Deciphering the genetics of speech & language disorders

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An instinct to acquire an art

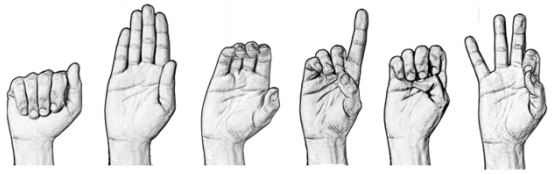
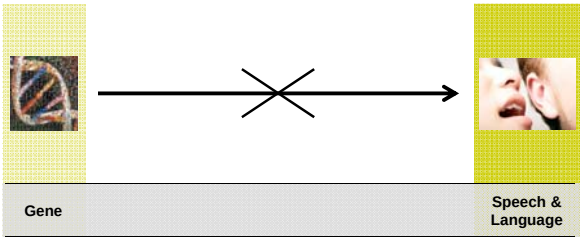


Image © William Vicars, at Lifeprint.com

The myth of the abstract gene



Genes should not be viewed as abstract entities with a mysterious ability to directly control a person's behaviour or cognitive skills

Beyond the abstract gene….

TCGATTAGCTAGAGGAGAGGAGAGTCGATTCTGGGGGCTCTCTCGGATAGTAGATAGCAGTCAGCATCGG
GATGCATGCTATTAGCTAGCTAGCAGCTAGCTACGTAGCTCTGATCGATCGGTAGCTAGCTATGCTAGCT
AGTCGAGGCGAAGGGGGCTCAGAGATCTCTCTCTTTTCTTCTTCGATAGCTAGCTAGCTAGCTAGCTAGC
GAGGAGCTAGCGTAGTCGATCGTCTCGAGAGGACTCTTCTGGGGGCTCTCGCTAGGGAGGAGAGGAGAGT
CTGTATGCTAGCTGCATGCTACGGAGGGGATAGTAGATAGCAGTCACGGTTAAATCGTACTGGAGCTAGC
TAGGGCGCGATAGCTAGCGATCGATCGAGGGGGCTCTCTCGATCGATCGATCGAGCATCGGATCGAGGAG
CGAGGAGCTAGCGTAGTCGATCGACTATGCGAGCGATCTATGCTATCGAGGGGGCTCTCTCGAATTGTAG
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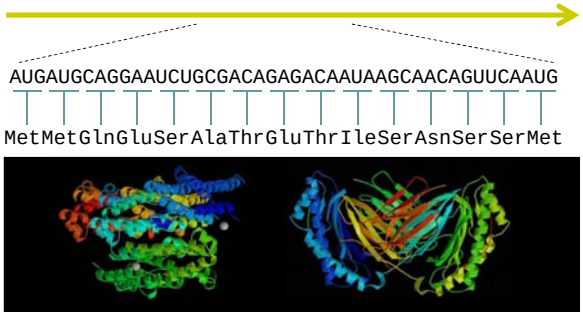
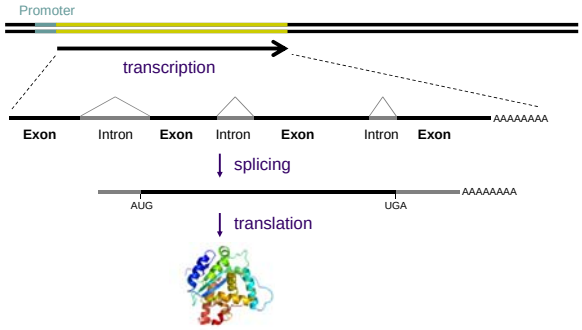
Cracking the code



Genome, Interrupted

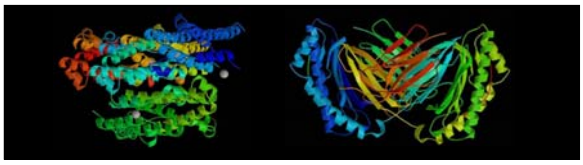


Variety is the spice of life

Cracking the code

AUGAUGCAGGAAUCUGCGACA**A**AGACAAUAAGCAACAGUUCAAUG

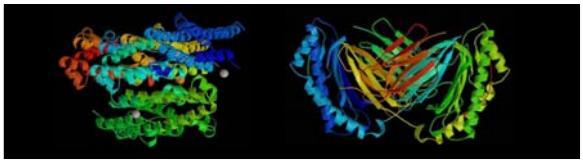
MetMetGlnGluSerAlaThr**Lys**ThrIleSerAsnSerSerMet



