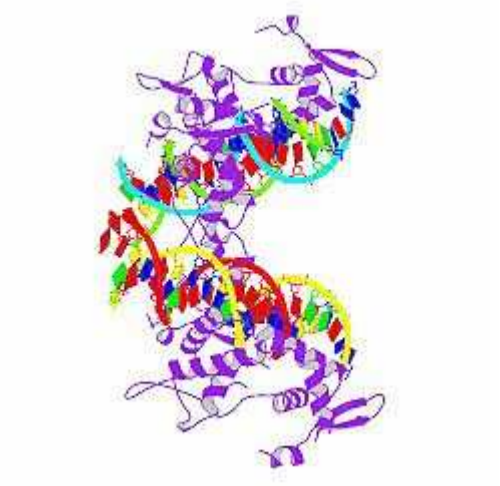
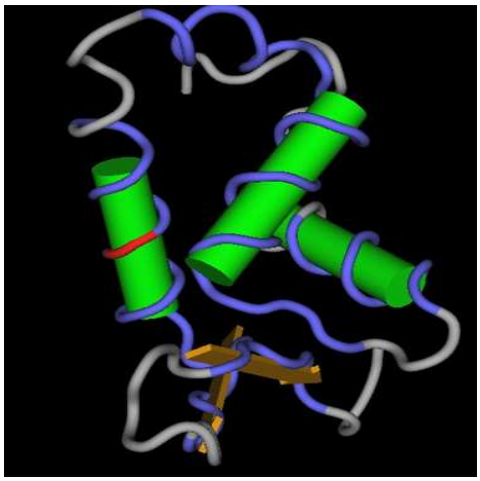
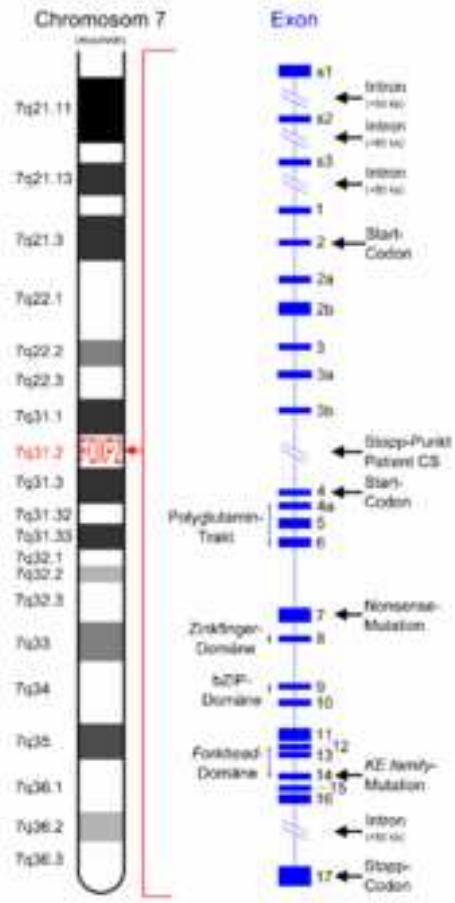
Description of FOXP2





The FOXP2 gene as illustrated by Simon Fisher (Oriel College, Oxford), the investigator who first isolated the FOXP2 gene.(1)

Forkhead box protein P2 also known as FOXP2 is a protein that in humans is encoded by the FOXP2.
The FOXP2 gene is located on human chromosome 7 (7q31, at the SPCH1 locus).
People normally have two copies of this chromosome.
Chromosome 7 is one of the 23 pairs of chromosomes in humans.
Chromosome 7 spans more than 158 million base pairs (building material of DNA).

