Genetics of Speech and Language Disorders[1]

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Keywords

stuttering, dyspraxia, specific language impairment, dyslexia, linkage, lysosomal targeting pathway, *FOXP2*, mouse vocalization

Abstract

Vocal communication mediated by speech and language is a uniquely human trait, and has served an important evolutionary role in the development of our species. Deficits in speech and language functions can be of numerous types, including aphasia, stuttering, articulation disorders, verbal dyspraxia, and specific language impairment; language deficits are also related to dyslexia. Most communication disorders are prominent in children, where they are common. A number of these disorders have been shown to cluster in families, suggesting that genetic factors are involved, but their etiology at the molecular level is not well understood. In the past decade, genetic methods have proven to be powerful for understanding these etiologies. Linkage studies and molecular genetic analyses in a large family containing multiple individuals affected with verbal dyspraxia led to the discovery of mutations in the *FOXP2* gene. This gene encodes a forkhead domain transcription factor, a finding that has led researchers to a new avenue of investigation into the substrates and mechanisms that underlie human speech development. In studies of stuttering, linkage and candidate gene approaches in consanguineous families identified mutations in the lysosomal enzyme-targeting pathway genes *GNPTAB*, *GNPTG*, and *NAGPA*, revealing a role for inherited defects in cell metabolism in this disorder. In specific language impairment, linkage studies have identified several loci, and candidate gene association studies are making progress in identifying causal variants at these loci. Although only a small fraction of all cases of speech and language disorders can be explained by genetic findings to date, the significant progress made thus far suggests that genetic approaches will continue to provide important avenues for research on this group of disorders.

INTRODUCTION

Humans are characterized by the remarkable richness and complexity of their verbal communication. Human communication is often divided into two aspects, speech and language. Speech generally refers to the mechanical aspects of verbal communication. It requires the proper use of articulation (making proper speech sounds), voice (generated by the vocal folds of the larynx), and fluency (smooth flow of syllables and words). Language is a higher-order function, based on accepted rules that govern what words mean, how to make new words, how to put words together, and what word combinations are appropriate in specific situations (**http://www.asha.org/public/speech/development/language_speech.htm**). Speech disorders include articulation disorders, such as a lisp; fluency disorders, such as stuttering; and dyspraxia, which is a failure to generate and properly sequence speech sounds. In contrast, language disorders are deficits in encoding or decoding information in phrases and sentences according to accepted rules, such as those of grammar. Language disorders include specific language impairment (SLI) and dyslexia. Most of these disorders have been the subject of genetic studies (**Table 1**).

Speech and language disorders can be classified as expressive, in which affected individuals have difficulties expressing speech or language; as receptive, in which individuals have problems understanding speech or language; or as mixed, in which both comprehension and production are impaired. In many cases, discriminating a speech disorder from a language disorder in a specific individual is difficult. This is particularly true in individuals who have suffered a stroke or other trauma to the brain, as such individuals may manifest both expressive and receptive speech and language deficits. In otherwise normally developing children, several speech and language disorders are commonly observed.

Although vocal communication is common in higher organisms, fully developed speech and language are unique to humans. This uniqueness and the fact that many of these disorders originate in the brain present significant challenges to research on speech and language disorders. However, many of these disorders run in families, raising the possibility that genetic approaches might be used to better understand their genesis and treatment.

GENETIC STUDIES OF STUTTERING

Evidence of Genetic Contributions to Stuttering

Stuttering is a common speech disorder affecting the flow of speech, characterized by uncontrollable repetitions or prolongations of words or syllables, or by silent interruptions of speech, known as blocks. It often arises in young childhood, typically at age two to four years, with an estimated lifetime incidence rate in the population of approximately 5% (12). In the majority of these cases (75%–80%), the individuals recover within a few years after onset, with recovery in females more common than in males. This results in a prevalence of persistent stuttering in the population of approximately 1%, with a male-to-female ratio of approximately 4:1 (2, 12, 110).

Although the etiology of stuttering has been poorly understood, there has long been evidence supporting genetic contributions to this disorder. Reports describing familial clustering of stuttering were made as early as 1939 in studies published by Nelson (68), Gray (34), Wepman (104), and West et al. (105). These investigators studied the families of individuals who stuttered, and compared the number of affected relatives in such pedigrees with that found in control pedigrees. The results of these three independent studies were similar, and overall, they found that the number of affected relatives in the families of individuals who stuttered was 4–6 times higher than that in the control families. Since then, multiple studies have reported familial clustering of stuttering (15, 34, 49, 59, 103, 111). Such familial clustering could arise from shared genes, shared environment, or both. A number of twin studies have helped to disentangle these

Table 1 Notable genetic studies of communication disorders

Method	Gene	Results	References
Stuttering			
Segregation analysis in families	—	Found complex inheritance pattern for stuttering	15
Twin study	—	Found a higher concordance rate in MZ twins than in DZ twins	3, 25, 45, 73
Sex ratio	—	Found that affected males outnumbered females	18, 110
Linkage analysis in families	—	Found suggestive linkage on chromosomes 2, 7, 9, and 15	95
Combined linkage and association analysis	—	Found suggestive linkage on chromosomes 3, 13, and 15 and association signal on chromosomes 3, 9, and 13	108
Linkage analysis in families	—	Found suggestive linkage on chromosome 18p	86
Linkage analysis in families and targeted candidate gene sequencing	*GNPTAB*	Found significant linkage on chromosome 12q23.3 as well as a missense mutation in four consanguineous families	47, 78
Systemic candidate gene sequencing	*GNPTG* and *NAGPA*	Found multiple mutations in unrelated stuttering cases	47
Verbal dyspraxia			
Family study	—	Reported on the KE family, which has multiple affected members of verbal dyspraxia	46
Linkage analysis in families and targeted sequencing in a family	*FOXP2*	Found significant linkage on chromosome 7q31 and mutated *FOXP2* gene in the KE family	29, 52, 53
Fine mapping in families	—	Found that *FOXP2* does not reside in the autism locus on chromosome 7q31	69
Candidate gene sequencing	*FOXP1*	Found two de novo mutations in FOXP1 in cases with intellectual disability and/or autism	39
Specific language impairment			
Linkage analysis in a family	—	Found significant linkage on chromosome 13q21	6
Association study of candidate gene	*CNTNAP2*	Showed that *CNTNAP2* is one of the target genes regulated by FOXP2, and found significant association of SNPs in *CNTNAP2* with SLI	101
Linkage analysis in families and association study in targeted region	*CMIP* and *ATP2C2*	Found significant linkage on chromosome 16q, and detected significant association of the SNPs in *CMIP* and *ATP2C2* with short-term memory	13, 14, 23, 70
Dyslexia			
Linkage analysis in families	—	Found significant linkage on chromosome 15 (LOD score = 3.2)	90