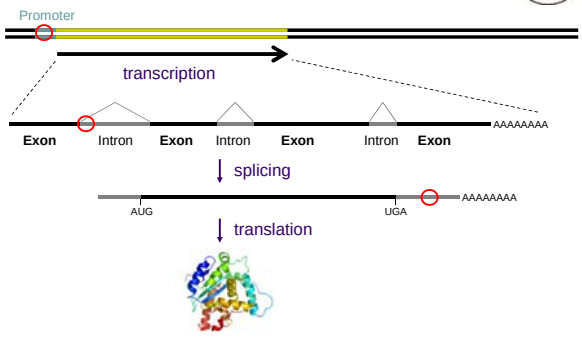
Cracking the code

AUGAUGCAGGAAUCUGCGACA**U**AGACAAUAAGCAACAGUUCAAUG

MetMetGlnGluSerAlaThr**Stop**

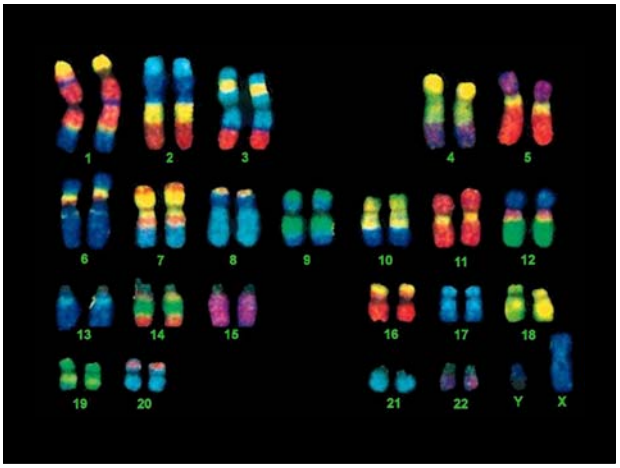


Genome, Interrupted

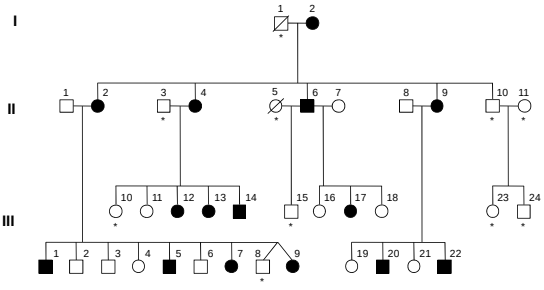


Lost for words

- A subset of children grow up in language-rich environments, but do not develop normal skills
- Sometimes there is no overt cause e.g. cerebral palsy, hearing loss, mental retardation, cleft palate
- Developmental language disorders are often found to cluster in families
- Twin studies consistently indicate high heritability i.e. role for genetic factors



The KE family



Fisher et al. (1998) *Nature Genet* **18:** 168-70

Childhood apraxia of speech

- Difficulties in the learning and production of sequences of mouth movements, impairs speech development

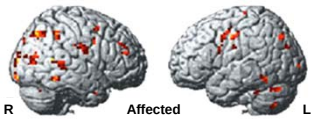
Watkins et al. (2002) *Brain* **125:** 452-64

