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Decoding the genetics of speech and language

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Researchers are beginning to uncover the neurogenetic pathways that underlie our unparalleled capacity for spoken language. Initial clues come from identification of genetic risk factors implicated in developmental language disorders. The underlying genetic architecture is complex, involving a range of molecular mechanisms. For example, rare protein-coding mutations of the *FOXP2* transcription factor cause severe problems with sequencing of speech sounds, while common genetic risk variants of small effect size in genes like *CNTNAP2*, *ATP2C2* and *CMIP* are associated with typical forms of language impairment. In this article, we describe how investigations of these and other candidate genes, in humans, animals and cellular models, are unravelling the connections between genes and cognition. This depends on interdisciplinary research at multiple levels, from determining molecular interactions and functional roles in neural cell-biology all the way through to effects on brain structure and activity.

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Introduction

The emergence of spoken language is one of the most prominent cognitive developments in the evolution of our species. Without needing explicit instruction, human children acquire large numbers of words, learn to assemble them into complex sentences following sophisticated sets of rules, and become adept in production and perception of the sound streams that constitute speech. Researchers have begun to decipher the molecular basis of this remarkable suite of abilities, catalysed by successful genomic studies of developmental speech and language disorders. Not all children develop linguistic skills at the same speed or to equivalent proficiency. Sometimes an otherwise normally-developing child has severe unexplained difficulties in language, speech or reading. Such disorders are heritable, presenting gateways into the underlying genetic landscape (Table 1) [1•,2•]. Their diagnosis, treatment, and study is complicated by heterogeneity and co-morbidity [3]. Nevertheless, significant progress has been made in identifying and studying risk genes, providing novel perspectives on the biological bases of human spoken language [4•].

FOXP2 – first clues

The first gene implicated in speech and language was the transcription factor *FOXP2* [5]. It was discovered through studies of a large pedigree, the KE family, in which fifteen people had severe problems co-ordinating speech (developmental verbal dyspraxia, DVD, or childhood apraxia of speech, CAS) accompanied by wide-ranging linguistic deficits [6]. Linkage analysis of the family, and mapping of a translocation breakpoint in an unrelated child with similar problems, led to identification of *FOXP2* [5,7]. All affected KE members carry a heterozygous missense mutation yielding an amino-acid substitution within the DNA-binding domain of the FOXP2 protein, one that interferes with transcription factor activity by preventing recognition of target sites [8]. Based on subsequent reports of additional cases and small families harbouring different *FOXP2* mutations (nonsense mutations, translocations and deletions), disruption of one gene copy appears sufficient to derail speech development [9–13]. No human has yet been identified with homozygous *FOXP2* loss. When mice completely lack functional *Foxp2* (the murine orthologue), they display severe motor impairment, reduced growth and delayed cerebellar development, dying 3–4 weeks after birth [14–17,18•].

The FOXP2 protein is a direct regulator (primarily a repressor) of transcription. Many potential targets have been discovered via chromatin immunoprecipitation (ChIP) screening using different cell types and organisms, a subset of which have been confirmed by functional assays [19–22,23••]. A recent study integrated ChIP data with expression profiling in embryonic mouse brain, revealing networks of neurite outgrowth genes that are regulated, directly and indirectly, by *Foxp2* [23••]. Focused functional investigations of cellular and mouse models uncovered connections between this gene and neurite growth and branching [23••].

Of birds, mice and men

Human *FOXP2* is expressed in distributed circuits involving multiple brain areas, including deep cortical layers, striatum, cerebellum, inferior olives and thalamus [24]. These neural expression patterns show intriguing overlaps with regions of structural and functional anomaly in