(*Continued*)

Table 1 (*Continued*)

Method	Gene	Results	References
Linkage and association studies in families	—	Replicated linkage of dyslexia to chromosome 15	35, 62, 65, 80
Targeted sequencing and association analysis	*DYX1C1*	Identified two SNPs associated with dyslexia	96
Association study in families	*DYX1C1*	Found a nonsynonymous SNP associated with dyslexia	7
Linkage analysis in a family	—	Detected significant linkage to chromosome 3 in a Finnish family	71
Candidate gene sequencing	*ROBO1*	Found that partial haploinsufficiency for ROBO1 may cause dyslexia in humans	40
Linkage and association studies in families	—	Suggested chromosome 6p21 as a locus for dyslexia	28, 35, 36, 89, 98
Association studies in a candidate locus	*DCDC2* and *KIAA0319*	Suggested *DCDC2* and *KIAA0319* as candidate genes for dyslexia	13, 30, 41, 64, 81

Abbreviations: DZ, dizygotic; MZ, monozygotic; SLI, specific language impairment; SNP, single-nucleotide polymorphism.

potential contributions. Although these studies differed in size, diagnostic methods, and other aspects, they all demonstrated a greater concordance of stuttering in monozygotic (MZ) compared with dizygotic (DZ) twins. Concordance rates for stuttering in MZ twins ranged from 20% to 63%, while concordance in DZ twin pairs ranged from 3% to 19% (3, 25, 45, 73). These results suggested substantial heritability for stuttering, in the range of 0.65–0.83 (3, 19, 25, 73).

In addition to twin studies, adoption studies have also been performed. Such studies have generally been too small to generate strong statistical significance. However, one study suggested that stuttering occurs in the adopted children of stuttering parents no more frequently than in the general population, arguing against the view that children learn to stutter by listening to their parents (26). In addition, studies have noted that the profile of stuttering symptoms at onset is relatively distinct from that seen in persistent adult stutterers, who typically have developed a variety of reactive secondary features to the disorder over time. This further suggests that stuttering is not a learned behavior (12).

The substantial evidence supporting genetic contributions to stuttering motivated several studies that included segregation analysis to determine the most likely mode of inheritance in this disorder. One study of 386 stuttering probands and their first-degree relatives suggested that polygenic genetic components, rather than a single major locus, were more likely to explain the mode of inheritance in stuttering (15). Thus, although genetic factors clearly contribute to stuttering, there has been little agreement on the most likely mode of inheritance of such factors, and the evidence for the existence of single alleles of large effect in stuttering has been inconsistent.

Genetic Linkage Studies of Stuttering

Despite uncertainties regarding some aspects of the genetics of stuttering, the ability to ascertain many families with multiple cases of stuttering motivated initiation of linkage studies. The first genome-wide linkage scan for stuttering was performed by our group at the National Institute on Deafness and Other Communication Disorders at the National Institutes of Health (86). We genotyped 392 microsatellite

markers in 68 families recruited from North America and Great Britain, and generated a maximum nonparametric linkage (NPL) score of 1.51 at the marker *D18S976*. Although this score was below the level necessary for genome-wide statistical significance, it suggested that chromosome 18 may harbor a locus for stuttering. No clear evidence supporting a particular mode of inheritance emerged from this study.

The Illinois International Genetics of Stuttering Project, led by Cox at the University of Chicago, also performed a genome-wide linkage scan in 100 families of European descent with at least two affected members in the family (95). They typed more than 10,000 single-nucleotide polymorphism (SNP) markers and performed nonparametric linkage and family-based association tests. They identified a sex-specific linkage on chromosome 7 (LOD score = 2.99) in the analysis for males, and on chromosome 21 (LOD score = 4.5) for females, suggesting that expression of genetic factors in stuttering varies according to the sex of the individuals carrying these genetic elements. Additional suggestive linkage was found on chromosome 9 (LOD score = 2.3) when both persistent and recovered stutters were included, and on chromosome 15 (LOD score = 1.95) for persistent stutters only. Family-based association tests (FBATs) produced no associations that were significant at the genome-wide level, and none of the suggestive FBAT signals overlapped with any of the most significant linkage signals.

Wittke-Thompson et al. (108) performed another interesting linkage study of stuttering in the Hutterites, a founder population in the United States. This study included 48 affected individuals connected in a single 232-person genealogy containing 9 generations. Linkage test statistics—including NPL_{all}, NPL_{pairs}, the transmission disequilibrium test, and a family-based association test—were used to search for linkage or association between stuttering and microsatellite and SNP markers. The study found nominally significant linkage on chromosomes 3 ($p = 0.013$), 13 ($p = 0.012$), and 15 ($p = 0.02$). A meta-analysis that pooled these results with those from the study of 100 families of European descent linkage resulted in nominal evidence for linkage on chromosomes 2 ($p = 0.013$) and 5 ($p = 0.0051$), although this linkage evidence did not meet the criteria for genome-wide significance. Thus, overall, the three genome-wide linkage studies described above found only modest evidence for linkage, and none of these linkage loci were replicated across different studies (86, 95, 108). These results may be due to several factors, including locus and allelic heterogeneity, reduced penetrance, and common occurrence of phenocopies, all of which have complicated the study of other complex diseases.