Simple inheritance, complex phenotype

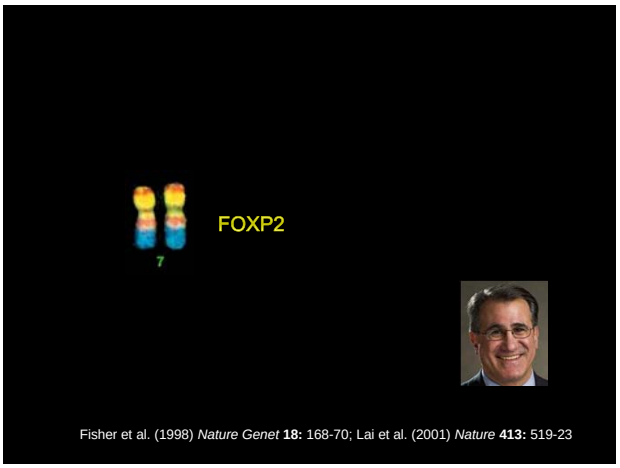
- Difficulty learning/producing sequences of complex orofacial movements underlying speech
- Deficits in wide range of language-related skills:
  - Spoken AND written language
  - Impairment extends to receptive domain
  - Comprehension and production of grammar affected
- Non-verbal deficits are not central to disorder:
  - Unaffected individuals with low non-verbal IQ
  - Affected individuals with normal non-verbal IQ
  - Deficits in verbal cognition more severe/wide-ranging

Imaging the brain

Functional MRI – silent verb generation task

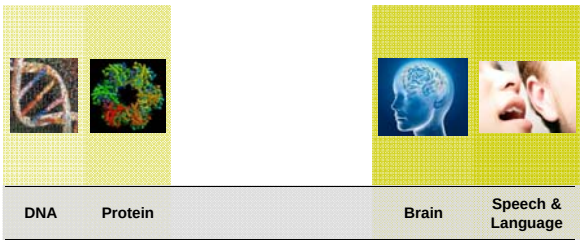


Liegeois et al. (2003) *Nature Neurosci* **6:** 1230-7



Fisher et al. (1998) *Nature Genet* **18:** 168-70; Lai et al. (2001) *Nature* **413:** 519-23

Mind the gap!



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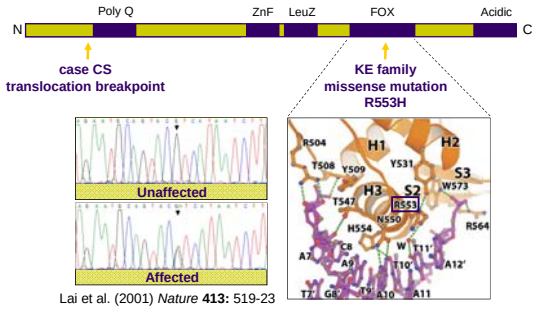
The FOXP2 protein



Lai et al. (2001) *Nature* **413:** 519-23

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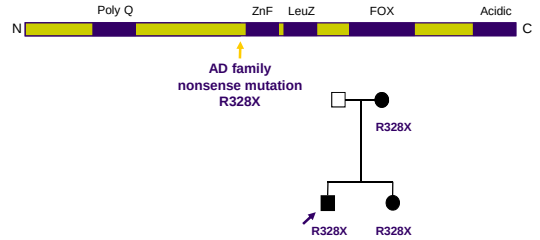
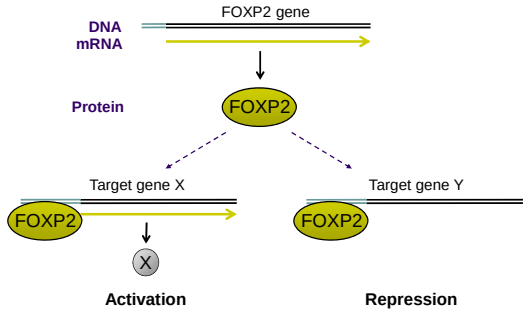
The FOXP2 protein