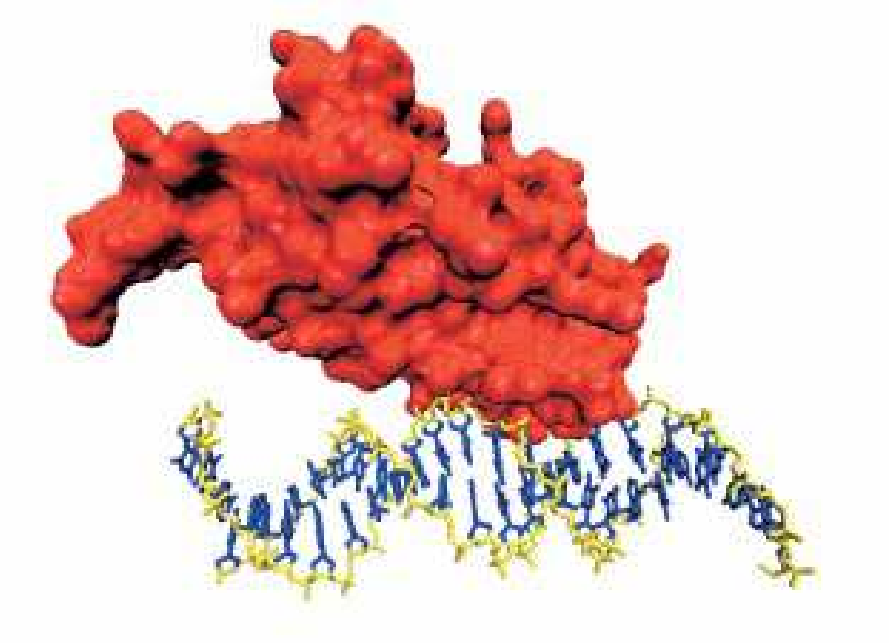


Im Namen FOXP2 steckt die Abkürzung für Forkhead Box – »Fox«. Dabei handelt es sich um einen charakteristischen DNA-Abschnitt, der in vielen Genen vorkommt.

Alle Gene,die eine solche Forkhead Box enthalten, gehören zur Familie der Forkhead-Box-Gene. Der Name rührt daher, dass Mutationen in diesen »Gabelkopf«-Genen den Kopf der Taufliege *Drosophila* gabelförmig verändern.

Die Fox-Genfamilie ist so groß und stark verzweigt, dass eine weitere Unterteilung indie Untergruppen A bis Q eingeführt wurde. FOXP2 bedeutet demnach:Forkhead-Box Genfamilie,Untergruppe P, Mitglied Nummer 2.

Folgerichtig gibt es noch Geschwister, nämlichFoxP1, FoxP3 und FoxP4. Die Forkhead Box codiert bei FOXP2 für jenen Teil des Proteins,der sich an DNA heftet (siehe Bild) und so die Regulation der Zielgene ermöglicht.

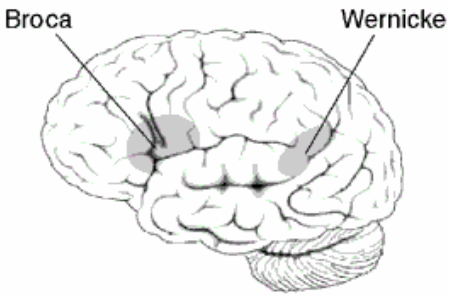


Function

FOXP2 in human beings

FOXP2 mutations in humans are associated with a disorder that affects both the comprehension of language and its production, speech. This discovery provided the first opportunity to analyze the genetics of language with molecular and neurobiological tools.

The function of FOXP2 in human are the followings:



- regulates genes involved in the proper development of tissues such as brain, lung, and gut.
- is a **"transcriptional regulator**," that is, it regulates the first biochemical step in the expression of a gene.
- produces a protein called a **transcription factor**, which attaches itself to other regions of DNA and switches genes on and off.
- switches genes on and off during the creation of a body's tissue.
- Basically, it says to a gene, "Get to work," and then some time later, "Stop. That's enough of your growing for now."
- In addition, FOXP2 is implicated in the **development of language skills.**

Developmental Dyspraxia

Several cases of **developmental verbal dyspraxia** in humans have been linked to mutations in the FOXP2 gene. Such individuals are unable to correctly perform the coordinated movements required for speech. MRI analysis of these individuals performing silent verb generation and spoken word repetition tasks showed underactivation of Broca's area and the putamen, brain centers thought to be involved in language tasks. Because of this, FOXP2 has been dubbed the "speech and language gene."