One approach to overcome these problems is to use highly consanguineous families. Consanguinity can reduce genetic heterogeneity because affected individuals are typically homozygous by descent from a very recent common ancestor. Consanguinity also generally increases homozygosity, which can raise the chances of being affected when alleles act in an additive fashion to produce the disorder. To pursue this strategy for stuttering, Riaz et al. (78) recruited 44 consanguineous families from the city of Lahore and surrounding areas in Pakistan. Each family had multiple cases of persistent stuttering. A genome-wide linkage scan was performed using the Marshfield Weber 9 microsatellite marker panel in a total of 199 individuals—144 affected and 55 unaffected—in these 44 families. Although nonparametric linkage analysis showed evidence of linkage on chromosomes 1, 5, and 7, the most significant linkage (NPL = 4.61) was found at the marker *PAH* on chromosome 12q23.3. The study also analyzed whether this linkage derived from the accumulation of small effects in multiple families or from a large effect in one or a few families. The analysis found that the largest family, designated PKST72, contributed the largest effect to the linkage score on chromosome 12.

Following up on this result, Kang et al. (47) determined that the linkage region extended from the marker *D12S101* to *D12S1597* (extending from base-pair position 94,220,151 to 104,175,626 in the March 2006 version of

the UCSC Genome Browser), and began an investigation of this 10-Mb linkage interval in detail. Bioinformatic analysis revealed 87 known and predicted genes in this interval. Exons, exon/intron boundaries, 5′UTRs, and 3′UTRs of 45 of these genes were sequenced for all the available individuals in the family PKST72. Several hundred common and rare variants were found, and their cosegregation with the stuttering in this family was evaluated. Many variants tightly cosegregated, which was expected because they were within the same linkage locus. The mutation showing the highest degree of cosegregation with stuttering was a variant predicted to result in the substitution of lysine for the normal glutamic acid at position 1200 (Glu1200Lys) in the *GNPTAB* gene (OMIM #607840). This gene encodes GlcNAc-1-phosphotransferase, alpha/beta subunits (EC 2.7.8.17). The normal glutamic acid at this position is fully conserved in all vertebrates, implying that it serves an important function in this enzyme. However, segregation of the Glu1200Lys mutation with stuttering in this family was not perfect because of the presence of several apparently nonpenetrant cases, and because three affected individuals lacked this mutation. Because the majority of stutterers, especially women, naturally recover (110), the finding of unaffected mutation carriers was not unexpected. In addition, PKST72 contains three affected individuals who did not carry the Glu1200Lys mutation. Given the heterogeneous genetic (86, 95, 108) and nongenetic causes of stuttering, such phenocopies were also not unexpected. Sequencing of the *GNPTAB* gene in other Pakistani stuttering families showed that the affected members of three other families carried the same Glu1200Lys mutation. Studies of unrelated stuttering subjects revealed that 5 out of 123 Pakistani cases and 1 out of 270 North American–British cases carried either one or two copies of this same mutation. None of 276 Caucasian controls carried this mutation, although it was found in one ostensibly normal Pakistani individual in heterozygous fashion. Additional sequencing of the *GNPTAB* gene in unrelated cases (all with a family history of stuttering) revealed three other mutations that were never observed in the 276 controls. Together, these results suggested that mutations in *GNPTAB* can cause stuttering.

Additional evidence came from studies of two other genes. One of these, *GNPTG* (OMIM #607838), encodes a protein subunit that combines with the product of the *GNPTAB* gene to form the functional GlcNAc-1-phosphotransferase enzyme. Sequencing of this gene identified three different mutations in four different cases, but no mutations in normal controls. Sequencing of another functionally related gene, designated *NAGPA*, revealed three different mutations in six unrelated cases, but no mutations in normal controls.

The *GNPTAB*, *GNPTG*, and *NAGPA* genes encode the components of the lysosomal enzyme-targeting pathway. This pathway results in the addition of the mannose-6-phosphate moiety to N-linked oligosaccharides on a diverse group of enzymes destined to reside in the lysosome (51). This process is known as the lysosomal enzyme-targeting pathway; it consists of an initial step, performed by GlcNAc-1-phosphotransferase (EC 2.7.8.17) encoded by the *GNPTAB* and *GNPTG* genes, followed by a second step, mediated by the product of the *NAGPA* gene, which encodes phosphodiester α-GlcNAcase (EC 3.1.4.45) (51). *NAGPA* (also known as the uncovering enzyme) cleaves off the GlcNAc moiety, uncovering terminal mannose-6-phosphate, which is recognized by the mannose-6-phosphate receptors, and results in the ultimate transport of the labeled enzyme to the lysosome. **Figure 1** illustrates this process.

