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A Window on the Genetics of Human Speech: The *FOXP2* Gene

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Abstract: The development of human speech seems to be a species-specific and genetically determined capacity and is considered an extremely important step in the rise of modern humans, human culture and civilisation. The multidisciplinary efforts of psychiatrists, linguists and human geneticists led to the identification of genetic elements in cohorts of patients, performing speech and language disorders. A form of special language impairment (SLI) has been identified in the KE family in Britain, as a dominant, autosomal trait, affecting the family members in three generations. Molecular genetic studies revealed a mutation in the *FOXP2* gene as possible basis of SLI in these patients. The unique, human variant of *FOXP2* is shared with Neandertals, indicating a common, ancestral population 3-400,000 years ago. Imprecise imitation of the tutor's song occurs in young canaries with lowered *FoxP2* expression.

Introduction

The spectacular development of molecular genetics has basically changed our view about living organisms. One of these aspects is the surprising fact that the species (fungi, plants, animals) harbour a very similar set of genes either structurally or functionally. Genes, basic regulatory circuits and systems, though developed hundreds of million years ago, are obviously similar in all species studied so far. This observation seems contradictory if we compare with the diversity of living/eradicated species, or even with the diversity of individuals within a non-selected population. This contradiction can be explained by the action of species-specific genes and alleles, determining ontogenesis. Decrease of the evolutionary distances increases the similarity of the genomes, regarding chromosomal numbers and organization, the nucleotide and amino acid sequences of genes and the encoded proteins.

The level of identity in the nucleotide sequence of humans and our nearest living relatives, the chimpanzees is 98.5 % (Ebersberger, 2002). An important difference between us – beyond anatomic, physiologic, social, etc. differences – is that we can talk and they can not. In spite of restless tuition efforts chimpanzees in human environment never acquire the capacity of speech (Terrace et al., 1979). Although the genomics of our nearest extinct relatives, the Neandertals is still in its infancy, the first results demonstrate a very close relationship with modern humans at the DNA sequence level. On the other hand, breakthrough DNA megasequencing approaches enable construction of the first draft of the Neandertal genome in the near future (Green et al., 2006).

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The children affected by SLI develop normally, but at the age of 3-4 years their communication is confined to words, while non-affected children use sentences at this age. Familial cases of SLI and twin studies implicated the involvement of genetic factors at chromosomes 7, 16 and 13. Furthermore, association of language impairment in a broad sense has been established to loci on chromosomes 1, 2, 3, 6, 15, 18, 19 and 21 (Lewis et al., 2006). Association of SLI with mutant alleles of the *FOXP2* gene demonstrated an apparent genetic basis of human speech.

In this paper we summarize the linguistic, psychiatric and genetic consequences of *FOXP2* gene mutations and their impact on human speech.

The involvement of genetic factors in speech disorders

A four-year-old child usually employs a vocabulary of thousands of words and creates complex sentences. In spite of stimulating and communicative environment there are always children suffering from communication deficits, although obvious mental or physiological reasons are missing. A recent survey reported that SLI affects 7% of the population in the USA at the age of six (Bishop, 2001).

The language disability and diagnosis of its deficits involves more or less arbitrary threshold values. The International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) is a coding of diseases and signs, symptoms, abnormal findings, complaints, social circumstances and external causes of injury or diseases, as classified by the World Health Organization (WHO). According to the ICD-10 guidelines a decline of 2-SD that normally holds for the chronologic age is required for a positive diagnosis.

The diagnostic system offered by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, American Psychiatric Association (DSM-IV, APA, 1994) includes three categories of language impairment: The phonological disorder, the expressive disorder and the combination of both. Whether these subtypes represent separate symptoms remains a question unsolved yet (Bishop et el., 1995).

To overcome the difficulties, rising during diagnosis/phenotype determination in an affected, but unrelated population, twin studies were performed. Monozygotic twins (MZT) are considered genetically equal, whereas dizygotic twins (DZT) share about 50 % of their genes as normal siblings do. MZT pairs diagnosed by criteria for specific speech or language impairment on a broader sense performed a concordance nearly 100 %, whereas DZT pairs showed a concordance rate approximately 50 %, and there was a similarity in the type of disorder in concordant twins also (Bishop et el., 1995).

