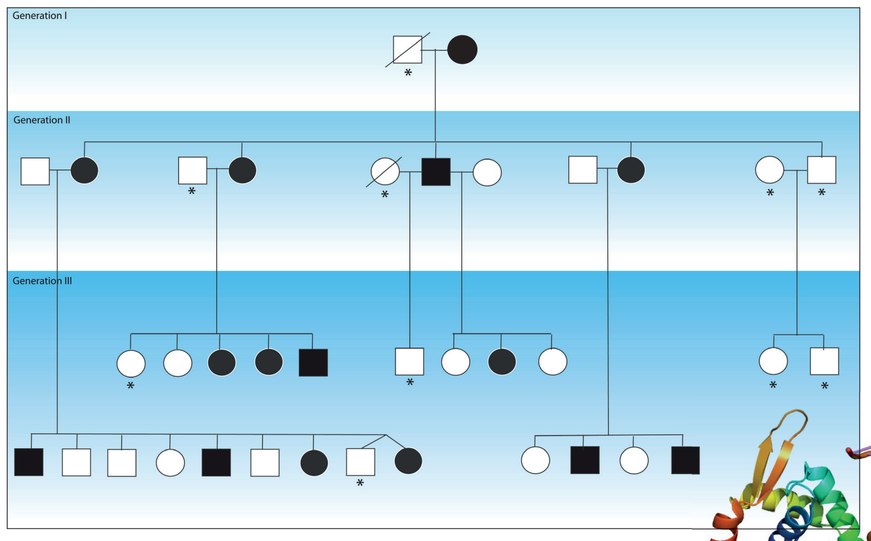
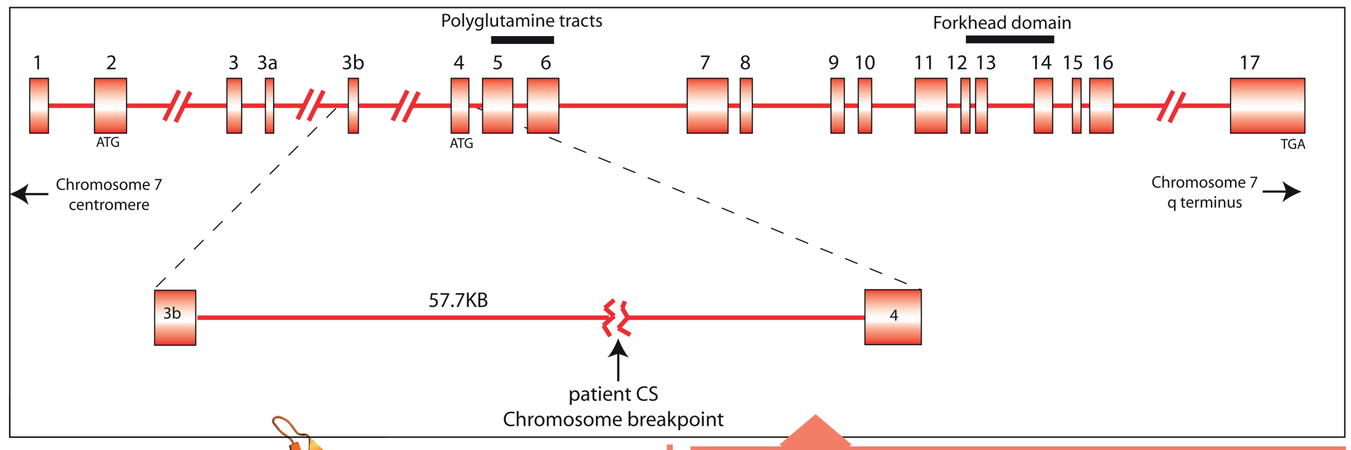
The Wellcome Trust Centre for
Human Genetics