Table 1

Heritable developmental disorders affecting speech and language

Disorder	Clinical observations	Genetic studies
Developmental Dyslexia/Reading Disability	A difficulty with reading and spelling that cannot be explained by obvious causes such as low IQ, physical impairment, or lack of opportunity to learn. Affects 5–10% of school-age children. Difficulties persist into adulthood. Often involve subtle underlying problems with language processing.	At least nine genomic loci (DYX1–9) identified by genome-wide linkage analysis. Candidate genes include *DYX1C1* at DYX1, *KIAA0319* and *DCDC2* at DYX2, and *ROBO1* at DYX5.
Specific language impairment (SLI)	Unexplained impairment in acquisition of spoken language, affecting one or more of morphology, syntax, semantics and pragmatics. Can disturb expressive and/or receptive language skills and also written language. Up to 7% of 5–6 year-olds may be affected. Language can improve but persistent deficits (e.g. in non-word repetition) are often detected in adulthood.	Genome-wide linkage analysis highlighted three chromosomal loci: 16q24 (SLI1); 19q13 (SLI2); 13 (SLI3). Association screening of SLI1 suggested *ATP2C2* and *CMIP* as candidates. Risk variants in a FOXP2-regulated gene *CNTNAP2* were identified through functional analyses followed by a targeted association study.
Developmental verbal dyspraxia (DVD)/childhood apraxia of speech (CAS)	Problems with learning to make coordinated movements needed for speech, yielding inconsistent errors in speech which increase with complexity of utterance. Typically accompanied by additional deficits in language function, both oral and written.	*FOXP2* mutations first identified by linkage in a large family. Multiple additional reports confirm role of *FOXP2* mutations, but only a small percentage of DVD/CAS cases are accounted for by this gene.
Speech sound disorder (SSD)	Difficulty with the production and proper use of speech sounds, most commonly omission or substitution of a small number of specific sounds. Common in young children, persists in 4% of 6-year-olds. Diagnostic overlaps with SLI and DVD/CAS, boundaries between conditions are unclear.	Dyslexia-linked loci were examined for linkage to SSD due to a possible shared problem with phonological awareness; most significant linkage is to chromosome 3 (DYX5).
Stuttering	Involuntary repetitions, prolongations of syllables, and pauses during speech. Generally resolves with age, but persistent in ~20% of cases. Linguistic function is usually normal.	Several genomic loci identified by genome-wide linkage analysis in large consanguineous pedigrees. Coding variants observed in genes of the lysosomal enzyme targeting pathway: *GNPTAB*, *GNPTG* and *NAGPA*.

Diagnosis of speech and language disorders is made on the basis of clinical assessment of speech and language skills and exclusion of explanatory medical conditions, generalised intellectual impairments or environmental factors. A child may fit the diagnostic criteria for more than one condition. For a detailed discussion of genetic studies of all these disorders, see refs [1•] and [2•]. In the present review we focus on key genes implicated in dyslexia, SLI and DVD/CAS, because these have been most informative for investigations of the neural basis of human language.

people with disruptions of the gene [24–27]. *FoxP2* is likely to be present in all vertebrates, and is highly conserved in neural expression pattern and amino-acid coding sequence [28,29]. Thus, ancestral versions contributed to brain development long before language appeared, lending validity to the study of its effects in animal models.

A juvenile male zebra finch learns its song by imitating an adult, a process which depends on Area X of the striatum [see Scharff, this issue]. FoxP2 levels in Area X show developmental increases during the vocal-learning period, but are temporarily downregulated by singing, except when directed to a female [30,31]. The gene may act as a 'plasticity gate' in Area X, high levels yielding song stability, low levels allowing vocal variability [30]. Expression profiling of Area X identified co-expressed gene networks correlated with singing, including a FoxP2-related module that also contains multiple known targets [32••]. FoxP2 knockdown in Area X by postnatal RNA-interference (RNAi) disrupts imitation of tutor song [33] and reduces dendritic spine density of Area X neurons [34•].

The laboratory mouse shows limited vocal learning [35,36,37•]. Potential links between mouse *Foxp2* and vocal behaviours remain poorly understood, with reports thus far focusing on innately-specified (non-learned) cries of young pups. Some authors argue that *Foxp2* loss specifically disrupts pup ultrasonic vocalizations [15,17]; others suggest this is secondary to other factors and not a reliable parallel of human speech dysfunction [16,18]. Even pups with two disrupted copies of *Foxp2* can still produce their full repertoire of vocalizations [16].