These results supported the observations reporting accumulation of speech disorders within families. Familial clustering of the disorders argues for genetic risk factors, but these observations may be compromised by the different environments of the family members (age, social background, communicative stimulations, etc.) in nuclear families, compared to the extended family (Lahey and Edwards, 1995). A further support for the involvement of genetic elements in speech disorders rather then environmental factors was provided in a study among adopted children: Speech impairment of the biological parents put their children in a high risk category to develop similar symptoms. This assumption holds for adopted, affected children living with unaffected adoptive parents. On the other hand, no increase of the risk was observed for unaffected children who had adoptive parents with speech impairment (Felsenfeld and Plomin, 1997). The data accumulated in the above family, twin and adopted children studies have furnished hint and encouragement for human geneticists for dissecting the genetic bases of speech disorders. Theoretically, two approaches can be utilized: The assessment of the candidate gene(s) based on the phenotype, and the positional cloning.

Candidate gene approach

There are sometimes pathologic events that allow insights into the protein function, encoded by a mutant gene. A recent paper describes mouse mutants for the a1 and a2 chains of type IV collagen, a major component of the basement membrane, a ubiquitous extracellular element, harboured by all multicellular animals, including humans. The authors suggest that the spontaneous intraorbital hemorrhages observed in the mouse are a clinically relevant phenotype with a relatively high predictive value to identify carriers of *COL4A1* or *COL4A2* mutations among humans (Favor et al., 2007). Indeed, different mouse mutants for the same gene manifest – among others – ophthalmologic phenotypes that may probably have diagnostic power for humans carrying similar mutations (Gould et al., 2005; Gould et al., 2006). Although the candidate gene approach is promising in terms of less labour invested, it can often lead to dead end, as our informations on gene and protein functions are limited.

Positional cloning approach

The vast majority of the human genome consists of non-coding, often repetitive elements. (A recent assessment puts the ratio of coding sequences of the human genome less, than 2%). The family of variable number of tandem repeats includes the microsatellite sequences in humans that consist of a simple DNA sequence (say, the CAT trinucleotide), repeated at variable extent. These microsatellite markers are components of the chromosomes, they are inherited in a Mendelian fashion, exactly as genes do, and are characteristic for each individual. Determination of the microsatellite pattern is therefore suitable for biological identification of human individuals that is widely applied in criminality and paternity tests, or in so called genetic fingerprinting.

Nowadays, positional cloning of a suspected disease gene involves cooperation of clinicians and geneticists, where clinicians establish a cohort of patients suffering in an inherited disease by strict diagnostic criteria, whereas geneticists analyze their genome by establishing linkage map of microsatellite markers, possibly within the same kinship of sanguineous relatives. As microsatellite markers at the same position of the different, individual chromosomes show different morphologies, or lengths in individuals, the probability of each morphologic variants can be determined in the average human population. If the genetic analysis reveals that the affected patients of the same kinship carry the same morphologic marker at certain position of their genome, it can be considered as linkage disequilibrium, i.e. the microsatellite marker may be at a close vicinity of the "disease gene". This observation allows then confining the search on the locus around the disequilibrium marker by involvement of further microsatellite sequences. Usually, the disease locus can be narrowed down to about one million base pairs that may consist of just a few genes and the site of the mutation can be determined by conventional mutational analysis of the coding regions, which normally means sequencing of about 20000 nucleotides.

The symptoms of SLI in affected members of the KE family

Hurst and coworkers described the large, three-generation KE family in Britain, consisting of 37 family members. 15 members of the family, 8 women and 7 men suffered in a severe speech disorder (Hurst et al., 1990). This spectacular way of transmission of the trait revealed that a mutation occurred in a single gene in the family, the gene was autosomal and not X-chromosomal, since roughly equal women and men were affected, and the mutation was dominant, as roughly the half of the family members showed language impairment.

This observation, established by means of classical Mendelian genetics, strongly suggested that even a single genetic variant could disrupt the capacity of speech and contributed to the hypothesis that oral communication was an innate human property (Pinker, 1994). To our knowledge, this is the only case demonstrating the deleterious effect of a single gene on human speech. Although the inheritance of the trait is simple autosomal dominant, the phenotype triggered by the mutation is rather complex. The pathology of the affected individuals arises from the central nervous system (CNS) that impairs several aspects of brain function. The phenotype includes articulatory problems, language impairment and cognitive deficits (Fisher et al., 2003; Fisher, 2005).

Affected individuals have difficulty in controlling the coordinated mouth movements needed for articulated, correct speech, referred to as motoric speech disorder or developmental verbal dyspraxia (Hurst et al., 1990; Vargha-Khadem et al., 1995), but they can execute slow oral movements correctly. The impairment remains in the adulthood even following speech therapy and is not a consequence of the failure of the facial musculature as these patients perform normally in all tests of their limbs (Watkins et al., 2002).