UNIVERSITY OF OXFORD

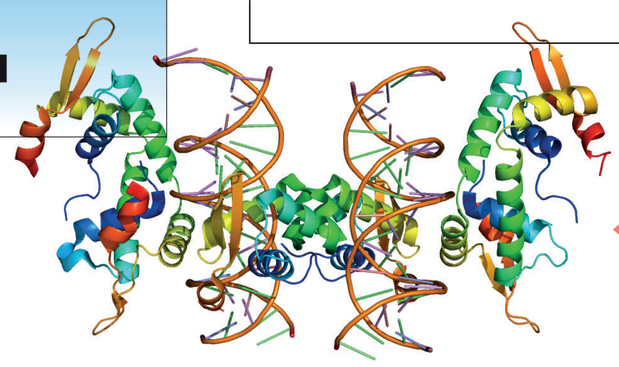
Identifying a genetic cause for a severe speech and language disorder reveals molecular processes underlying a uniquely human trait



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

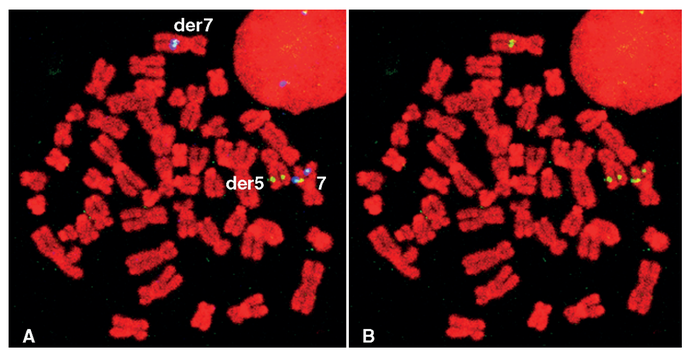


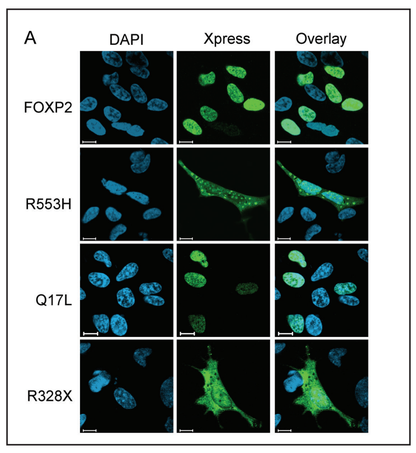
The translocation breakpoint in patient CS falls near the forkhead domain locus on chromosome 7 where mutations occur in the KE family



3-D structure of a normal FOXP2 protein

Fluorescent labelling shows the breakpoint on chromosome 7 in patient CS (from Lai et al (2000) Am J Hum Genet 67: 357–68)





Immunofluorescence shows that FOXP2 protein (green) is normally localized in nuclei (blue), but that some mutant forms of FOXP2 are also mislocalised in the cytoplasm (from Vernes et al (2006) Hum Mol Genet 15: 3154–67)

WHAT WAS KNOWN

- Children with developmental language disorders have difficulty acquiring speech and language despite being of normal intelligence and showing no obvious sensory or neurological impairment
- Twin studies implicate a genetic cause but family pedigrees often show a complex pattern of inheritance
- No underlying gene that could point to the involvement of a particular molecular pathway had previously been identified

WHAT WE DID

- Mapped the defect in a rare family, KE, with a dominantly inherited speech disorder over three generations, to a locus on the long arm of chromosome 7
- Identified an unrelated patient, CS, with a strikingly similar speech and language disorder who had a chromosome translocation at the same locus
- Sequenced this region in KE family members to uncover any point mutations

WHAT THIS ADDS

- Meticulous genetic mapping in CS localised a translocation breakpoint to a 200bp region of the FOXP2 gene, one of a family of transcription factors
- Sequencing this gene in the KE family identified a G to A mutation in affected but not unaffected family members or controls
- The mutation causes a switch from a highly conserved arginine residue to histidine in the 'forkhead' binding domain of the FOXP2 protein
- Suggests that inactivation of FOXP2 during embryogenesis leads to abnormal development of neural structures that are key for speech and language development
- FOXP2 is the first gene to be implicated in the molecular pathways underlying language, a unique and complex human trait

REFERENCES

A forkhead-domain gene is mutated in a severe speech and language disorder.

C S L Lai, S E Fisher, J A Hurst, F Vargha-Khadem & A P Monaco.

Nature 413, 519–523 (2001).