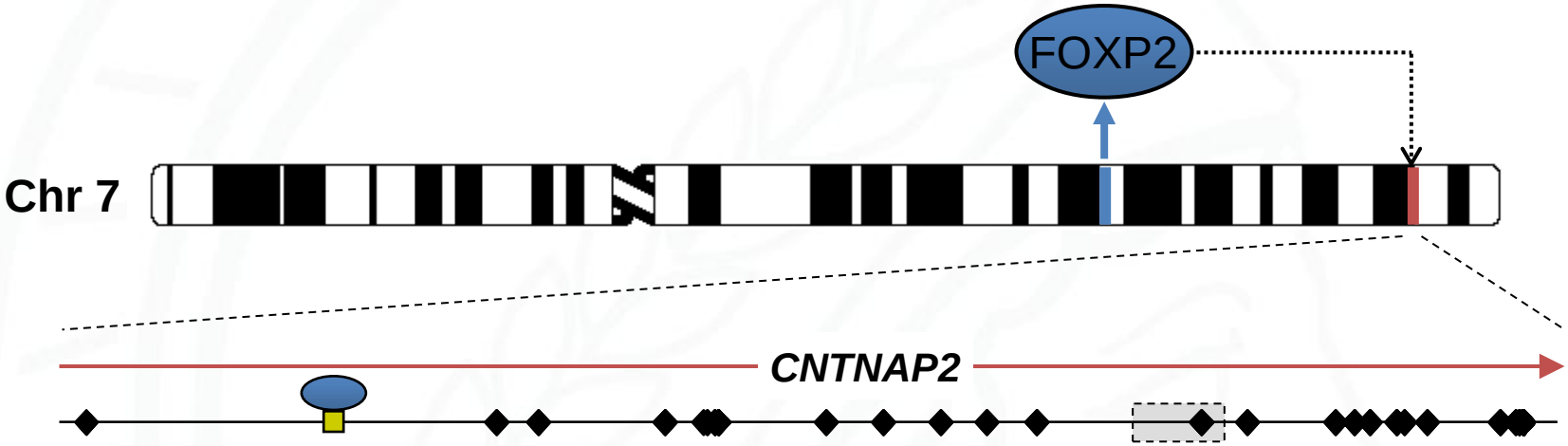
A new candidate for language disorder?

- Screening CNTNAP2/CASPR2
  - 38 markers (SNP's) across CNTNAP2
  - Screen in cohort of 184 SLI families (SLI Consortium)
  - Measures of expressive and receptive language
  - Significant association with expressive and receptive language scores incl. non-word repetition (NWR)



Vernes et al. NEJM, 2008

A new candidate for language disorder?



- CNTNAP2 “risk” variants correlated with reduced abilities in common forms of language impairment
- First mechanistic link between clinically distinct syndromes involving disrupted language

Vernes et al. NEJM, 2008

CNTNAP2 and language related disorders

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Primary diagnosis	Quantitative measure	SNP	Sample size	Ref
Autism	Age at first phrase	rs1718101 rs17236239	1301 families	Anney et al 2012, Arking et al, 2008, Alarcon et al, 2008
	Age at first word	rs2710102	304 families	
	Risk of autism	rs7794745	217 families	
	Non-word repetition	rs10246256 rs17236239 rs2710117 rs2710102	184 families, 181 families	Vernes et al, 2008, Newbury et al 2011
SLI	Non-word repetition	rs851715 rs759178 rs1922892 rs2538991 rs2538976	184 families	
	Receptive language	rs4431523		
	Receptive language Expressive language	rs10246256 rs17236239 rs2710117 rs2710102	181 families	
Dyslexia	Non-word repetition	rs2710102	188 family trios	Peter et al, 2011
Schizophrenia	Risk of schizophrenia	rs802524 rs802568	653 patients	Ji et al, 2012
Bipolar disorder	Risk of bipolar disorder	rs802524 rs802568	1172 patients	
Normal population	Early communicative behaviour	rs2710102 rs759178 rs17236239 rs2538976	1149 normal patients	Whitehouse et al, 2012

CNTNAP2 & brain imaging genetics

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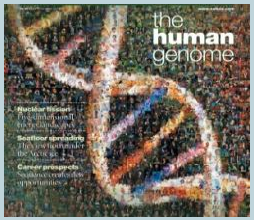
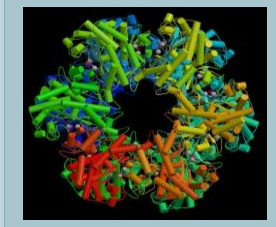
Population	Imaging study	Test	Sample size	SNP	Results	Ref
Normal population	Structural morphology	MRI & DTI	314	rs7794745	Risk allele (TT) caused altered white matter connectivity and reduced frontal and cerebellar grey matter	Dennis et al, 2011
Normal population	Functional imaging during language task	fMRI	66	rs7794745	Risk allele (TT) increased right middle temporal gyrus activation	Tan et al, 2010
				rs2710102	Risk allele (CC) increased right IFG and decreased left superior parietal lobule activation	
Autistic vs Normal children	Functional imaging during implicit learning task	fMRI	16 autistic, 16 control	rs2710102	Risk allele (CC) caused abnormally high mPFC activity during task. Also loss of left lateralised network due to increased bilateral connectivity	Scott-Van Zeeland et al, 2010
Normal population	Event related brain potentials (ERP)	EEG	60	rs7794745	Carrying risk allele (TT or TA) results in altered brain response during syntactic processing	Kos et al, 2012

Language & Genetics





DNA	Protein	Neuron	Neural Circuits	Brain	Speech & Language

Questions?