Mutations in *GNPTAB* that completely abolish the activity of GlcNAc-phosphotransferase cause the fatal lysosomal storage disease mucolipidosis II (I-cell disease, OMIM #252500). Mutations that reduce the GlcNAc-phosphotransferase activity to 2%–15% of normal cause mucolipidosis III_A (pseudo-Hurler polydystrophy, OMIM #252600), which displays a milder phenotype (42, 77). Mutations in *GNPTG* are known to

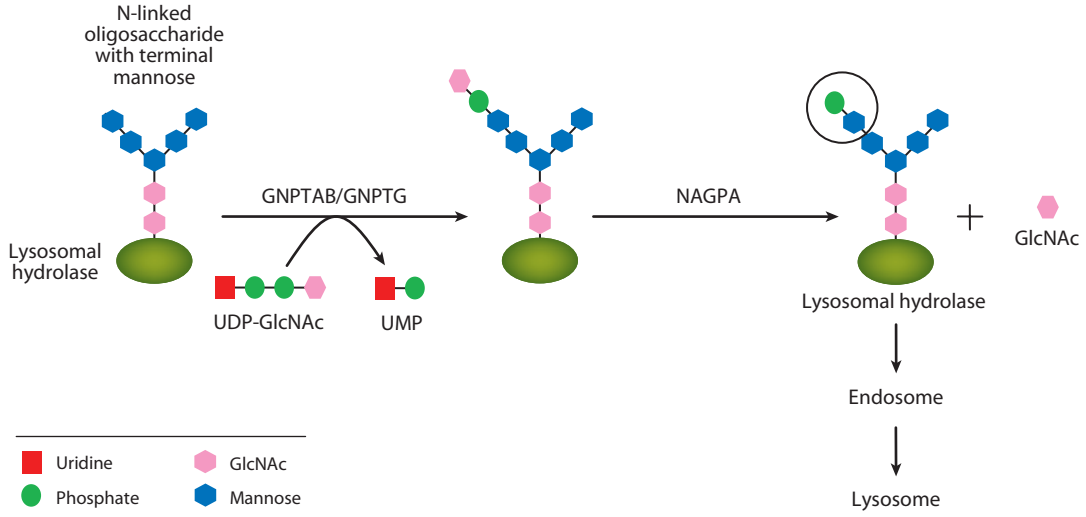

Figure 1

Generation of the mannose-6-phosphate recognition markers on lysosomal enzymes. In the first step, GlcNAc-phosphotransferase (GNPTAB/GNPTG) catalyzes the transfer of GlcNAc-1-phosphate from UDP-GlcNAc to the terminal mannose residues of N-linked oligosaccharides on enzymes destined to reside in the lysosome. In the second step, phosphodiester α-GlcNAcase (NAGPA), also known as the uncovering enzyme, cleaves off the GlcNAc moiety, uncovering mannose-6-phosphate (*circled*). These tagged enzymes are recognized by mannose-6-phosphate receptors and transported to the lysosome.

cause mucolipidosis III_C (OMIM #252605), which is the least severe of these diseases. All three mucolipidoses are rare autosomal recessive disorders that cause severe symptoms characterized by coarse facies, psychomotor retardation, mental retardation, radiologic changes in skeleton, connective tissue abnormalities, and respiratory insufficiency. No human disease had been previously reported to be associated with mutations in the *NAGPA* gene. A clinical examination of several individuals who stutter and who carry mutations in these genes failed to reveal any signs or symptoms of mucolipidosis. These results suggest that mutations in these three genes are capable of causing nonsyndromic stuttering, and that such individuals do not simply have a mild form of mucolipidosis. Overall, in a group of 393 unrelated individuals who stutter, mutations in one of these three genes were observed in 21 individuals, or approximately 5%.

Interestingly, mucolipidosis II patients have severe speech deficits and are largely unable to speak (55, 75). There is also a case report of a patient with mucolipidosis III with stuttering and unclear speech (91). More generally, deficits in one of the individual enzymes that reside in the lysosome also may cause stuttering or similar disorders. Speech deficits have been reported in other lysosomal storage diseases, including Tay–Sachs disease, Salla disease, and sialuria (56, 60, 82, 99). For example, in patients with late-onset Tay–Sachs disease, stuttering has been suggested to be an early disease marker, presenting earlier than other symptoms such as muscle weakness, gait disturbance, or psychiatric disturbances (82). MacQueen et al. (60) surveyed the neuropsychiatric aspects of 64 cases with late-onset Tay–Sachs disease, and found that 11 of these (17%) were stutterers, a rate greatly exceeding that in the normal adult population. So, although the results of Kang et al. (47) suggest that stuttering can be associated with abnormal function of the lysosomal enzyme-targeting pathway, it appears that other inherited lysosomal dysfunctions may lead to stuttering as well.

Mutations in the lysosomal enzyme-targeting pathway account for only a fraction of familial stuttering. However, additional studies in consanguineous Pakistani families suggest that a similar approach should be effective for identifying other genes underlying nonsyndromic stuttering. For example, Raza et al. (76) recently identified linkage at a locus on chromosome 3q13.2-3q13.33 that generated a LOD score of 4.23 under an autosomal recessive model, with no evidence for linkage under other models. This location does not overlap with any of the loci identified in the linkage studies described above. Thus, although stuttering remains a genetically complex trait, such approaches in consanguineous families hold the promise of identifying additional genes that cause this disorder, which at this point seem likely to exist.

Analysis of the mutations identified in *GNPTAB* has begun to offer insights into the population history of stuttering mutations. The one North American–British stuttering case carrying the Glu1200Lys mutation was of Asian Indian ancestry. The finding that all eight individuals carrying this mutation were of either Pakistani or Indian ancestry raised the question of whether this might represent a founder mutation with a single origin. Fedyna et al. (24) genotyped 33 SNPs surrounding the *GNPTAB* gene in individuals carrying this mutation. Haplotype analysis showed that all eight individuals shared a single haplotype block, which is at least 6.67 kb in length, surrounding this mutation. The data suggest an estimated age of this mutation of approximately 572 generations, or 14,300 years based on a 25-year generation time.

