CHAPTER 9

FOXP Genes, Neural Development, Speech and Language Disorders
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Abstract

Foxp subfamily genes were recently recognized to be members of the Fox gene family. Foxp subfamily members contain a zinc finger domain and a leucine zipper motif in addition to a forkhead domain and their DNA binding capacities and transcriptional activities are regulated by homo- and heterodimerization via a zinc finger and a leucine zipper motif. Three Foxp subfamily members are abundantly expressed in developing brains. The expression patterns of these genes are overlapping, but they are distinctly expressed in some regions. Thus these genes appear to be involved in the development control of the central nervous system. Recently, FOXP2, a member of the Foxp subfamily, was identified as the first gene to be linked to an inherited form of language and speech disorder. The discovery of a mutation in FOXP2 in a family with a speech and language disorder opened a new window to understanding the genetic cascades and neural circuits that underlies speech and language via molecular approaches. The spatiotemporal FOXP2 mRNA expression pattern suggests that the basic neural network that underlies speech and language may include motor-related circuits, including frontostriatal and/or frontocerebellar circuits. This assumption is supported by brain imaging data obtained by using fMRI and PET on the FOXP2-mutated patients and also by analysis of Foxp2 mutant mice.

Introduction

The Fox gene family encodes a large group of transcription factors that share a common DNA binding domain of sequences called the forkhead or winged helix motif after the founding member of this gene family, forkhead in Drosophila. Many Fox family members are involved in embryonic morphogenesis and mutations in Fox genes have been implicated in a range of human developmental disorders. Foxp subfamily genes were recently recognized to be members of the Fox gene family. Members of the Foxp subfamily contain a zinc finger domain and a leucine zipper motif in addition to a forkhead domain. Recent studies have revealed that three Foxp subfamily members are abundantly expressed in developing brains and that the expression patterns of these genes are overlapping, but distinctly in some regions. Thus these genes appear to be involved in development of the central nervous system. Recently, FOXP2, a member of the Foxp subfamily, was identified. It is the first gene to be linked to an inherited form of language and speech disorder. The discovery of a mutation in FOXP2 in a family with a speech and language disorder opens a new window to understanding of the genetic cascades and neural circuits that underlies speech and language via molecular approaches. In this chapter, we focus on the neural expression of FOXP2 as a 'Language Gene' as well as the expression patterns of other Foxp subfamily members and their correlation with anatomical and functional abnormalities in the brains of FOXP2-mutated patients.

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The Foxp Subfamily

The Foxp subfamily, which consists of four members, Foxp1, Foxp2, Foxp3 and Foxp4, is characterized on the basis of its members containing a C2H2-type zinc finger domain and a leucine zipper motif in addition to a forkhead domain at the C-terminus. C-terminal location of the forkhead domain is an atypical feature in the Foxp subfamily, as most other Fox family members have this domain in N-terminal portion. Among the subfamily members, Foxp1, Foxp2 and Foxp4 are highly homologous (showing more than 60% identity at the amino acid level); in particular, their forkhead domains show approximately 80% identity at the amino acid level. Also, Foxp1 and Foxp2, but not Foxp4, have polyglutamine tracts at the N-terminus and these may be involved in protein-protein interactions.

Members of the Fox family of proteins have been demonstrated to bind to target DNA as monomers. By contrast, Foxp1, Foxp2 and Foxp4 proteins require dimerization for DNA binding and their transcriptional activities are regulated by homo- and heterodimerization. The dimerizations are dependent on the conserved stretch of sequence, containing a zinc finger and a leucine zipper motif.

Although one might suspect that the FOXP2 gene, being linked to an inherited language and speech disorder, might be a human-specific gene, because speech and language is unique to humans, orthologs exist in many species. Comparison of the Foxp2 genes of many organisms has revealed that the Foxp2 protein is rather extraordinarily conserved (among the 5% most conserved proteins) among mammals. There are only two amino acids different (out of 715 amino acid residues) between humans and chimpanzees and three different between humans and mice. Surprisingly, the amino acid sequence of the forkhead domain is completely identical among rodents, nonhuman primates and humans. Recently, Krause and colleagues reported that the Neanderthals carried a FOXP2 protein that was identical to that of modern humans in the two positions that differed between humans and chimpanzees.

Discovery of FOXP2 as a ‘Language Gene’

Speech and language disorders are common in childhood. Although twin studies have shown that genetic factors play an important role in the etiology of such disorder, a gene that predisposes individuals to speech and language disorders had not been identified until FOXP2 was discovered. In 1990, Hurst and colleagues reported a unique case of a large three-generation pedigree (called the KE family), half of whose members have a developmental verbal dyspraxia that is inherited in a pattern consistent with an autosomal dominant penetrance. (Details of the language impairments of the KE family will be addressed later). Using standard positional cloning techniques in combination with bioinformatics, Fisher and colleagues performed a genome-wide search for the candidate gene underlying the speech and language disorders in this family. They mapped the gene locus to the long arm of chromosome 7. In 2001, they finally identified FOXP2 as the gene responsible for this speech and language disorder by further analyzing the breaking point of the genome of a patient, CS, who had similar symptoms to the affected members of the KE family and a translocation between chromosomes 5 and 7.

The one point mutation in the FOXP2 gene of the affected members of the KE family is predicted to result in an arginine-to-histidine substitution (R553H) in the forkhead domain of the FOXP2 protein. R553 is invariant among all FOX proteins in species ranging from yeast to humans. This mutation occurred in every affected KE family member, but not in unaffected members, nor in unrelated control subjects. The translocation breakpoint in CS disrupted the gene structure of FOXP2. Furthermore, a nonsense mutation at arginine 328 (R328X) in the FOXP2 gene was found in a family, whose affected members had orofacial dyspraxia. Therefore, it is likely that the amino acid substitution in FOXP2 protein leads to a loss of function of one copy of the FOXP2 gene and that the remaining copy is insufficient for FOXP2 function (haploinsufficiency). There are several examples of human disease states regarded to be the consequence of haploinsufficiency of FOX proteins: mutations in FOXCl, FOXC2, FOXE1 and FOXL2 in humans are associated with