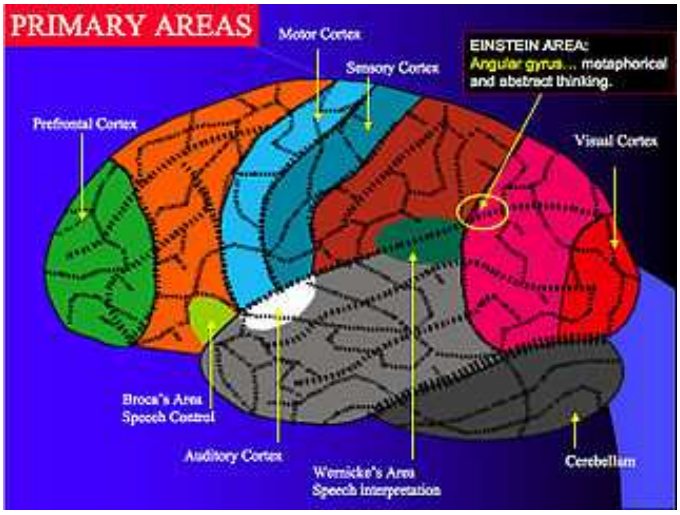
Developmental dyspraxia is one of development disorders affecting the initiation, organization, and performance of action. It is a diagnosis of exclusion which entails the partial loss of the ability to coordinate and perform certain purposeful movements and gestures, in the absence of other motor or sensory impairments. Various areas of development can be affected by developmental dyspraxia and many or all can persist into adulthood. Developmental verbal dyspraxia is a type of ideational dyspraxia, causing linguistic or phonological impairment.

Key problems include:

- Difficulties controlling the speech organs.
- Difficulties making speech sounds
- Difficulty sequencing sounds
    - Within a word
    - Forming words into sentences
- Difficulty controlling breathing and phonation.
- Slow language development.

FOXP2 in animals

If language is uniquely human, is FOXP2 a uniquely human gene? What about FoxP2 in other species? Different studies of FOXP2 in **songbirds** suggest that FOXP2 may regulate genes involved in neuroplasticity. The gene's role in vocalization has been strengthened by evidence that FOXP2 is crucial in songbirds for enabling young birds to learn how to imitate the songs of their elders. During song learning FOXP2 is upregulated in brain regions critical for song learning in young **zebra finches**. Knockdown of FOXP2 in **Area X** of the basal ganglia of these birds results in incomplete and inaccurate song imitation.



Similarly, in adult **canaries** higher FOXP2 levels also correlate with song changes. FOXP2 has also been implicated in the development of **bat** echolocation.