The language impairment extends on both oral and written communications (Vargha-Khadem et al., 1995; Watkins et al., 2002). Affected family members perform significantly worse in written tests of verbal fluency and in spelling unfamiliar words or nonwords (sublexical processes) than the unaffected persons. The phenotype includes deficits in receptive domain, measured by tests of lexical decision, where they were not able to decide whether the presented word is real or nonword in English. Finally, the disorder disrupts both comprehension and grammar production, they have serious difficulties in understanding complex sentences, generating word inflections or word derivation.

The symptoms of the affected KE family members include cognitive deficits also. Their mean nonverbal IQ is significantly lower, than in unaffecteds (Vargha-Khadem et al., 1995; Watkins et al., 2002). This observation raised the hypothesis that the deficit is a consequence of a general cognitive impairment. However, a moderate reduction in nonverbal cognition can be observed in unaffected family members that may mean that this deficit does not necessarily follow the dominant inheritance of the trait, as these persons do not perform speech and language impairments. The other way around, some affected individuals, who have severe speech difficulties, perform normally in nonverbal cognition tests (Vargha-Khadem et al., 1995; Watkins et al., 2002). Inspection of subtests of IQ measurements indicated that the affected individuals had a deficit compared to unaffecteds in learning arbitrary associations between symbols and digits (Watkins et al., 2002). The complexity of the KE phenotype left a question open about the core deficit; Watkins and coworkers (2002) suggest that the performance on a nonword, complex articulated repetition task may be considered the biological marker of the phenotype. This deficit includes impairment in sequencing or procedural learning.

Molecular genetic deciphering the phenotype: The *SPEECH1* gene

Although the debates continued about the core KE deficit, a consensus raised following the above studies that a single, autosomal dominant gene mutation is suitable to disrupt articulated speech and to trigger severe language disability. Taking the advantages of positional cloning, Fisher and coworkers (1998) set up a genome-wide search in the KE family and identified a region on chromosome 7 showing the properties of linkage disequilibrium, a locus in the affected individuals that inherited unchanged. The affected individuals carried the same microsatellite markers in this chromosomal segment, suggesting a common core genetic element of about six million base pairs at 7q31 (chromosome 7, longer arm, band 31). Further narrowing of the map was not possible at that time, since

microsatellite markers were not available in such a great variability and number as today. The human genome consists of three billion base pairs; therefore the identified locus represents about two thousandths of the whole genome, but still is a huge chromosomal segment, which may contain 50-100 genes, including the mutant allele of the desired but unknown *SPEECH1* gene, observed in the KE family. Discovery of further microsatellite markers in the 7q31 region allowed narrowing the locus of *SPEECH1* gene up to about three millions of base pairs (Lai et al., 2000).

This achievement itself did not solve the enigma of the exact position of *SPEECH1* gene; fortunately, Lai and coworkers (2000) studied an unrelated patient, CS, who was diagnosed with developmental verbal dyspraxia and language impairment. Karyotyping of CS demonstrated a chromosomal mutation, a reciprocal exchange, or translocation of genetic material between the long arms of chromosomes 7 and 5. This translocation was not observed in the patient's parents and there was no family history of any speech and language impairment. These data suggest that the translocation in patient CS may have occurred during early embryonic development. The observed symptoms and the cytogenetic data suggested the involvement of the *SPEECH1* region in the breakpoint on chromosome 7. The subsequent molecular genetic analysis explored the exact position of the breakpoint within a yet uncharacterized gene, which became literally disrupted. Normally this gene codes for a transcription factor protein, a polypeptide that regulates the transcription of other genes, for example according to the needs of the developing embryo, and provides a spatially-temporally regulated expression of the target genes. Transcription factors are numerous structurally-functionally; the compromised allele in patient CS encodes a protein called forkhead box, family P, member 2 (FOXP2). The spatial structure of this protein family resembles a forkhead or the opened wings of a bird; these domains of the protein interact with the regulatory regions of the target genes, represented by short, special nucleotide sequences, and enhance their expression.