FOXP2 AND VERBAL DYSPRAXIA

Mutated *FOXP2* in Verbal Dyspraxia

The identification in 1987 of a family with a striking speech disorder, designated the KE family, was an important early milestone in the genetics of communication disorders. This large family consisted of three generations containing 37 members, 15 of whom display a severe developmental verbal dyspraxia characterized by a failure to generate proper orofacial movements required for speech. A number of these 15 individuals also displayed features of language disorder characterized by grammar deficits (46). This disorder displayed an autosomal dominant, monogenic mode of transmission. A genome-wide linkage scan in this family identified significant linkage (maximum LOD score = 6.62) within a 5.6-cM interval on chromosome 7q31 (29). Without additional families with the same disorder that showed linkage to the same locus, further refinement of the gene location proved difficult. However, a subsequent study used fluorescence in situ hybridization (FISH) to study two unrelated patients with a similar speech and language disorder. In one of these patients (designated CS), they localized a de novo reciprocal translocation with breakpoints on chromosomes 7q and 5q:t(5;7)(q22;q31.2) (52). This translocation appeared to disrupt a gene on chromosome 7 called *FOXP2*. Sequencing of this gene revealed a mutation in the KE family. A substitution of A for the normal G, resulting in a histidine in place of the normal arginine (R553H), was found in exon14 of all the affected individuals in a heterozygous form in the KE family (53). This mutation was not found in unaffected family members, and the *FOXP2* gene was proposed as the likely gene involved in this disorder (53). A subsequent study evaluated this gene in 49 unrelated cases of developmental verbal dyspraxia (58), and identified three exonic variants in three different cases, including a nonsense mutation (R328X). None of these variants were found in controls, and mutations in *FOXP2* became widely accepted as a cause of developmental verbal dyspraxia. However, *FOXP2* mutations were found in only a few percent of such cases, which suggested that *FOXP2* mutations are not a common cause of speech disorders in the general population. Additional studies also showed that they are not a common cause of SLI or autism (69).

FOXP2 encodes a transcription factor that contains a polyglutamine tract and a forkhead DNA-binding domain. The R553H mutation is located in the DNA-binding domain at a position fully conserved in all the known members of the large family of forkhead domain-containing proteins. This implied that the normal arginine residue is important for forkhead domain function, and that the mutant histidine affects the DNA-binding activity and nuclear localization of FOXP2 (53, 102). FOXP2 is known to act as a transcriptional repressor by directly binding to the regulatory region of target genes (102). In an effort to investigate the effects of the R553H mutation on DNA-binding function, electromobility shift assays and luciferase assays were performed, and the results showed that mutant FOXP2 could not repress the SV40 promoter because of its failure to bind to the target DNA (102). This supported the view that *FOXP2* encodes a developmental transcriptional regulator that controls the growth and differentiation of a class of neurons destined to innervate tissues primarily involved in speech production.

In an effort to understand this developmental process, investigators have sought to identify the target genes regulated by FOXP2. In an initial study, Spiteri et al. (93) performed chromosome immunoprecipitation followed by microarray analysis using human fetal brain. Out of the 285 different genes bound by FOXP2, 34 were expressed in both the basal ganglia and the inferior frontal cortex, and were postulated to be involved in speech and language. Identification of the transcriptional targets of FOXP2 may reveal a gene linked to speech and language in the developing human brain. Many of these presumptive targets of FOXP2 encode proteins involved in neurite outgrowth and neural plasticity. A subsequent comparative study in humans and chimpanzees demonstrated that the two forms of FOXP2 present in these two species confer different transcriptional specificities, and a network analysis of the regulated genes identified relationships among them that are postulated to at least partly underlie differences in the vocal communication abilities of these two species (50). These studies have helped lay the foundations for understanding the speech and language circuitry within the brain.

Animal Models of Mutated *FOXP2*

Human speech and language are exceptionally complicated processes, requiring a large array of rapid motor functions and the use of complex rules of grammar. As such, it is currently uncertain how well the results obtained from animal models will apply to human speech and language. Mice are known to emit ultrasonic vocalizations—pups do so when they are removed from the nest, for example, as do adult males when they encounter female mice or their pheromones (20, 44). These vocalizations have frequencies that range between 30 and 110 kHz and have syllable types organized into phrases and motifs. Although these vocalizations do not mimic the complex communications of humans, mouse models may provide insights into the biological function of *FOXP2* in human.

Several knock-out (*Foxp2*-KO, *Foxp2*-flox) and knock-in (R552H-ENU, R552H-KI) mouse models were generated in which *Foxp2* was disrupted (21, 31, 32, 37, 84). Homozygous mice with two copies of disrupted *Foxp2* consistently displayed developmental delay accompanied by severe motor impairment, resulting in early death 3–4 weeks after birth. This may explain why none of the affected individuals in the KE family were homozygous for the *FOXP2*-R553H mutation, as homozygosity for this mutation may result in embryonic lethality. In contrast to the homozygotes, heterozygous mice showed normal development or only modest developmental delay. However, they emitted significantly altered vocalizations when isolated from their littermates (32, 84). Instead of a relatively pure tone (a "whistle"), the mutant mice generated a more broadband vocalization. These animals were evaluated at eight days of age, substantially before the development of hearing in mice (33, 83). Thus, although an alteration in expressive communication was clear, it was not clear how

this deficit affected the two-way interactions often present in vocal communication.

Evolutionary genetic analyses of *FOXP2* sequences suggested that two amino-acid substitutions (T303N and N325S) have recently undergone natural selection in humans, perhaps because of their advantageous effects on the speech and language function (22, 112). In an effort to investigate the effects of these human-specific alleles on speech and language function, Enard et al. (22) generated humanized knock-in mice by introducing these amino-acid substitutions into the orthologous exon of the mouse *Foxp2* gene. The knock-in mice with humanized *Foxp2* emitted ultrasonic vocalizations at approximately 5 KHz lower frequencies at peak compared with those from wild-type mice. Humanized *Foxp2* mice also displayed reduced dopamine levels, increased length of dendritic trees of medium spiny neurons, and long-term synaptic depression. Although these results confirm the role of *FOXP2* as a developmental regulator of neurons, including those involved in speech production, the complete identification of the target neurons and the understanding of how these neurons function uniquely in humans to generate speech remain tantalizing goals for future studies.