Analyses of other behaviours in mouse models may yield mechanistic accounts that are more relevant to human disorder. For example, affected KE family members have difficulty acquiring rapid complex motor programs underlying speech [6], along with structural and functional abnormalities in the striatum [26,27], a FOXP2-expressing structure involved in learning motor skills. Heterozygous mice carrying the KE family mutation display significant deficits in motor-skill learning on running wheels and accelerating rotarods, and impaired long-term depression (LTD) at glutamatergic inputs into the striatum [16]. *In vivo* electrophysiology in awake-behaving mice revealed abnormally high basal activity in striatal medium spiny neurons (MSNs) of the heterozygous mutants, with reduced firing during motor-skill learning, contrasting with the positive modulation of MSN firing in wild type littermates [38••]. Moreover, the temporal coordination of MSN firing was disturbed in the mutants [38••].

Mouse *Foxp2* may also affect processing and integration of auditory information. Auditory stimulation has been associated with increased Foxp2 expression in the thalamus [39]. In addition, mice heterozygous for the KE family mutation have subtly altered auditory brainstem responses to sound, although these effects were not seen for another aetiological mutation – a truncation mutation matching that of another family with speech and language problems [40]. Mice carrying either aetiological *Foxp2* disruption are impaired in auditory-motor association learning, with the truncation mutation producing more severe deficits [41].

Given its expression in multiple neural sites, along with the observed phenotypic complexity, selective gene disruption in particular circuits/structures, and at specific developmental time points, is needed for properly mapping the connections between *Foxp2* and mouse behaviour [14]. Additional model systems being used to study this gene include zebrafish [42] and fruit fly [43].

Is human *FOXP2* special?

Against a generally low background of FoxP2 protein change during vertebrate evolution, two amino-acid substitutions occurred on the human lineage since splitting from the chimpanzee [44,45•]. One of these substitutions independently arose and became fixed on at least two other mammalian lineages [45•]. The substitutions are relatively conservative, outside known functional domains, and do not affect protein dimerization or transcriptional regulation from canonical binding sites. However, quantitative differences in target regulation were reported for human cells transfected with human FOXP2, compared to those receiving a chimpanzee version [22]. When the two substitutions were introduced into a mouse model, increased dendritic length was observed in key neurons of the striatum, thalamus and cortex, contrasting with reduced neurite outgrowth of mice lacking functional Foxp2 [23,46,47]. The partially 'humanized' mice also showed increased LTD at cortico-striatal synapses, contrasting with the decreased LTD of mice heterozygous for the KE family mutation [16,46,47]. Thus, intriguing data are emerging on potential *in vivo* functional effects of these coding changes. However, their contributions to evolution of human-specific traits remain uncertain, since both changes are also present in Neanderthal DNA [48], and cannot explain a recent (<200 000 year old) selective sweep observed at the human *FOXP2* locus [49,50]. Assuming that this selective sweep is not a false-positive finding, it may have instead involved non-coding functional changes at the locus (e.g. affecting regulation of FOXP2 expression), a hypothesis that is currently being tested [49]. Regardless, the evolution of language is unlikely to be accounted for by only a single gene [51].

Linking language disorders with functional genomics

FOXP2 mutations are rare and do not explain common language impairments [9,52]. Nevertheless, as a neurally-expressed transcription factor gene, *FOXP2* is likely to be a hub in gene networks with relevance to speech and language phenotypes, and its targets represent strong candidates for involvement in related disorders. An example is the discovery that the *CNTNAP2* gene contributes to typical forms of specific language impairment (SLI) [21]. *CNTNAP2* encodes a cell-surface neurexin protein with crucial roles in brain development; homozygous loss-of-function mutations cause infant-onset epilepsy followed by mental retardation and language regression [53]. FOXP2 binds the first intron of *CNTNAP2* and downregulates transcription; expression levels of the two genes are inversely correlated within fetal cortex [21]. In a cohort of >180 SLI families from the UK, a cluster of single nucleotide polymorphisms (SNPs) in *CNTNAP2* showed association with language deficits, in particular with reduced performance on non-word repetition (NWR), a task in which subjects repeat pronounceable but meaningless words [21]. NWR deficits have high heritability and are resistant to environmental factors, persisting in people who compensate for language difficulties, and so have been proposed as an important endophenotype [54]. Association of *CNTNAP2* variation with NWR deficits was replicated in an independent study of developmental dyslexia (specific reading disability) [55]. The same SNP cluster was associated with age-at-first-word in children with autism spectrum disorder (ASD) [56], and with an early measure of language acquisition (assessed at 2 years of age) in a large Australian population sample [57•]. Thus, effects of these *CNTNAP2* variants extend between different neurodevelopmental disorders [58], and also beyond, into the normal range of variation.