A gene mutation of *FOXP2* in the KE family

All data suggested that the underlying mutation occurred in the *FOXP2* gene of KE family members. Sequencing of the gene revealed a guanine to adenine nucleotide transition in all affected members that caused an arginine to histidine amino acid substitution at the protein level. The arginine exchanged in the affected persons of the KE family can be found in all members of the FOX protein family in one of the "wings" of the polypeptide. This arginine occurs in FOX proteins of all organisms studied so far, in baker yeast *Saccharomyces cerevisiae*, in the worm *Caenorhabditis elegans*, in the fruit fly *Drosophila melanogaster*, up to humans. A mutation of this residue in the FoxN1 protein of the mouse triggers a severe developmental disorder, an immunodeficient nude phenotype, owing to loss of function of the mutated gene product (Schlake et al., 2000). Patient CS and affected KE family members carry one disrupted *FOXP2* allele and harbour an intact copy too. The basis of the onset of the language impairment is therefore haploinsufficiency, the desired protein is present only at a 50 % concentration and can not fulfill its function in critical steps during development of the foetal brain, where *FOXP2* is expressing at a high level among other organs (intestine, lungs) (Lai et al., 2001; Bruce and Margolis 2002).

Animal models for *FOXP2* mutations

Mice are genetically tractable and a mouse model of the orthologous *FoxP2* gene has recently been developed by the gene knock-out technique. This multistep approach results in targeted gene disruption and generates loss of function or null alleles. Mice, like humans, are

diploid organisms, and harbour two copies of homologous autosomes inherited from their mum and dad that usually carry the same genes in the same order. Directed crossings of transgenic animals enables generating -/+ heterozygotes, -/- homozygotes and their phenotype can be compared to +/+ homozygotes or wild-type animals. Disruption of both copies of the *Foxp2* gene in -/- homozygotes caused severe motor impairment; the newborn pups died prematurely, and demonstrated an absence of ultrasonic social vocalizations that are elicited when pups are removed from their mothers. Disruption of a single copy of the gene in -/+ heterozygotes led to modest developmental delay but to a significant alteration in ultrasonic vocalization in response to separation from the mother (Shu et al., 2005).

The spatiotemporal expression of the *FOXP2* gene among humans and songbirds is very similar, and confines to the analogous anatomical structures. Therefore, learning of human speech and tutored vocalization of songbirds are comparable behavioral and neural events. During song learning from adult individuals the expression of the *Foxp2* gene increases in the basal ganglia song nucleus, called Area X in young zebra finches. Local inhibition of *FoxP2* expression in Area X of young canaries compromises their ability to incorporate most new syllables of the seasonally changing song (Haesler, 2007). The phenotypes observed in mice and zebra finches strongly resembles the overlapping CS and KE phenotype.

Slightly altered genetic variants of FOXP2 in mammals

The FOXP2 protein is extremely conserved among different mammalian species. The chimpanzee, pygmy chimp, gorilla and rhesus macaque FOXP2-s are identical compared to each other, display one amino acid difference from the mouse, and two differences from the human protein. Orang-utan has two differences from mouse and three from humans (Enard et al., 2002; Zhang et al., 2002). Therefore, only humans among living organisms harbour a protein that shows two different amino acid substitutions: Threonine to asparagine at position 303 and asparagine to serine at 325. The human *FOXP2* gene was sequenced in 54 individuals from all of the continents and these substitutions remained unchanged, indicating that these amino acid alterations in the FOXP2 protein should have been fixed in humans (Enard et al., 2002; Zhang et al., 2002). The study was extended into 29 nonhuman species including one bird and 28 placental organisms. The majority of these species carry a FOXP2 variant with the animal-specific threonine-asparagine substitution with an exception of Carnivora (cat, dog, wolf, wolverine, bear, fox, seal, sea lion), which have a threonine-serine substitution at positions 303 and 325, respectively. This observation suggests that a single human-like substitution is insufficient for acquiring speech and language (Zhang et al., 2002). The time of the onset of these mutations/changes in the human *FOXP2* gene was estimated to occur 200.000 years ago (Enard et al., 2002), or not earlier than 5000 generations or 100.000 years ago. Both estimations are concomitant with the proposed rise of anatomically modern humans about 150.000 years ago. The appearance of the language based oral, and then written communication provided humans with an enormously important selection advantage that lead to the emerging of the early human civilizations as early as ~5000-10,000 years ago.

These estimations must be revised in the light of recent results of Neandertal genomics. Well preserved skeletal parts of Neandertals were discovered at the El Sidrón cave site (Asturias, Spain) with the average calibrated age of about 43000 years (Rosas et al., 2006). Inspection of the *FOXP2* gene of our closest extinct relatives revealed that they shared our *FOXP2* variant. This observation puts the genetic change leading to the present human *FOXP2* gene 300.000-400.000 years ago in the common ancestor of modern humans and Neandertals (Krause et al., 2007), but does not answer the question whether acquiring human *FOXP2* genetic variant itself is sufficient for articulated speech.

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