GENETIC STUDIES OF SPECIFIC LANGUAGE IMPAIRMENT

SLI is a disorder characterized by significant delay of language development in the absence of other impairments known to delay language acquisition, such as a speech disorder, hearing loss, neurological disease, brain damage, cognitive impairment, or autism spectrum disorder (ASD) (9), and in the absence of conditions that merely prevent verbal expression of language, such as motor impairment. Although the overall prevalence of SLI ranges from 5% to 8% among preschool children, it is frequently found together with other disorders, particularly ASDs, poor limb motor skills (43), or attention deficit/hyperactivity disorder (54). Thus, the frequency of nonsyndromic SLI subjects is somewhat less than the frequency of all disorders with SLI as a feature (74). Although the molecular mechanisms underlying SLI are unclear, there is substantial evidence for genetic factors associated with this disorder. A twin study showed that the concordance rate for SLI in 63 MZ twins was almost 100%, whereas in a sample of 27 DZ twin pairs, the concordance rate was 50% (10). In addition, familial clustering of this disorder has been reported (6, 87). In the past decade, the SLI Consortium (SLIC) at the Wellcome Trust Centre for Human Genetics has been organized with the goal of finding genetic causes of SLI, and significant progress on the identification of genetic factors has been made, as described in the following section.

CNTNAP2

Vernes et al. (101) hypothesized that downstream genes regulated by FOXP2 might be candidates for genes involved in SLI, in addition to their role in verbal dyspraxia. To test this idea, they performed a chromatin immunoprecipitation assay in an effort to identify genes bound by FOXP2. As described above, among the interesting DNA fragments that bind to FOXP2, they identified a number that reside within intron 1 of *CNTNAP2.* This gene encodes contactin-associated protein-like 2 (CASPR2), which is expressed in the developing human cerebral cortex. These investigators demonstrated that *CNTNAP2* expression was downregulated by the binding of FOXP2. A previous study found homozygous mutations in this gene in Old Order Amish children with cortical dysplasia–focal epilepsy (CDFE) syndrome. This syndrome features language regression, hyperactivity, impulsive and aggressive behavior, and mental retardation (94). In addition, multiple studies have suggested an association of *CNTNAP2* variants with ASD (1, 4, 5). These findings led Vernes et al. (101) to genotype 38 SNPs in the *CNTNAP2* gene in 184 families with SLI. Analysis with the quantitative transmission disequilibrium

test revealed that nine intronic SNPs, all in introns 13 and 14, were associated with the ability to repeat nonsense words (nonword repetition), a well-characterized subphenotype used in the diagnosis of SLI. In addition, some of these SNPs showed nominally significant association with expressive and receptive language abilities. However, functional studies of variants in *CNTNAP2* have not provided evidence for the mechanism of action of these variants in language impairment disorders.

Genome-Wide Linkage Scan for Specific Language Impairment

Several genome-wide linkage scans have been performed in an effort to identify SLI loci (6, 87, 88). Bartlett et al. (6) recruited five extended Canadian SLI families of Celtic ancestry and performed genome-wide linkage analysis. Three phenotypic measurements (clinical diagnosis, language impairment, and reading discrepancy) were analyzed under both dominant and recessive modes of inheritance. They reported linkage with a reading discrepancy measure, with a maximum multipoint LOD score of 3.92 on chromosome 13q21 (designated *SLI3*) under a recessive model.

The SLIC performed a much larger-scale genome-wide linkage study, with 98 families containing 473 individuals (87). Study subjects were evaluated for three quantitative traits (nonword repetition and the receptive and expressive scales of the *Clinical Evaluation of Language Fundamentals, Revised*). They identified two linkage loci, on chromosomes 16q (designated *SLI1*) and 19q (designated *SLI2*). The linkage loci identified by Bartlett et al. (6) and the SLIC groups (87, 88) did not overlap, a situation that has been commonly observed in genetic studies of many different complex traits. To increase their statistical power, the SLIC recruited an additional set of 86 families from four different centers in Great Britain. Phenotypes were gathered for the expressive language scores, receptive language scores, nonword repetition, and Wechsler Objective Reading Dimensions. Reading comprehension and spelling were also evaluated. Analysis of this additional data set produced evidence for linkage (maximum LOD score = 2.84) of markers at 16q (*SLI1*) with the nonword repetition phenotype, consistent with previous findings. Linkage evidence was also found on chromosome 19q for nonword repetition scores (maximum LOD score = 2.31), but not for expressive language (maximum LOD score = 0.27), which was the phenotype measure that displayed linkage in the previous SLIC study (87, 88).

CMIP and *ATP2C2*

Overall, the most promising linkage findings for SLI implicated chromosome 16q and nonword repetition, a finding that was replicated in two independent analyses (87, 88). To better understand these results, Newbury et al. (70) performed a targeted association study by genotyping 2,044 SNPs across the 10-Mb region containing the *SLI1* locus. Study subjects included 806 individuals from 211 SLIC families. Significant association was found between nonword repetition scores and seven SNPs in the *CMIP* gene, which encodes the c-Maf-inducing protein. *CMIP* is known to be highly expressed in the brain, but functional information regarding this gene is limited (67). Another association signal was found with six SNPs in the *ATP2C2* gene, which encodes the secretory pathway Ca^{2+}, Mn^{2+} transporting ATPase (the so-called SPCA2). This gene is prominently expressed in the brain and testis, and is involved in transporting cations, displaying a higher affinity for Mn^{2+} than for Ca^{2+} (109). Depletion of Mn^{2+} within the Golgi complex inhibits O-linked glycosylation of erythropoietin (EPO) and macrophage colony stimulating factor (M-CSF) in Chinese ovary hamster cells (48). Thus, abnormal transport of Mn^{2+} in the Golgi network may disrupt proper oligosaccharide processing of multiple enzymes, which could affect their transport to their final destinations, including the lysosome. A testable hypothesis would then be that *ATP2C2* variants may be associated with other speech disorders, particularly stuttering.