A functional magnetic resonance imaging (fMRI) study of children with and without ASD described effects of *CNTNAP2* risk alleles on connectivity during an implicit learning task, independent of whether the children were diagnosed with ASD [59]. The group of children with non-risk alleles displayed a discrete left-lateralised frontotemporal network, overlapping with language-related regions, including left inferior front gyrus (IFG) and left superior temporal gyrus, while the group of risk carriers showed a more diffuse bilateral network [59]. In a subsequent fMRI study of normal adults performing a language task, people carrying *CNTNAP2* risk alleles exhibited increased activation of language homologues in the right hemisphere (including right IFG and lateral temporal cortex), although task performance was normal [60•]. Further supporting the view that these variants have an impact beyond any disorder, investigations of healthy adults have suggested altered structural connectivity associated with *CNTNAP2* risk alleles, determined by whole-brain fiber tractography [61]. The molecular basis of these *CNTNAP2* effects on linguistic, cognitive and neuroimaging phenotypes remains unknown. The investigated risk alleles are likely to be in linkage disequilibrium with the true functional variants, which are predicted to impact on some undetermined aspect of *CNTNAP2* regulation.

Multiple additional *FOXP2* targets have been implicated in disorders involving language dysfunction, including the receptor tyrosine kinase MET in ASD [62], the schizophrenia candidate gene *DISC1* [63], and the SRPX2-uPAR complex, involved in epilepsy of speech-related brain areas and DVD/CAS [64]. Similar connections may apply for key interacting proteins, as illustrated by the recent finding that FOXP1 (which heterodimerizes with FOXP2) is involved in ASD and intellectual disabilities (ID) with severe language impairments [65,66••].

Complex genetic architecture supporting language

Genome-wide linkage screens in cohorts of families affected by dyslexia or SLI have identified several loci that may harbour susceptibility variants, and suggested multiple candidate genes [1•,2•]. Although the primary symptoms of dyslexia are problems learning to read and spell, many researchers view it as a language-related disorder. People with dyslexia may not show overt problems with expression or comprehension of language, but typically manifest underlying deficits in relevant aspects of cognitive processing, such as the manipulation of phonemes. Dyslexia and SLI often co-occur and may share genetic aetiology [3]. Therefore, studies may evaluate candidate genes from both conditions against reading-related and language-related measures, within these disorders and in general population samples.

Following a genome-wide linkage screen of SLI families from the UK, targeted association analyses of the most strongly linked region identified the chromosome 16 genes *ATP2C2* and *CMIP* as susceptibility candidates [67]. *ATP2C2* encodes a calcium-ATPase regulating cellular calcium and manganese levels, while *CMIP* encodes an adaptor protein which may be a cytoskeletal component. SNPs within both genes were quantitatively associated with NWR performance. Two recent studies evaluated these candidates and found association between *CMIP* variants and reading-related measures in SLI and population samples, but no additional support for *ATP2C2* [68,69•]. Interestingly, independent genome-wide association screening for normal variation in hearing thresholds identified *CMIP* as one of the most significantly associated genes [70]. Moreover, a case study of a child with *de novo* deletion of the gene suggests CMIP haploinsufficiency may be implicated in ASD, pointing again to shared mechanisms across different disorders [71].

Chromosomal regions that have been repeatedly linked to dyslexia include 3p12-q13, 6p22.3-p21.3, and 15q15.1-q21.3. *DYX1C1*, in 15q21.3, was the first candidate gene proposed, based on its disruption by a translocation in one small Finnish family, and putative risk polymorphisms associated with dyslexia in additional Finnish cases [72]. In the majority of follow-up studies with dyslexia samples from other parts of the world, these initial SNP associations failed to replicate [2•,73]. However, recent reports describe associations between other *DYX1C1* SNPs and reading or spelling abilities in population samples [74–76]. *In utero* RNAi knockdown of rat *Dyx1c1* in developing neocortex has been reported to disrupt neuronal migration [77]. Earlier studies of a small number of human postmortem brains from dyslexic people described subtle malformations involving displaced neurons and glia, mainly localised to left-hemisphere regions of the cortex [78]. Rats that underwent *in utero* *Dyx1c1* RNAi are reported to show impairments in rapid auditory processing and spatial working memory [79]. Most recently, transcriptomic and proteomic analyses suggested that *DYX1C1* connects with molecular factors involved in neuronal migration and cytoskeletal function, as well as estrogen receptor signalling pathways [80].