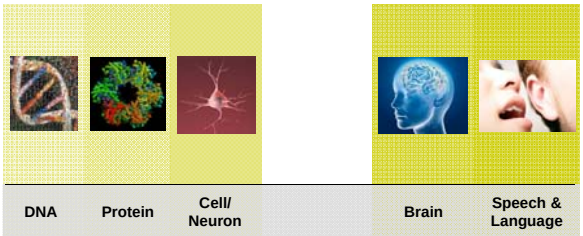


MacDermot et al. (2005) *Am J Hum Genet* **76:** 1074-80

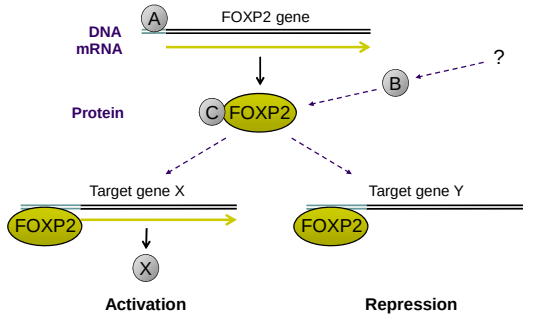
FOXP2 is a transcription factor



Mind the gap!



FOXP2 as a molecular window



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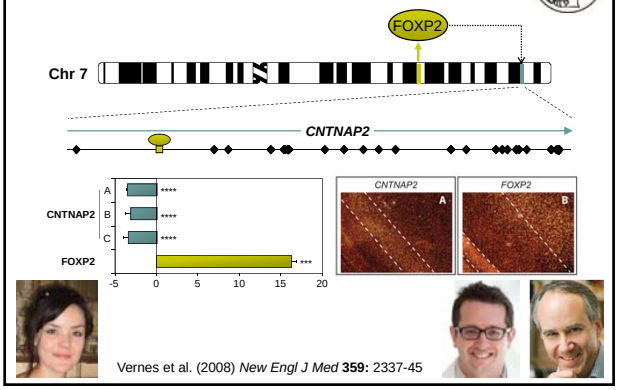
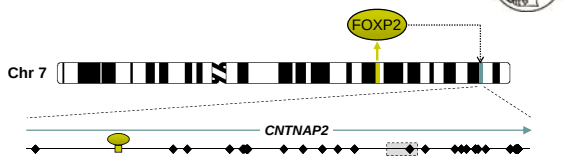
FOXP2 as a molecular window



Vernes et al. (2008) *New Engl J Med* **359:** 2337-45

FOXP2 as a molecular window



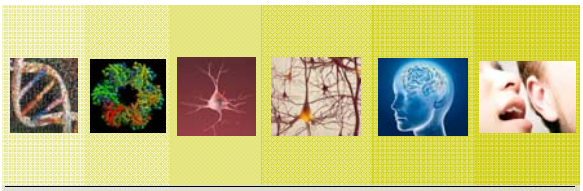
- 184 families with common forms of language impairment; CNTNAP2 "risk" variants correlated with reduced abilities
- These variants are independently associated with delayed language ("age-at-first-word") in autistic children
- Alleles are correlated with early language in general population

Vernes et al. (2008) *NEJM* **359:** 2337-45;
Alarcón et al. (2008) *Am J Hum Genet* **82:**150-9;
Whitehouse et al. (2011) *G2B* **10:** 451-6

A tale of two genes

- Distinct types of genetic effects:
- **FOXP2** = rare coding mutations change the sequence of the encoded protein, causing a monogenic speech/language disorder
- **CNTNAP2** = common variants outside the protein coding regions are associated with increased risk of language problems
- Converge on a shared functional pathway

Mind the gap!

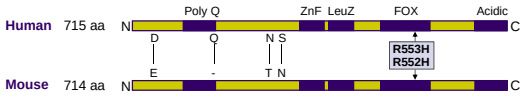


DNA | Protein | Cell/ Neuron | Neural Circuits | Brain | Speech & Language

A tale of two genes……

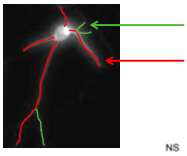
Does this mouse have a speech and language disorder?

What is Foxp2 doing in a mouse?