FOXP1

FOXP2 is a member of the forkhead domain transcription factor family, which includes other FOX family proteins such as FOXP1, FOXP3, and FOXP4 (57). Among the corresponding genes, *FOXP1* was regarded as a potential candidate for developmental verbal dyspraxia, because it is expressed where *FOXP2* is expressed (97) and the encoded protein interacts directly with FOXP2 (57). In addition, FOXP1 and FOXP2 share target genes, such as the *T1α* gene (85). Vernes et al. (100) sequenced *FOXP1* in 49 unrelated individuals with verbal dyspraxia and reported the presence of a nonsynonymous SNP changing proline to alanine at amino acid 215 (Pro215Ala), but this variant was also found in a control group at a similar frequency. This implies that *FOXP1* variants are not significant contributors to verbal dyspraxia.

Hamdan et al. (39) used a SNP-array-based genomic hybridization assay to search for association of copy-number variation with sporadic nonsyndromic intellectual disability (NSID) ($n = 30$) or ASD ($n = 80$). A de novo deletion was found in one NSID patient. This ~390-kb deleted region included exons 4–14 of *FOXP1*. Subsequent sequencing of all the exons of *FOXP1* in the 245 cases (110 with NSID, 84 with ASD, and 51 with both NSID and ASD) and 570 controls revealed another de novo nonsense mutation (p.R525X) in a patient with both NSID and ASD. The prospect of a pathogenic role for these two mutations is intriguing, but it is still unclear whether *FOXP1* mutations are informative for SLI, because the study subjects had phenotypes that included intellectual disability or ASD, which are exclusionary criteria for the diagnosis of SLI.

GENETIC STUDIES OF DYSLEXIA

Dyslexia is a common childhood disorder manifested by difficulty in reading and spelling in individuals who otherwise have normal educational opportunities and intelligence, and who do not otherwise have psychiatric or neurologic disorders. A deficit in phonological processing, which involves perception of speech sounds, has been suggested to be a prominent characteristic of dyslexia (27, 66, 92). However, because dyslexia is frequently accompanied by attention deficit/hyperactivity disorder (107) and SLI (11), clear and distinct phenotyping of this disorder is often difficult.

Dyslexia runs in families (35, 62, 65, 80, 90). A twin study showed that the concordance rate in MZ twins was 68%, compared with 38% in DZ twins (16), indicating that this familial clustering is at least partly due to genetic contributions. In a pioneering linkage study, analysis using 21 markers and chromosomal heteromorphisms revealed a LOD score of 3.2 at the marker *DYX1* on chromosome 15 (90). This linkage was supported by other subsequent linkage studies (35, 62, 65, 80). Subsequently, Nopola-Hemmi et al. (72) identified two translocations, t(1;15)(p13;q22) and t(2;15)(q11q;21), in the 15q21-q22 region. The translocation t(2;15)(q11q;21) was found in three affected members in one family. Further analysis of this breakpoint region by Taipale et al. (96) showed that the translocation occurred between exons 8 and 9 of the *DYX1C1* gene on 15q21. They sequenced the exons and UTR regions of the *DYX1C1* gene in 55 unrelated individuals with dyslexia and in 113 normal controls. They found 8 polymorphisms in this gene and observed suggestive association with dyslexia with two variants, −3G>A and 1249G>T. The −3G>A SNP lies within 5′UTR. The 1249G>T SNP is in exon10, and results in a truncated protein missing four amino acids at the C-terminus.

Further studies using populations from multiple regions—including the United Kingdom, Canada, Italy, and Finland—failed to confirm the association of these SNPs with dyslexia (8, 14, 62, 63, 79, 106). In contrast, Bates et al. (7) performed a family-based association study in 790 families in which they genotyped 13 SNPs in *DYX1C1*. They found that one nonsynonymous SNP, which encodes isoleucine in place of the normal valine in exon 2, was nominally associated with reading measures and spelling

of irregular words in a lexical-processing measure. The discrepancy between these replication studies may be due to the lack of uniform phenotype measurement, the different populations studied, or differences in the statistical analyses used. Therefore, the degree to which variations in the *DYX1C1* gene lead to dyslexia remains somewhat unclear.

An interesting and more complex story has emerged from studies of dyslexia in Finland. Initially, a genome-wide linkage scan was performed using a large Finnish family with 21 dyslexic individuals. This study produced a multipoint LOD score of 3.84 at a locus in the pericentromeric region (designated *DYX5*) of chromosome 3 (71). In addition, FISH analysis in an unrelated individual with infertility accompanied by dyslexia identified a balanced reciprocal translocation t(3;8)(p12;q11). Further analysis of the linkage region and the translocation breakpoint on chromosome 3 led the authors to propose the axon guidance receptor gene *ROBO1* (Roundabout, OMIM #602430) as a candidate for the causative gene at the *DYX5* locus (40). Further haplotype analysis surrounding *ROBO1* in the original Finnish family showed that 19 dyslexic family members shared one copy of a single rare *ROBO1*-associated haplotype. Expression of *ROBO1* was absent or highly attenuated in the individuals carrying this rare haplotype, indicating that haploinsufficiency of this gene may cause dyslexia (40).