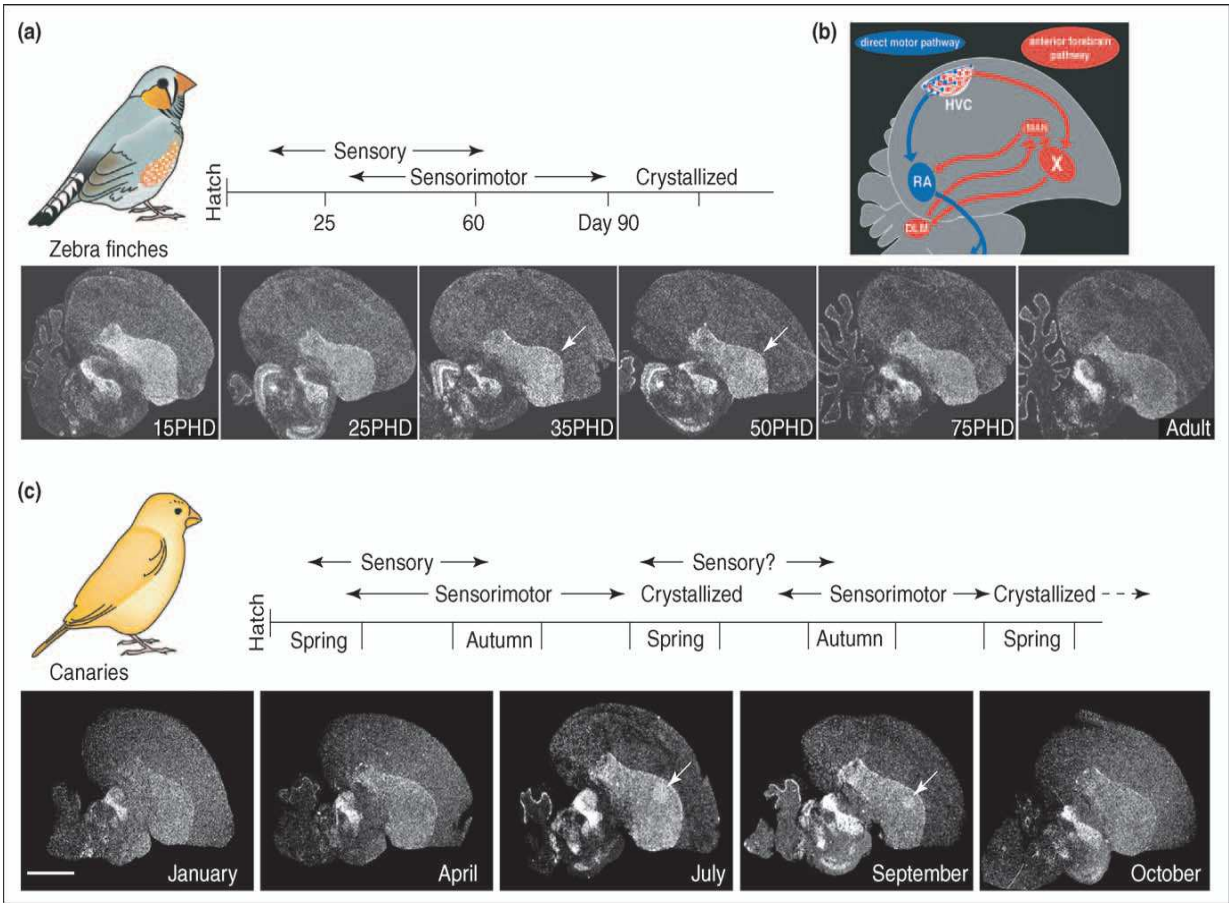
<u>The function of FOXP2 in animals are the followings:</u>

- FOXP2 proteins can be found in songbirds, zebra finches, canaries, bats, chimpanzee, whales, dolphin, fish, and reptiles (such as alligators)
- Many other animals have FOXP2, but the human version differs at two links in the chain of amino acids that make up the protein.
- Human FOXP2 differs from chimp FOXP2 by two amino acids, mouse FOXP2 by 3 amino acids, and zebra finch FOXP2 by 7 amino acid



Songbirds

Because of the well-established behavioral and neurobiological parallels between speech learning in human infants and song learning in birds we will focus particularly on songbirds. Recent studies in songbirds show that during times of song plasticity FOXP2 is upregulated in a striatal region essential for song learning.



FOXP2 expression is increased during times of vocal plasticity. Zebra finches learn to sing by imitating the song of an adult tutor. During the 'sensitive learning phase' birds memorize the tutor song but vocalize little. During the 'sensory–motor phase' they start singing and use auditory feedback to modify their imperfect rendition of the memorized tutor song. This process culminates in a final, 'crystallized' song.

(a) In zebra finches, adult song changes little, in contrast to canaries who continue to modify their song throughout life.
(b) Before and after the breeding season they incorporate new syllables into their song, which correlates with seasonal plasticity in the neural circuits that mediate the learning and/or production of song.
(c) The anatomy and connectivity of the song circuit HVC and RA are part of the motor pathway necessary for song production (blue). HVC also provides input to the anterior forebrain pathway (AFP) (red).

It is essential for song learning during development and for periods of song plasticity in adulthood. FOXP2 expression in Area X is elevated during times of song plasticity both in juvenile zebra finches (a) and in adult canaries (b).

