FOXP2

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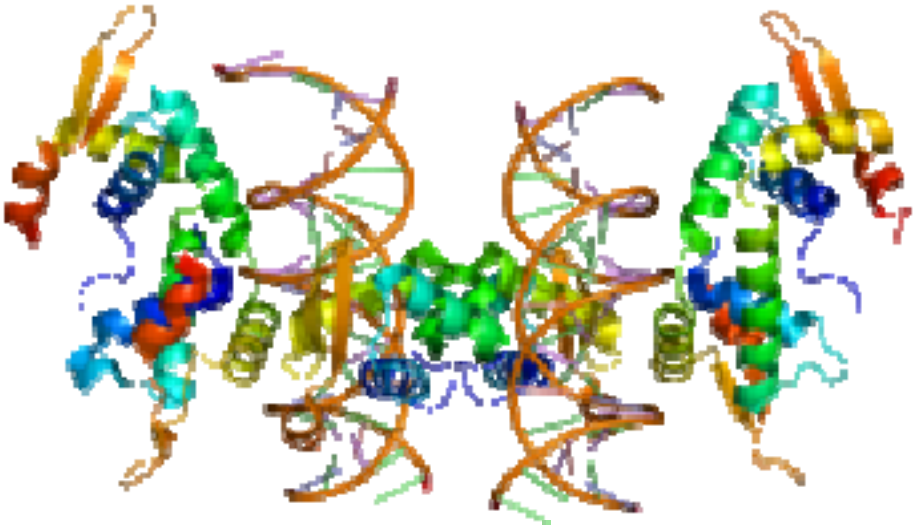


PDB rendering based on 2a07. // FOXP2 gene is located on the long (q) arm of chromosome 7 at position 31.

Forkhead box protein P2 (**FOXP2**) is a protein that, in humans, is encoded by the *FOXP2* gene, also known as *CAGH44*, *SPCH1* or *TNRC10*, and is required for proper development of speech and language.[1] Initially identified as the genetic factor of speech disorder in KE family, its gene is the first gene discovered associated with speech and language.[2] The gene is located on chromosome 7 (7q31, at the *SPCH1* locus), and is expressed in fetal and adult brain, heart, lung and gut.[3][4] *FOXP2* orthologs[5] have also been identified in other mammals for which complete genome data are available. The *FOXP2* protein contains a forkhead-box DNA-binding domain, making it a member of the FOX group of transcription factors, involved in regulation of gene expression. In addition to this characteristic forkhead-box domain, the protein contains a polyglutamine tract, a zinc finger and a leucine zipper. The gene is more active in females than in males, to which could be attributed better language learning in females.[6]

In humans, mutations of *FOXP2* cause a severe speech and language disorder.[1][7] Versions of *FOXP2* exist in similar forms in distantly related vertebrates; functional studies of the gene in mice[8] and in songbirds[9] indicate that it is important for modulating plasticity of neural circuits.[10] Outside the brain *FOXP2* has also been implicated in development of other tissues such as the lung and gut.[11]

FOXP2 is popularly dubbed the "language gene", but this is only partly correct since there are other genes involved in language development.[12] It directly regulates a number of other genes, including *CNTNAP2*, *CTBP1*, and *SRPX2*.[13][14]

Two amino acid substitutions distinguish the human *FOXP2* protein from that found in chimpanzees,[15] but only one of these two changes is unique to humans.[11] Evidence from genetically manipulated mice[16] and human neuronal cell models[17] suggests that these changes affect the neural functions of *FOXP2*.

Discovery

FOXP2 and its gene were discovered as a result of investigations on an English family known as the KE family, half of whom (fifteen individuals across three generations) suffered from a speech and language disorder called developmental verbal dyspraxia. Their case was studied at the Institute of Child Health of University London College.[18] In 1990 Myrna Gopnik, Professor of Linguistics at McGill University, reported that the disorder-affected KE family had severe speech impediment with incomprehensible talk, largely characterized by grammatical deficits.[19] She hypothesized that the basis was not of learning or cognitive disability, but due to genetic factors affecting mainly grammatical ability.[20] (Her hypothesis led to a popularised existence of "grammar gene" and a controversial notion of grammar-specific disorder.[21][22]) In 1995, the University of Oxford and the Institute of Child Health researchers found that the disorder was purely genetic.[23] Remarkably, the inheritance of the disorder from one generation to the next was consistent with autosomal dominant inheritance, i.e., mutation of only a single gene on an autosome (non-sex chromosome) acting in a dominant fashion. This is one of the few known examples of Mendelian (monogenic) inheritance for a disorder affecting speech and language skills, which typically have a complex basis involving multiple genetic risk factors.[24]