Finally, interesting linkage and association signals for dyslexia have been found on chromosome 6p at a locus designated *DYX2*. Smith et al. (89) first suggested this as a locus for dyslexia based on a linkage study, a finding that was subsequently replicated in multiple studies (28, 35, 36, 98). At this locus, there are two suggested candidate genes, *DCDC2* (64, 81) and *KIAA0319* (13, 30, 41). These two genes are 200 kb apart, and the associations of the markers in these two genes with dyslexia were independent from each other. Together, these results provide convincing evidence that one or more genetic variants in this region play a role in dyslexia. Dennis et al. (17) subsequently analyzed this locus and identified seven SNPs in the promoter region of *KIAA0319* associated with the risk haplotype. Of these SNPs, the minor allele of rs9461045 had the strongest association with dyslexia. Using a luciferase reporter assay, they showed that the promoter region harboring this minor allele reduced the expression level of luciferase by creating a binding site for the transcriptional silencer OCT-1.

FUTURE ISSUES

Improved Gene-Finding Methods

Most familial speech and language disorders have demonstrated themselves to be complex traits, and it is therefore not surprising that linkage studies in families have frequently been disappointing. As suggested for other complex traits, such results are likely due to factors such as locus heterogeneity, incomplete penetrance, and diagnostic heterogeneity. Given the large efforts to date to ascertain and enroll multiplex families that segregate speech and language disorders, it seems unlikely that the existing linkage results will be significantly improved by repeating this strategy. However, linkage studies in highly consanguineous populations or in rare large families that display Mendelian segregation continue to hold promise for identifying variant alleles of large effect in these disorders.

Beyond linkage studies, population-based association studies have been a popular strategy for identifying causative variants underlying complex traits. In general, such studies have demonstrated the ability to clearly identify associated genetic variants, and case-control studies of targeted SNPs at loci previously suggested by linkage studies have provided important advances in our understanding of SLI and other communication disorders. Nevertheless, numerous shortcomings of genome-wide association studies have been documented (38, 61), suggesting that this approach alone may not be the most efficient path to understanding the molecular deficits that underlie these disorders. The ultimate level of genetic resolution is

provided by whole-genome sequencing, which is rapidly making its way into standard human genetics practice. At this time, it remains unclear what population sizes will be needed in such studies to ensure that the relatively vast amount of incidental genomic variation can be distinguished from the variation that causes familial speech and language disorders.

Functional Studies

Genetic linkage and association studies have suggested multiple candidate genes as the cause of speech and language disorders. However, at this time, relatively few functional mutations resulting in disruptions at the gene or protein level have been demonstrated in these disorders. By this criteria, for example, *FOXP2* is clearly established as a cause of verbal dyspraxia because several coding sequence mutations have been found in this gene, some of which affect the nuclear localization of the protein and change the activity of FOXP2 as a transcriptional repressor.

Several variants in *GNPTAB*, *GNPTG*, and *NAGPA* have been reported as mutations causing stuttering; however, the effects of these mutations on the activities of the encoded enzymes remain to be investigated. Further enzyme assay experiments may answer a number of outstanding questions, such as why stuttering individuals carrying mutations in these genes do not show any of the other symptoms associated with mucolipidosis. Additionally, an animal model for stuttering could provide a significant resource for functional studies of these genes. Because mouse strains engineered to contain knock-out mutations of these genes typically result in a phenotype similar to mucolipidosis, knock-in models of human mutations found in stuttering will be needed to understand the functional effects related to nonsyndromic stuttering.

Although multiple candidate genes have received experimental support as causative in SLI and dyslexia, the variations reported to date may be common or rare polymorphisms, and knowledge of the functional effects of these variants remains limited. Moving beyond genetic evidence for involvement of these genes will be needed to make progress in our understanding of the pathological mechanisms underlying these disorders.

Neuropathology

The notable successes that have identified specific causative genes in these disorders have not yet yielded similar advances in knowledge of how these gene defects lead to the observed pathology. A large part of this is due to our lack of understanding of the neural substrates and mechanisms that underlie speech and language in humans. Understanding the neural components of speech and language poses many challenges, but we suggest that knowledge of the genetic deficits that specifically lead to disorders of these functions may provide important new tools for this effort. Identification of the cells and pathways within the brain that are uniquely affected by these mutations presents exciting opportunities for future studies of these disorders as well as studies of normal speech and language development.

SUMMARY POINTS

1. Deficits in human communication can be categorized into speech and language disorders. Verbal dyspraxia and stuttering represent speech disorders; SLI and dyslexia represent language disorders.
2. Genome-wide linkage analysis in consanguineous families identified linkage to stuttering on chromosome 12q23.3. Subsequent analysis of this locus identified the Glu1200Lys mutation in *GNPTAB*, which is commonly associated with stuttering in South Asian populations, and other mutations in this gene in affected individuals in other populations.

3. Additional studies revealed mutations in *GNPTG* and *NAGPA* in stuttering. These two genes are functionally related to *GNPTAB*, and together, they encode the primary components of the lysosomal enzyme-targeting pathway, implicating an inherited deficit of intracellular lysosomal function in this disorder.
4. A genome-wide linkage analysis in a unique large family segregating verbal dyspraxia identified linkage to chromosome 7q31, and subsequent analysis of this region revealed that mutations in *FOXP2* cause this disorder. Comparative studies have implicated variation in this gene as important to the development of human speech, and chromosome immunoprecipitation studies have generated a number of candidate genes regulated by this transcription factor.
5. Mice are known to communicate via ultrasonic vocalization, and analysis of these vocalizations may result in useful animal models for human speech and language disorders. In early studies, mice with a mutated or humanized version of *Foxp2* have been shown to produce altered patterns of ultrasonic vocalization.
6. Efforts to identify the downstream genes regulated by the FOXP2 transcription factor have implicated the *CNTNAP2* gene, variants of which appear to be associated with SLI.
7. Linkage analysis and subsequent targeted association analyses have suggested that *CMIP* and *ATP2C2* are associated with language disorders (especially nonword repetition) and well-characterized phenotypic measures in these disorders.
8. Genetic studies of dyslexia proposed *ROBO1*, *DCDC2*, and *KIAA0319* as potential candidate genes for this disorder.

DISCLOSURE STATEMENT

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