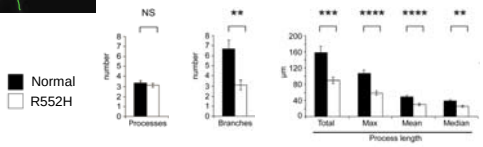


- Mouse Foxp2 differs from human protein by only 3 substitutions, and slightly shorter stretch of Q residues
- Switched on in corresponding regions in rodent and human brain => includes neuronal subpopulations in the cortex, basal ganglia, thalamus & cerebellum
- Circuits implicated in multimodal sensory processing, sensorimotor integration and motor-skill learning

Foxp2 and neural connectivity

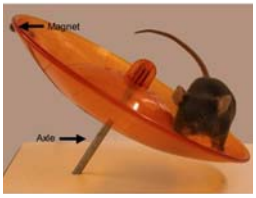


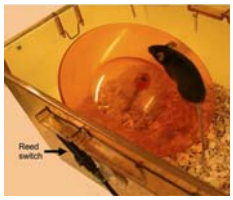
number branches
number processes
Process length



Vernes et al. (2011) *PLoS Genet* **7(7):** e1002145

Voluntary motor-skill learning

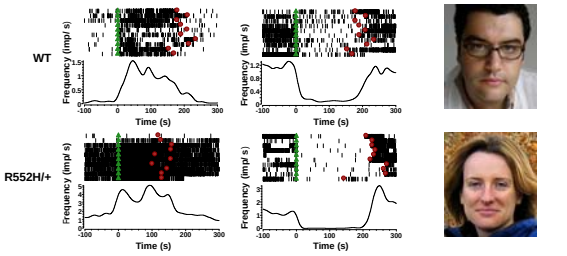




De Bono et al. (2006) *Am J Physiol Regul Integr Comp Physiol* **290:** R926-34

Disruption of one Foxp2 copy leads to normal base-line motor behaviour, but significant deficits in motor-skill learning Groszer et al. (2008) *Curr Biol* **18:** 354-62

Foxp2 and striatal plasticity

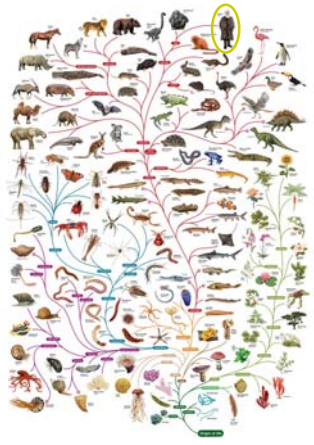


French et al. (2011)
Mol Psychiatry doi: 10.1038/mp.2011.105

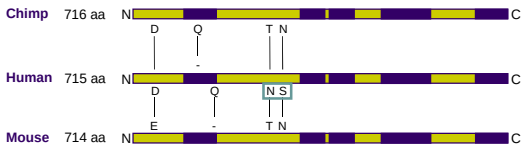
Not the "gene for language"




- Versions of FOXP2 found in highly similar form in vertebrate species that lack speech and language
- Ancient role(s) in brain of common ancestor?
- FOXP2 likes moonlighting – it is also switched on in parts of developing lung, intestines and heart
- Like other regulatory genes, FOXP2 does several different jobs, interacting with other factors



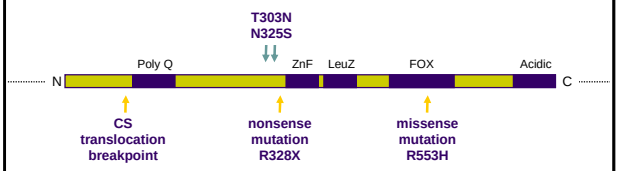
FOXP2 in primate evolution



When it comes to FOXP2 protein, a chimpanzee is more similar to a mouse than it is to a human….

