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Genetics of language

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Abstract

It has long been hypothesised that the human faculty to acquire a language is in some way encoded in our genetic program. However, only recently has genetic evidence been available to begin to substantiate the presumed genetic basis of language. Here we review the first data from molecular genetic studies showing association between gene variants and language disorders (specific language impairment, speech sound disorder, developmental dyslexia), we discuss the biological function of these genes, and we further speculate on the more general question of how the human genome builds a brain that can learn a language.

Since the beginning of the cognitive revolution, it has been hypothesised that the human faculty to acquire a language is "innate", that is, part of our species' biological makeup, and, therefore, encoded in some way in our genetic program (Chomsky, 1959). Over the years, a wide variety of arguments have been advanced in support of this view: the universality of some properties of human languages (Chomsky, 1957), the "poverty of the stimulus" available for language acquisition (Chomsky, 1965), the spontaneous emergence of languages (Bickerton, 1984; Goldin-Meadow & Mylander, 1998), biological adaptations such as that of the vocal tract (Lenneberg, 1967), the existence of inherited disorders that may specifically affect language (Gopnik & Crago, 1991), the heritability of language abilities and disorders (Stromswold, 2001), the adaptiveness of language as a communication system (Pinker & Bloom, 1990), and the plausibility of a gradual evolution of the language faculty (Jackendoff, 1999) (on the special topic of language evolution, see the chapter by Fitch, this volume).

Although the evidence gathered in the last decades in favour of a biological basis of language looks convincing to many scientists, until recently genetic evidence has remained relatively indirect, in the sense that it has not addressed the fundamental questions: if there is a genetic basis for language, then what exactly is there in the human genome, that is different from other species, and that gives us language? How does it build a brain that can learn a human language?

There is no easy way to obtain a direct answer to this fascinating question. Genetic differences between species are only beginning to be

systematically searched, and the many differences that are found are not straightforwardly identifiable as associated with language (Fisher & Marcus, 2006). However, part of the answer will likely come from addressing a related but different question: what human genetic variations are associated with variations in the ability to learn a language? Indeed, most genetic methods rely on detecting correlations between variations in the genotype and variations in the phenotype. The capacity to acquire spoken language is usually treated as a universal characteristic of our species. Nevertheless, like many other traits, the language abilities that are observed in the human population vary along a normal distribution. Cases in the lower end of the distribution ("disorders") are typically the most informative, as they may highlight causal relationships between genes, brain, and cognition, that are often not readily apparent in normal development. Indeed, disorders of language acquisition have so far provided almost all the available data on language genetics. Furthermore, developmental language disorders are diverse, affecting different aspects of language, therefore promising to illuminate putative genetic influences on particular components of language (phonology, morphology, syntax, articulation…). Accordingly, this chapter reviews the genetic data gathered on the various types of language-related disorders (specific language impairment, speech sound disorder, developmental dyslexia…) and reflects on what they teach us about the genetic basis of language.

Evidence for genetic influences on language

Historically, the first hint at a genetic influence on language abilities came from the observation that language-related disorders tend to run in families (Hallgren, 1950; Morley, 1967; Stephenson, 1907; Tallal et al., 2001): when one person has language problems, the risk in 1st degree relatives is around 50%, far above the normal population prevalence. Although the inheritance pattern in many families may appear consistent with autosomal dominant transmission[1], this is not sufficient to prove genetic involvement, as members of a family share not only genes but also a linguistic environment. It is conceivable that parents with a language disorder would constitute a less favourable environment for the acquisition of language by their children, so studies of familial clustering inevitably confound genetic and non-genetic (shared environmental) factors.

Twin and adoption studies are the usual method to try and disentangle genetic and environmental factors. In the most classic twin studies, one compares the concordance of a given disorder[2] between monozygotic (MZ)

[1] E.g., the transmission of a dominant gene variant carried by a non sexual chromosome.

[2] The probability that the disorder, when present in one twin, is present in the other one.

and dizygotic (DZ) twins[3]. For instance, in a meta-analysis of twin studies by Stromswold (2001), the concordance of spoken language disorders was found to be around 84% for MZ twins and 48% for DZ twins. Both figures are far above the typical prevalence of spoken language disorders (1-3%), and the substantial difference between MZ and DZ twins can largely be attributed to differences in their genetic similarity. Such concordance measures thus allow estimation of heritability, that is, the proportion of phenotypic variance than can be attributed to genetic variance. Although diagnostic criteria and precise definition of disorder has varied from one twin study to the next, Stromswold's review of the published research estimated heritabilities of 70% for spoken language disorders and 64% for written language disorders (dyslexia). These estimates have not been significantly challenged, either by more recent studies, or by adoption studies that rely on slightly different assumptions (Felsenfeld & Plomin, 1997).