Evolution Aspect and Scientific Background

Scientists find gene 'switch' linked to speech

The letter, titled, **"Human-specific transcriptional regulation of C[entral] N[ervous] S[ystem] development genes by FOXP2,"** was written by a large team represented by Genevieve Konopka and Daniel Geschwind . The journal also had a summary article on the study, "The Importance of Being Human," by Martin H. Dominguez and Pasko.

Scientists have identified a gene that **"switches on"** our ability to talk, landmark findings that may lead to treatments for possible speech conditions. **Dr Daniel Geschwind,** who led the research team at the University of California, at Los Angeles (UCLA), findings are reported in the science journal **Nature.**

He urged the FOX2P gene,

"appears to act like a **light switch,** switching on the circuits in the brain associated with learning language".(2) FOX2P gene had been associated with speech in the past and that people with a mutated or damaged version struggled with learning languages and how to talk. Our findings may shed light on why human brains are born with the circuitry for speech and language and chimp brains are not."

Dr. Genevieve Konopka, the co-author of the study, said "genetic changes between the human and chimp species hold the clues for how our brains developed their capacity for language. By pinpointing the genes influenced by FOXP2, we have identified a new set of tools for studying how human speech could be regulated at the molecular level," he was quoted as saying by the British daily.

The target of **Geschwind's analysis was FOXP2,** subsequent research has shown FOXP2 to be play a role not only in acquiring grammar and syntax, but in developing motor skills and helping brain cells form new connections.

Geschwind's team engineered lines of brain cells in which they could turn FOXP2 on and off, and measure what happened to other genes as they did so. Then they did the same thing with brain cells into which the human version of FOXP2 had been replaced with its chimpanzee counterpart.

Armed with a list of genes linked to FOXP2 in both species or just one, the researchers then measured the activity levels of those genes in brain tissue samples from humans and chimps. This revealed 116 genes connected only to the human version of FOXP2, which indeed appears to have accumulated many new functions in humans neurogeneticist Daniel Geschwind of the University of California, Los Angeles and colleagues report in the **Nov. 12. 2009 Nature.**

"We found that the targets of the gene are not only involved in brain function. Some of them are involved in the development of non-nervous system tissue and cranial structures involved in speech production. That's remarkable," said Gerschwind.(3)

The importance of being human*

*Nature 462, 169-170 **(12 November 2009)** | doi:10.1038/462169a; Published online 11 November 2009Language evolution: The importance of being human Martin H. Dominguez1 & Pasko Rakic1
http://www.nature.com/nature/journal/v462/n7270/full/462169a.html
http://www.nature.com/nature/journal/v413/n6855/full/413519a0.html

The FOXP2 gene is implicated in the development of human speech and language. A comparison of the human and chimpanzee FOXP2 proteins highlights the differences in function in the two species.

The gene was first found to be mutated in a family with language dysfunction, hence its implication in the development and evolution of human speech and language, and its reputation as the 'language gene'. Examination of the human FOXP2 gene and protein sequences reveals that the gene has a prominent role in the acquisition of language in humans.

But like the leading character in **Oscar Wilde's play The Importance of Being Earnest,** FOXP2 leads a **double life:**

- it has a starring role as the language gene.
- the underpinnings of its gene-regulatory networks, especially those conferring functions that are unique to humans.

FOXP2 is present in vocal and non-vocal animals, is important for muscle coordination in vocalization, but is also associated with many other motor functions in all vertebrate species examined. The most obvious consequence of loss of function of FOXP2 in humans and rodents is impairment of motor skills and coordination. Problems in motor sequencing actions or procedural learning (the acquisition of fine motor skills), including those related to the mouth and face, thus can manifest as disorders of speech and language. Impairment of motor-learning skills can have profound effects in humans, in whom a loss-of-function FOXP2 mutation causes disturbances in language comprehension, grammar and syntax. (4)

Mice Given 'Human' Version of Speech Gene

Wolfgang Enard of the Max-Planck Institute for Evolutionary Anthrophology states that "the finding may help shed light on how humans evolved language and speech. Mice are often used to study the causes and effects of human diseases because they share many genetic similarities with human. They may not be the talking mice of cartoons, but real mice carry a "humanized version" of a gene thought to be involved in speech".