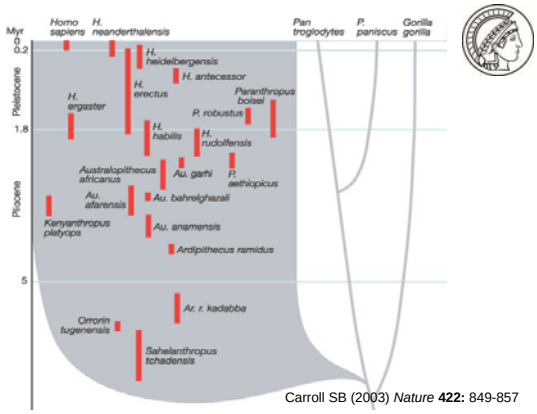
Enard et al. (2002) *Nature* **418:** 869-72

SUBSTITUTIONS ON HUMAN LINEAGE



MUTATIONS IN DISORDERS

Lai et al. (2001) *Nature* **413:** 519-23; MacDermot et al. (2005) *AJHG* **76:** 1074-80



Carroll SB (2003) *Nature* **422:** 849-857

Molecular evolution of FOXP2

- Accelerated change of FOXP2 on human lineage after split from chimpanzee
- This does not mean that FOXP2 was *the* driving force behind evolution of spoken language
- Modifications of ancient role(s) in neural circuits of the vertebrate brain
- Just one piece of a complex jigsaw
- **Can we empirically test whether evolutionary changes have any functional significance?**

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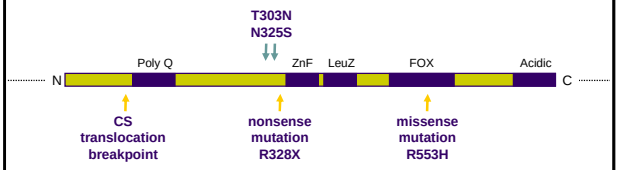
Enard et al. (2009) *Cell* **137:** 961-71
Reimers-Kipping et al. (2011) *Neuroscience* **175:** 75-84

Konopka et al. (2009) *Nature* **462:** 213-7

SUBSTITUTIONS ON HUMAN LINEAGE



MUTATIONS IN DISORDERS

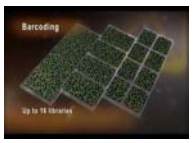
Groszer et al. (2008) *Curr Biol* **18:** 354-62
Gaub et al. (2010) *Genes Brain Behav* **9**: 390-401
French et al. (2011) *Mol Psychiatry* doi: 10.1038/mp.2011.105
Kurt et al. (2012) *PLoS One* **7:** e33130

The FOXP2 story

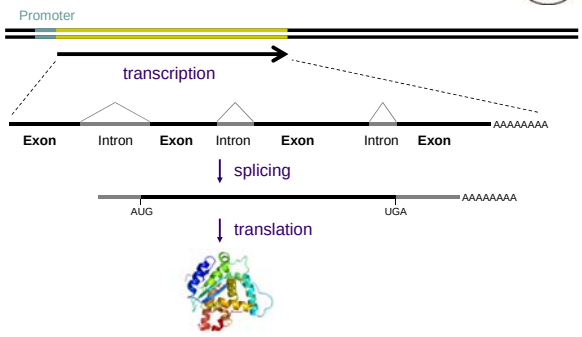
- Missense & nonsense mutations in FOXP2 cause a severe speech & language disorder in humans
- FOXP2 is a regulatory gene – its downstream targets (e.g. CNTNAP2) offer entrypoints into neural pathways involved in speech & language
- Not a “gene for speech” - versions of FOXP2 in many species e.g. affects motor learning in mice
- Helps modulate neural plasticity of brain networks, including cortico-basal ganglia circuitry
- Our unique capacity for complex spoken language is built on evolutionarily ancient systems

The next generation.....

- Initial human genome sequence: 10 yrs, $3 billion
- By 2010, a human genome could be sequenced in less than a month, for <$30,000
- Now: Genome in a few days for <$4,000
- The era of personal genomics

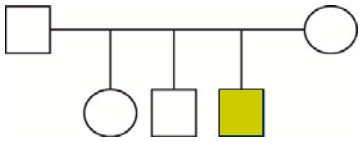


Genome, Interrupted

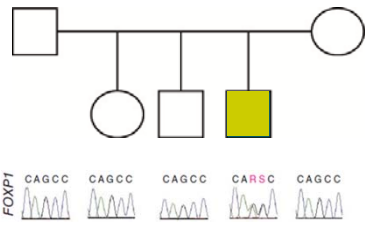


Exome sequencing in autism

- Autism = pervasive impairment in language, communication and social reciprocity, restricted interests or stereotyped behaviours
- Hypothesis: de novo (i.e. new non-inherited) protein-coding mutations may contribute
- Study families where a single child has autism:



Exome sequencing in autism

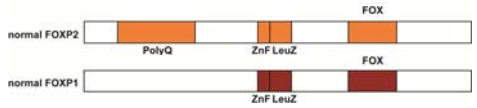


- A de novo mutation of the FOXP1 gene that disturbs the sequence of the encoded protein….

