

PLINX204 PSYCHOLINGUISTICS

LANGUAGE ACQUISITION – 2006 - 6

Molecular genetic evidence (1)

FOXP2 – the KE family revisited

Basic reading: Marcus & Fisher, 2003

Additional reading: Plomin et al, 2000; Newbury et al, 2005; Liegois et al, 2003; Shu et al, 2005.

1. Background:

a. The epidemiology of the KE family (handout 4). A three-generation family of over 30 members, half of whom have a clinically diagnosed speech and language problem, traceable to the maternal grandparent.

b. Elementary genetics shows that this is uncontroversially a case of classical Mendelian inheritance – autosomal dominant transmission - with an identifiable polymorphism.

c. Pleiotropy is common but there may be polygenic considerations (as found in e.g. autism) and also epigenetic factors to take into account. (That is, despite the Mendelian pedigree, lots of genes may be involved).

2. FOXP2 (previously known as ‘SPCH1’): the first gene directly implicated in our ability to acquire language.

a. On the basis of KE family data, the use of ‘markers’ – led researchers to identify a small region (a ‘locus’ about 70 genes long) on the long arm of chromosome 7 (7q31 to be precise).

b. Comparison with another unrelated case of a boy with a similar phenotype led to the identification of a gene belonging to a group of genes encoding forkhead transcription factors. ‘FOXP2’ refers to Forkhead bOX P2 (where the ‘P’ just refers to the Pth branch of the forkhead family, and ‘2’ indicates that it was the second gene on this branch to be identified). It transpired that all affected members of the KE family had inherited a single nucleotide change in the gene sequence, disrupting the function of the resulting protein.

Forkhead genes are transcription factors (see ‘RNA’ in the glossary) which inter alia affect the growing embryo. The ‘forkhead box’ is a string of 80-100 amino acids forming a motif that binds to DNA (the name comes from the shape of mutations to the head of the embryo of the fruit fly).

The *deficit* caused by the mutation is restricted to the central nervous system.

- c. In the normal population FOXP2 is virtually invariant.
- d. FOX genes occur in animals (e.g. fruit flies) and fungi, but not plants. FOXP2 occurs in chimpanzees and mice, with the mouse version probably being more similar to our version than to the chimp's. Chimps have roughly 98.5% of their DNA in common with us, but gene expression differences may be much greater (cf. cooking). The implication is that FOXP2 should be expected to have non-linguistic effects, as well as linguistic ones. It does:

FOXP2 acts like a master control gene, regulating how many copies of a gene's mRNA are made, hence determining the amount of protein in a particular cell at a given moment (cf. cooking again). This gives rise to a cascade effect in which hundreds or thousands of genes 'downstream' of FOXP2 are involved. FOXP2 also affects the lungs, the gut and the heart and its effects persist epigenetically into adult life.
- e. Our genome is diploid – we get FOXP2 from both parents. Half the usual dosage seems to be enough for the lungs, the gut and the heart to develop properly but not for the brain to do so. (Marcus & Fisher's [2003] speculation).
- f. FOXP2 has also been noted as a potential susceptibility locus for autism (which seems increasingly unlikely) and SLI in general.

3. Phenotypic recapitulation.

- a. The KE family's problem clearly involves orofacial dyspraxia (the clinical diagnosis is made partly on the basis of subjects' inability to simulate biting, blowing or kissing), hence their problems with articulation, leading to dysarthria or apraxia of speech.
- b. But it is not a simple motor deficit or just a motor deficit:
 - i. They are normal in their ability to produce single movements and have no limb apraxia. Similarly, they are able to pronounce one item normally but stumble on several (diadochokinesis). That is, their articulatory apparatus is intact but fine motor control is defective.
 - ii. Their speech/non-speech problems do not correlate
 - iii. Language comprehension is impaired, and they have problems with e.g. lexical decision, non-word repetition, use of tense and aspect, understanding complex sentence structure, etc.
 - iv. The deficit extends to writing
 - v. IQ levels in the affected and unaffected family members overlap, and some of the affected members have non-verbal IQs in the normal range.
 - vi. Verbal IQ is more severely affected than performance IQ.

4. Imaging evidence

fMRI studies indicate that the KE family show functional brain abnormalities in language-related cortical regions associated with this mutation. (Liegeois et al, 2003).

Two fMRI language experiments, one involving (silent) verb generation and one (spoken) verb generation and word repetition.

- a. *Unaffected* family members showed a typical left-dominant distribution of activation involving Broca's area in the generation tasks and a more bilateral distribution in the repetition task.
- b. *Affected* members showed an atypical more posterior and more extensively bilateral pattern of activation in all tasks. They also showed significant underactivation relative to the unaffected members in Broca's area and its right homolog, as well as in other cortical language-related regions.
- c. “Our findings suggest that the FOXP2 gene is critically involved in the development of the neural systems that mediate speech and language.” (Liegeois et al, 2003).

5. Of Mice and Men (and zebra finches) (Shu et al, 2005)

- a. Mice have FOXP2 too – “with a nucleotide coding sequence that is 93.5% identical to the human version” (Marcus & Fisher, 2003:260). Like us, mice are also diploid. Shu et al bred ‘knock-out’ mice, with FOXP2 disrupted.
- b. In mice with both copies of FOXP2 disrupted (homozygous mice), the result was severe motor impairment, an absence of the ultrasonic vocalisations that are elicited when pups are removed from their mother, and premature death.
In mice with one copy of FOXP2 disrupted (heterozygous mice), the result was modest developmental delay and a significant alteration in ultrasonic vocalisation in response to separation.
Learning and memory appear normal in the heterozygous animals. (cf. (2e)).
- c. “Repeated measures analysis demonstrated differences in mean number of vocalizations ($P < 0.0005$ for wild-type versus knockout and $P = 0.008$ for wild-type versus heterozygotes”.
- d. “... an interference in Foxp2 function influences neuronal migration and/or maturation in the development of the cerebellum”. The apparatus necessary for the production of vocalisations, including the neural control in the vocal tract and brain stem is normal. (cf. (3bi)). “Our findings support a role for FOXP2 in cerebellar development and in a developmental process that subsumes social communication functions in diverse organisms” (Shu et al, 2005:9643).

- e. Fisher is sceptical (lecture 25.01.06), but he is part of a rival team...
- f. FOXP2 is expressed at high levels in the striatal nucleus area X during vocal learning in zebra finches, and in canaries expression of FOXP2 varies seasonally, and correlates with (in-) stability of the song. Expression in songbirds and humans seems to be comparable at the molecular level.

6. Implications

- a. “The genetic mechanisms involved in speech and language development are likely to involve recruitment and modification of pre-existing genetic cascades” (Marcus & Fisher, 2003:261).
- b. SLI is clinically heterogeneous and is probably influenced by many genes that interact with each other and with the environment (see Newbury et al, 2005).
- c. Cf. the title of Bartlett et al, 2002: “A major susceptibility locus for Specific Language Impairment is located on 13q21”
- d. It looks more and more as if the relation between genotype and phenotype is:
 - i. indirect
 - ii. never peculiar to language
 - iii. usually both pleiotropic and polygenic.
- e. The (sub-)title of Lucentini, 2005, “Could a single gene have made communication possible?” is silly, but:
- f. The discovery of FOXP2 and its role in speech and language is further corroboration of the (partial) genetic determination of the human language faculty.

Additional reference:

Liegeois, F., T. Baldeweg, A. Connelly, D. Gadian, M. Mishkin & F. Vargha-Khadem (2003) “Language fMRI abnormalities associated with FOXP2 gene mutation”. *Nature Neuroscience* 11:1230-1237.

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