

# On Genes, Speech, and Language

Simon E. Fisher, D.Phil.

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Learning to talk is one of the most important milestones in human development, but we still have only a limited understanding of the way in which the process occurs. It normally takes just a few years to go from babbling newborn to fluent communicator. During this period, the child learns to produce a rich array of speech sounds through intricate control of articulatory muscles, assembles a vocabulary comprising thousands of words, and deduces the complicated structural rules that permit construction of meaningful sentences. All of this (and more) is achieved with little conscious effort.

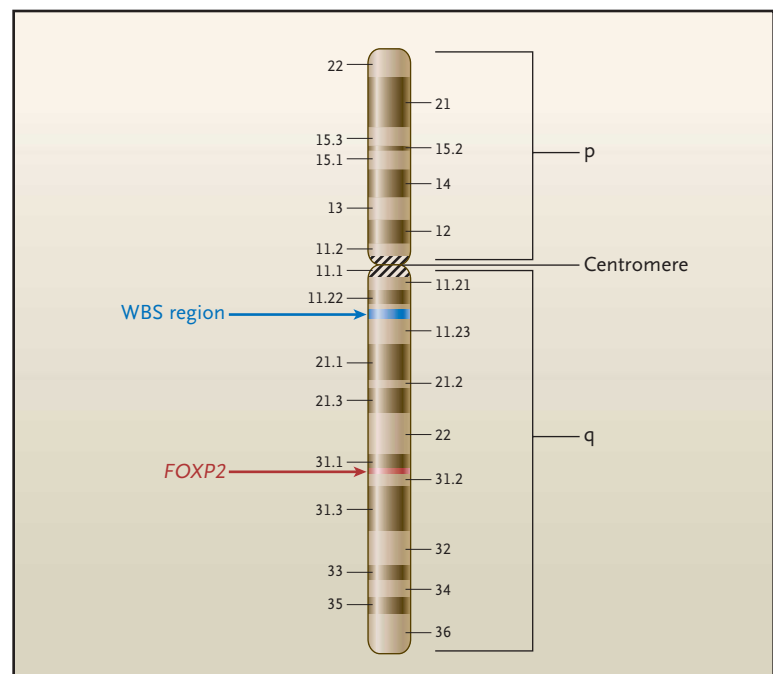
The acquisition of language usually proceeds along robust lines without any need for explicit tuition, in stark contrast to other complex learned abilities, like reading, writing, and mathematics. However, a small minority of children are unable to acquire speech and language proficiency, despite growing up in language-rich environments and showing adequate performance in other areas, such as hearing and non-verbal cognition. For some of these children, early difficulties with communication resolve with age, but for others the problems continue into adulthood. Since modern society depends heavily on language and literacy skills, persistent impairment is often accompanied by wider problems in educational, social, and emotional development in later life.

Developmental communication disorders are diagnosed in an ex-

clusionary manner (the presence of speech or language problems that cannot be explained by an obvious medical condition) and so encompass a wide variety of phenotypes.<sup>1</sup> For example, linguistic deficits can be confined to expressive language or can extend to receptive abilities, although pure receptive impairment is seldom seen. When it comes to speech output, affected children may fail to produce sounds that would be expected on the basis of age and dialect, which may be associated with difficulties in the planning and execution of the

fine motor sequences that underlie speech. This large variety of communication problems is reflected by diagnostic schemes that contain several distinct categories (expressive, mixed, phonologic, apraxic–dyspraxic, and so on). In practice, there frequently are co-existing disorders involving various types of impairment, and the boundaries between these disorders can be fluid; a person may move from one category to another at various stages of life.