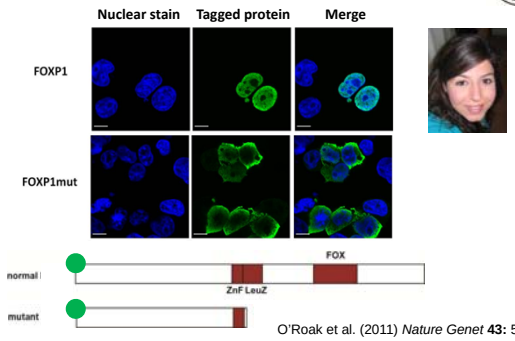
O'Roak et al. (2011) *Nature Genet* **43:** 585-9

FOXP1? Sounds familiar….

- The most similar gene in humans to FOXP2
- Like FOXP2, it encodes a protein which regulates the transcription of other genes
- In some parts of the brain, FOXP1 and FOXP2 are switched on together (co-expressed)
- The proteins can directly interact with each other and may work together to regulate target genes

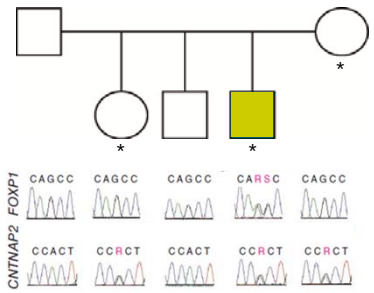


Testing the FOXP1 mutation



O'Roak et al. (2011) *Nature Genet* **43:** 585-9

Same child, second mutation…



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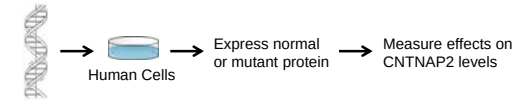
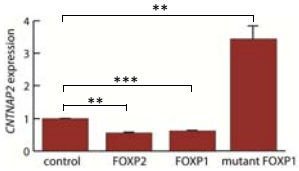
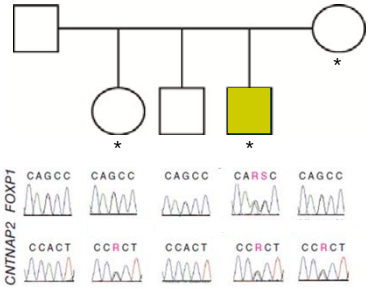
FOXP1 regulates CNTNAP2 ?





O'Roak et al. (2011) *Nature Genet* **43:** 585-9

FOXP1-CNTNAP2 dual-hit model

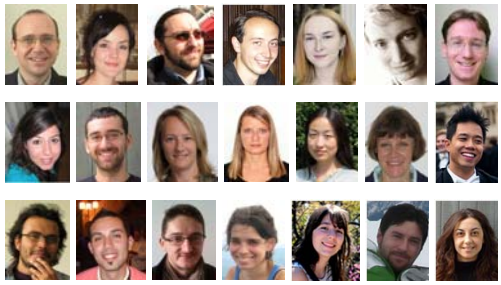


- FOXP1 mutation yields elevated CNTNAP2 levels => amplifies deleterious effects of damaged CNTNAP2?

NGS in language impairments

- Next generation sequencing coupled to cell based assays is a powerful tool
- We recently completed exome sequencing in 50 individuals with language disorder
- Knowledge of functional neurogenetic pathways will help to identify the critical variants
- Insights from language disorders promise to shed light on the contribution of genes to normal speech and language processing

Language and Genetics, MPI



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