The 6p22 region contains two neighbouring dyslexia candidate genes which, despite lying close together, are not in significant linkage disequilibrium: *KIAA0319* and *DCDC2*. The*KIAA0319* gene encodes a plasma-membrane protein with a large extracellular domain, which undergoes ectodomain shedding and intramembrane cleavage, and may be important for neuronal adhesion/attachment [81]. *DCDC2* encodes a doublecortin-domain protein that may be involved in regulating cytoskeletal dynamics, and has suggested roles in the structure and function of primary cilia [82]. Each gene has been

associated with language and reading phenotypes in multiple reports, and each is suggested to have effects extending into the normal range of language ability [2•,68,69•,83,84]. Recent neuroimaging genetics studies explored the relationships between SNPs in these genes and functional/structural brain phenotypes [85–87]. For example, an fMRI study assessed healthy subjects performing a reading task, looking for correlations with common *KIAA0319* gene variants. Putative risk alleles were associated with reduced asymmetry of activation of the superior temporal sulcus, an area previously suggested to harbour anatomical and functional anomalies in dyslexics [88••]. (Interestingly, in these same subjects, common variants of *FOXP2* were associated with variability in activation of left frontal cortex regions during the task [88••].) Dyslexia-associated variants in *KIAA0319* and *DCDC2* have been linked to reduced expression of the respective candidate gene in cell-based studies [89–91]. As for *DYX1C1*, *in-utero* RNAi of either *Kiaa0319* or *Dcdc2* in rats has been reported to disturb neuronal migration, with subsequent associated deficits in behaviour [92,93]. However, constitutive loss of *Dcdc2* in mouse models yields impaired visuo-spatial memory, visual discrimination and long-term memory, but with no evidence of neuronal migration abnormalities [94•]. Given the emerging discrepancies between different functional models, the links between dyslexia candidate genes, neuronal migration pathways and behavioural/cognitive outcomes require further clarification.

The 3p12-q13 region was initially linked to dyslexia in a large Finnish pedigree [95] and in quantitative-trait linkage scans of UK and US families [96]. Subsequently, the *ROBO1* gene in 3p12 was found to be disrupted by a translocation breakpoint in an independent dyslexia case [95,97]. Analyses of *ROBO1* markers in the original Finnish family identified a putative risk haplotype, correlated with variable reduction in gene expression in a sample of four affected individuals [97]. Since *ROBO1* encodes a guidance receptor for midline-crossing axons [98], a defect in inter-hemisphere connections may contribute to the associated phenotype. Consistent with reduced hemispheric connectivity, affected members of the Finnish family did not display normal suppression of magneto encephalography (MEG) response during binaural compared to monaural listening [99••]. Associations between *ROBO1* SNPs and NWR, but not reading and spelling measures, have been reported in a population sample [100].

The above represent the best studied candidates, but others have received less attention, or were described only recently, including several alternatives in 15q [2•,101–104]. Moreover, it is clear that the known candidate risk variants can still explain only a tiny proportion of the total variance in reading-related and language-related traits. Thus, this remains an active field of investigation.

The future

When it comes to the intricate networks of molecular interactions which underlie the neural circuitry mediating language, researchers are just scratching the surface. Based on findings thus far, genetic contributions to typical language disorders and normal variation are likely to involve common variants with small effect sizes, requiring genome-wide association in very large samples, whereas rare and *de novo* variants underlying high-penetrance disorders may be revealed by new DNA sequencing technologies. Decoding the genetics of language disorders and the relation to normal variation promises not only to aid diagnosis and inform educational methodology, but also to shed light on the molecular underpinnings of a central yet enigmatic aspect of being human.

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