In 1998, Oxford University geneticists Simon Fisher, Anthony Monaco, Cecilia S. L. Lai, Jane A. Hurst, and Faraneh Vargha-Khadem identified an autosomal dominant monogenic inheritance that is localized on a small region of chromosome 7 from DNA samples taken from the affected and unaffected members.[3] The chromosomal region (locus) contained 70 genes.[25] The locus was given the official name "SPCH1" (for speech-and-language-disorder-1) by the Human Genome Nomenclature committee. Mapping and sequencing of the chromosomal region was performed with the aid of bacterial artificial chromosome clones.[4] Around this time, the researchers identified an individual who was unrelated to the KE family, but had a similar type of speech and language disorder. In this case the child, known as CS, carried a chromosomal rearrangement (a translocation) in which part of chromosome 7 had become exchanged with part of chromosome 5. The site of breakage of chromosome 7 was located within the SPCH1 region.[4]

In 2001, the team identified in CS that the mutation is in the middle of a protein-coding gene.[1] Using a combination of bioinformatics and RNA analyses, they discovered that the gene codes for a novel protein belonging to the forkhead-box (FOX) group of transcription factors. As such, it was assigned with the official name of FOXP2. When the researchers sequenced the *FOXP2* gene in the KE family, they found a heterozygous point mutation shared by all the affected individuals, but not in unaffected members of the family and other people.[1] This mutation is due to an amino-acid substitution that

inhibits the DNA-binding domain of the *FOXP2* protein.[26] Further screening of the gene identified multiple additional cases of *FOXP2* disruption, including different point mutations[7] and chromosomal rearrangements,[27] providing evidence that damage to one copy of this gene is sufficient to derail speech and language development.

Function

Foxp2 is expressed in the developing cerebellum and the hindbrain of the embryonic day 13.5 mouse. Allen Brain Atlases

FOXP2 is required for proper brain and lung development. Knockout mice with only one functional copy of the *FOXP2* gene have significantly reduced vocalizations as pups.[28] Knockout mice with no functional copies of *FOXP2* are runted, display abnormalities in brain regions such as the Purkinje layer, and die an average of 21 days after birth from inadequate lung development.[11]

FOXP2 is expressed in many areas of the brain[15] including the basal ganglia and inferior frontal cortex where it is and is essential for brain maturation and speech and language development.[13]

A knockout mouse model has been used to examine *FOXP2*'s role in brain development and how mutations in the two copies of *FOXP2* affect vocalization. Mutations in one copy result in reduced speech while abnormalities in both copies cause major brain and lung developmental issues.[11]

The expression of *FOXP2* is subject to post-transcriptional regulation, particularly micro RNA, which binds to multiple miRNA binding-sites in the neocortex, causing the repression of FOXP2 3'UTR.[29]

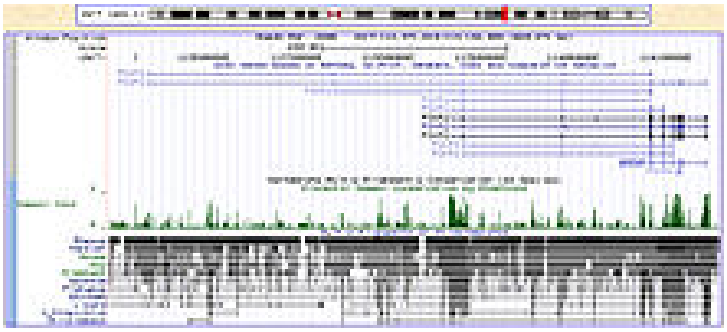
Clinical significance

There are several abnormalities linked to *FOXP2*. The most common mutation results in severe speech impairment known as developmental verbal dyspraxia which is caused by a translocation in the 7q31.2 region [t(5;7)(q22;q31.2)].[1][4] A missense mutation causing an arginine-to-histidine substitution (R553H) in the DNA-binding domain is thought to be the abnormality in KE.[30] A heterozygous nonsense mutation, R328X variant, produces a truncated protein involved in speech and language difficulties in an individual and two of their close family members.[7] R553H and R328X mutations also affected nuclear localization, DNA-binding, and the transactivation (increased gene expression) properties of *FOXP2*.[31][32] Although DVD associated with *FOXP2* disruptions are thought to be rare (~2% by one estimate),[7] a faulty copy of *FOXP2* in individuals always causes speech and language problems.