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

Enard and his colleagues used this genetic similarity to gain insights the evolution of human speech.

Enard studies the genetic differences among humans and primate relatives. For example, humans have two amino acid (the building blocks of proteins) substitutions on a gene called FOXP2 compared to chimpanzees. The changes in this gene became fixed after the evolutionary lineage for humans split from the one for chimpanzees.

People who carry one nonfunctional version of the FOXP2 gene have impairments in the timing of the facial movement required for speech, which suggests that the amino acid substitutions contribute to fine-tuned motor control for muscle movements of the lips, tongue and larynx.

The researchers **introduced the human substitutions into the FOXP2 gene of mice.** The mice with the human FOXP2 gene didn't start babbling like babies of course, but they showed changes in brain circuits that have previously been linked to human speech. The genetically altered mouse pups also showed differences in ultrasonic vocalizations they use when placed outside the comfort of their mothers' nests.

Another mice-study in **Mount Sinai School of Medicine, New York, NY, May 5, 2005;** Communicated by Peter Palese,(received for review October 13, 2004), they characterized mice with a disruption in the murine FOXP2 gene. Disruption of both copies of the FOXP2 gene caused severe motor impairment, premature death, and an absence of ultrasonic vocalizations that are elicited when pups are removed from their mothers. Disruption of a single copy of the gene led to modest developmental delay but a significant alteration in ultrasonic vocalization in response to such separation.

The findings of the study are detailed in the May 29 issue of the journal Cell (5)

Conclusion

They are many other factors that enable speech. The genetic basis for language will be found to involve many more genes that influence both cognitive and motor skills. Therefore, it is not possible to imagine that the development of language relied **exclusively on a single mutation in FOXP2.**

Human larynx has descended so that it provides a resonant column for speech; for example, genetically encoded modifications of vocal tract morphology, which give us a **longer oral cavity and lower larynx** than other primates, are crucial for modern human speech, allowing us to produce a dramatically increased repertoire of sounds. Human mind needs human cognition and human cognition relies on human speech. We cannot envisage humanness without the ability to think abstractly, but abstract thought requires language.

Shortly, Konopka and colleagues' work does what important discoveries usually do:

- answers many questions, but raises even more.
- may show evolutionary relationships between FOXP2 proteins in different species revealed through genome sequencing, and uncovers potential mechanisms underlying the elaboration of human-specific traits such as speech. However, it also provides a starting point for future studies of the molecular basis of language and human evolution.

In a paper published in Nature, **Geschwind** and fellow UCLA neurogeneticist **Genevieve Konopka** provide this approach:

"But though FOXP2 has been dubbed “the language gene,” language is certainly far more complicated, involving hundreds and probably thousands of genes, interconnected and ever-shifting in their activity. Researchers needed an approach that delved into this complexity. We were able to identify a network of genes connected to FOXP2. Maybe this will give us an entry into to the broader view of what’s going on. We won’t just study one gene, but the whole biological network related to language. FOXP2 is the window, but the network is going to be the story.”(6)

In his **‘Essay concerning Humane Understanding’ the English Philosopher Locke wrote in 1689** under the heading ‘Brutes have memory’: ‘‘Birds learning of Tunes and the endeavors one may observe in them to hit the notes right put it past doubt with me, that they have Perception, and retain Ideas in their Memories and use them for Patterns. (. . .) It cannot with any appearance of Reason, be suppos’d (much less proved) that Birds, without Sense and Memory, can approach their Notes, nearer and nearer by degrees, to a Tune played yesterday’’.

By turning to birds to understand the role of FOXP2 in song learning we might in turn discover something about how language evolved for the purpose of ‘Humane Understanding’. (7) As a consequence, FOXP2 cannot be called **directly ‘the gene for speech’ or ‘the gene for language’**. It is just one element of a complex pathway involving multiple genes, and it is too early to tell whether its role within that pathway is special but future studies of FOXP2 could provide a significant wedge into the understanding of our unique linguistic heritage.

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