Although the causes of these kinds of disorders remain largely elusive, familial clustering and



**Chromosome 7 Gene Dosage and Speech and Language Disorder.**

An ideogram of chromosome 7 shows cytogenetic banding (with two regions of the long q arm highlighted), a 600-kb region containing the *FOXP2* gene, and a 1.5-Mb interval that is commonly deleted in the Williams–Beuren syndrome (WBS). Point mutations and chromosomal abnormalities involving *FOXP2* are one cause of developmental verbal dyspraxia. Duplication of the WBS region may also be associated with a delay in speech.

twin-based heritability studies provide strong evidence of genetic influences.<sup>1</sup> At the same time, it is clear that the observed phenotypic heterogeneity is underpinned by a mixture of genetic effects, which range from common risk alleles acting in a multifactorial framework to rare instances of highly penetrant point mutations behaving in a classic mendelian fashion.<sup>2</sup> The dissection of such a complicated state of affairs calls on geneticists to use multiple complementary strategies of both a traditional and a novel nature. By adopting a variety of approaches, linkage studies of prevalent types of speech and language disorders have implicated several regions of the genome, most notably on chromosomes 3, 13, 16, and 19. The putative risk genes underlying these linkages have yet to be identified, but progress is encouraging.

In the case of a rare dominant mendelian form of impairment, it has been possible to go even further and home in on a specific gene, known as *FOXP2*, located in chromosomal band 7q31 (see diagram). People who carry heterozygous disruption of this gene have problems sequencing the precise movements of tongue, lips, jaw, and palate that contribute to intelligible speech (known as verbal dyspraxia or childhood apraxia of speech).<sup>3,4</sup> They also have difficulties with learning and production of non-speech sequences involving the orofacial musculature (orofacial dyspraxia) and have a broad profile of linguistic deficits in expressive and receptive domains — problems that affect both oral and written language. It has

been hypothesized that reduced amounts of functional *FOXP2* protein yield subtle anomalies in neural organization that impair speech and language acquisition.

A report in this issue of the *Journal* (pages 1694–1701) presents evidence that alteration in dosage of genes elsewhere on the long arm of chromosome 7 may be another cause of speech and language disturbances. Previously, studies of a rare cytogenetic abnormality known as supernumerary ring chromosome 7 indicated that large duplications of 7q are associated with severely retarded speech development.<sup>5</sup> In the current study, Somerville and colleagues have identified a boy with childhood apraxia of speech accompanied by dramatic disruption of expressive language, a disorder that appears to be caused by a 1.5-Mb duplication of 7q11.23.

These findings are intriguing on a number of counts. First, they add support to the hypothesis that the development of neural circuitry involved in speech and language acquisition can be highly sensitive to gene copy number. Although *FOXP2*-related disorder has thus far been linked to reduced functional dosage, the present study shows that increased levels of transcription of one or more genes may also be an important mechanism accounting for cases of speech and language disorder. Second, the duplicated interval of 7q11.23 corresponds directly with the region most commonly deleted in the Williams–Beuren syndrome (WBS), a neurodevelopmental disorder in which language tends to be an area of relative strength. Thus,

the consequences of deletion and duplication of this same interval appear to be strikingly different, at least with respect to speech articulation and expressive language. Third, the present report concerns only a single case, but the investigators speculate that duplication of the region could occur at a frequency similar to that of the common WBS deletion, since it is mediated by a related mechanism of interchromosomal recombination, involving flanking low-copy-number repeats. As such, 7q11.23 duplications may contribute to the incidence of unexplained deficits in speech and language in human populations.

The duplicated region in this case contains as many as 27 genes, and it is unclear which of these genes are relevant to the disorder. Somerville et al. demonstrate increased expression of several of the duplicated genes in lymphoblastoid cells, but relating this sort of finding to neurodevelopment could be difficult, particularly since neural tissue may tolerate changes in dosage of some genes but not others. Moreover, the genes whose increased dosage leads to language disruption in the child carrying the duplication may not necessarily be the same as the genes that yield an uneven linguistic profile in WBS. A proper understanding of genotype–phenotype relationships will require extensive future study and may depend on discovery of partial duplications of the common WBS region, as well as investigation of 7q11.23 gene polymorphism in cohorts of children with speech and language disorders, particularly those with speech apraxia.

We are just starting to unravel the genetic causes of developmental communication disorders and explore how they relate to language problems in other neurodevelopmental syndromes, such as autism and dyslexia. Success in this area raises the possibility of using molecular diagnostics for early identification of children who are at increased risk, thus enabling environmental interventions to begin at a younger age. Overall, genetic studies, in com-

ination with findings from other disciplines, such as neuroimaging and developmental psychology, hold promise for shedding light on the mechanisms by which speech and language acquisition can go awry.

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Dr. Fisher is a Royal Society Research Fellow at the Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, England.

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