Several cases of developmental verbal dyspraxia in humans have been linked to mutations in the *FOXP2* gene.[27][33][34][35] Such individuals have little or no cognitive handicaps but are unable to correctly perform the coordinated movements required for speech. fMRI 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 "language gene". People with this mutation also experience symptoms not related to language (not surprisingly, as *FOXP2* is known to affect development in other parts of the body as well).[36] Scientists have also looked for associations between *FOXP2* and autism, and both positive and negative findings have been reported.[37][38]

There is some evidence that the linguistic impairments associated with a mutation of the *FOXP2* gene are not simply the result of a fundamental deficit in motor control. For examples, the impairments include difficulties in comprehension. Brain imaging of affected individuals indicates functional abnormalities in language-related cortical and basal/ganglia regions, demonstrating that the problems extend beyond the motor system.

Evolution



Human *FOXP2* gene and evolutionary conservation is shown in a multiple alignment (at bottom of figure) in this image from the UCSC Genome Browser. Note that conservation tends to cluster around coding regions (exons).

The *FOXP2* gene is highly conserved in mammals.[39] Human gene differs from non-human primates by the substitution of two amino acids, threonine to asparagine substitution at position 303 (T303N) and asparagine to serine substitution at position 325 (N325S).[30] In mice it differs from that of humans by three substitutions, and in zebra finch by seven amino acids.[15][40][41] One of the two amino acid difference between human and chimps also arose independently in carnivores and bats.[11][42] Similar *FOXP2* proteins can be found in songbirds, fish, and reptiles such as alligators.[43][44]

DNA sampling from Neanderthal bones indicates that their *FOXP2* gene is similar to those of modern humans.[45]

The *FOXP2* gene showed indications of recent positive selection.[39][46] Some researchers have speculated that positive selection is crucial for the evolution of language in humans.[15] Others, however, have been unable to find a clear association between species with learned vocalizations and similar mutations in *FOXP2*.[43][44] Insertion of both human mutations into mice, whose version of *FOXP2* otherwise differs from the human and chimpanzee versions in only one additional base pair, causes changes in vocalizations as well as other behavioral changes, such as a reduction in exploratory tendencies. A reduction in dopamine levels and changes in the morphology of certain nerve cells are also observed.[16]

However, *FOXP2* is extremely diverse in echolocating bats.[47] Twenty-two sequences of non-bat eutherian mammals revealed a total number of 20 nonsynonymous mutations in contrast to half that number of bat sequences, which showed 44 nonsynonymous mutations.[42] Interestingly, all cetaceans share three amino acid substitutions, but there are not differences between echolocating and non-echolocating baleen cetaceans.[42] Within bats, however, amino acid variation correlated with different echolocating types.[42][42]

Interactions

FOXP2 interacts with a regulatory gene *CTBP1*.[48] It also downregulates *CNTNAP2* gene, a member of the neurexin family found in neurons. The target gene is associated with common forms of language impairment.[49] It regulates the repeat-containing protein X-linked 2 (*SRPX2*), which is an epilepsy and language-associated gene in humans, and sound-controlling gene in mice.[50]

Mice

In a mouse *FOXP2* knockout study, loss of both copies of the gene caused severe motor impairment related to cerebellar abnormalities and lack of ultrasonic vocalisations normally elicited when pups are removed from their mothers.[28] These vocalizations have important communicative roles in mother-offspring interactions. Loss of one copy was associated with impairment of ultrasonic vocalisations and a modest developmental delay. Male mice on encountering female mice produce complex ultrasonic vocalisations that

have characteristics of song.[51] Mice that have the R552H point mutation carried by the KE family show cerebellar reduction and abnormal synaptic plasticity in striatal and cerebellar circuits.[8]

Birds

In songbirds, *FOXP2* most likely regulates genes involved in neuroplasticity.[9][52] Gene knockdown of *FOXP2* in Area X of the basal ganglia in songbirds results in incomplete and inaccurate song imitation.[9] Similarly, in adult canaries higher *FOXP2* levels also correlate with song changes.[41] Levels of *FOXP2* in adult zebra finches are significantly higher when males direct their song to females than when they sing song in other contexts.[52] Differences between song-learning and non-song-learning birds have been shown to be caused by differences in *FOXP2* gene expression, rather than differences in the amino acid sequence of the *FOXP2* protein.[36] Knockout of *FOXP2* reduced dendritic spines of spiny neurons in Area X which was even more pronounced when knockout occurred before they differentiated into spiny neurons.[53]

FOXP2 also has possible implications in the development of bat echolocation.[30] [42][54]