Beyond the categorical classification of individuals as having a disorder or not, the same approach can be generalised to any quantitative measure of language abilities (e.g., vocabulary, syntactic or morphological abilities…). Then the correlation of quantitative scores (rather than the concordance of disorders) between twins can be compared between MZ and DZ twins, revealing again higher correlations for the former than for the latter, hence a significant heritability of these scores. One advantage of this approach is that since it does not require twins to have a disorder, it opens the possibility of assessing genetic influences on variations in normal language abilities as well as on more pathological variations. It turns out that the heritability of normal language abilities is typically lower than that of disorders, yet remains significantly above zero (Colledge et al., 2002; Stromswold, 2001).

Furthermore, quantitative genetic analyses also lend themselves to investigations of specific components of language. As an example, in a recent study including twin pairs with or without language disorders, the heritability of deficits in various language tests varied depending on whether they tapped primarily phonological short-term memory (61%), morphology (74%), syntax (82%), or vocabulary (1%) (Bishop, Adams, & Norbury, 2006). It is also possible to analyse to what extent the covariance between two phenotypic variables is itself due to genetic and to non-genetic variance. It is generally found that most cognitive abilities are correlated and share genetic variance (Oliver & Plomin, 2007). Nevertheless, it is not the case that all cognitive variables share a single genetic source of variance. For instance, in the study by Bishop, Adams and Norbury (2006), morphological and syntactic abilities shared a substantial amount of genetic variance (around 40%), but these

[3] Monozygotic MZ twins share 100% of their genome, while dizygotic DZ twins share only 50% of their gene variants (like ordinary siblings). Note that the MZ-DZ twin method usually assumes that environmental factors are not more similar for MZ twins than for DZ twins; this assumption may not necessarily be valid.

abilities in turn did not seem to share much genetic variance with phonological abilities. This raises the possibility that certain genetic factors might influence differentially the components of language.

There have been huge debates around twin studies and their implications (Gould & Lewontin, 1979; Joseph, 2002). Their assumptions have been questioned, and their heritability estimates have been argued to be inflated. The fact is that there is no "true" value for heritability; this depends on the particular population considered and on the range of genetic and environmental variance that it presents. Nevertheless absolute heritability estimates do not matter much. Twin and adoption studies have established beyond reasonable doubt that there are significant genetic influences on cognitive performance and on language disorders in particular. The more important matter now is to identify those genetic factors, and understand how they exert their effects. The fact that this approach is now bearing fruit provides a post-hoc confirmation of heritability.

A series of progressive advances in molecular biology, culminating with the sequencing of the human genome, now make it possible to carry out the appropriate empirical investigations. Several types of approaches can provide relevant data on language genetics, such as:

- Linkage studies, carried out on families, typically analyze which chromosomal regions have genetic markers that are inherited more frequently in family members with a language disorder, than in those without. The "linked" chromosomal regions may still contain hundreds of genes, many with unknown function, but they help restrict the search space for association studies.
- Association studies look for gene variants that occur more often in affected than in control individuals, usually at the population level. They can lead to identification of an allele of a gene that increases significantly the risk of developing the disorder. In the case of disorders that are common in the population (like SLI and dyslexia), such alleles may be relatively frequent, also appearing in unaffected individuals. These common alleles may have only subtle effects on gene function, such as reducing the amount of a particular protein that is made.
- Occasionally, sequencing of candidate genes in some families can identify rare mutations that co-occur with the disorder, and that severely interfere with the function of the gene in question.
- Comparative studies look for a homologous form of a candidate gene in other species. They typically find one (at least in mammals). They can then analyse the similarity between the sequences in the various species and attempt to reconstitute the evolutionary history of the specific gene variants that have appeared in the human lineage. Moreover, prior knowledge of the gene's function in other species can give the first clues to its role in humans.

- Expression studies investigate the expression pattern of the candidate gene (where and when the protein is synthesised), as another important clue to its function.
- Many other approaches may be used to further investigate the function of a candidate gene: detection of familiar parts in the sequence and comparison with other, similar genes, algorithmic predictions of the shape of the protein, in vitro experiments to study the mechanisms of action of the target protein and its interactions with other molecules, in vivo experiments to study the effects of disrupting its expression, particularly on brain development and function, etc.

We now turn to the specific results obtained on the different forms of language disorders.

Developmental dyslexia

Developmental dyslexia is by definition a disorder of reading and spelling acquisition, despite adequate intelligence and opportunity, and in the absence of obvious sensory, neurological or psychiatric disorder. Nevertheless, it has been well established over the last three decades that most cases of dyslexia can be attributed to a subtle disorder of oral language (the "phonological deficit")[4], whose symptoms happen to surface most prominently in reading acquisition (Lyon, Shaywitz, & Shaywitz, 2003; Ramus, 2003; Snowling, 2000). Therefore dyslexia is expected to ultimately reveal something about genetic factors implicated in language, in particular in phonology. However, both the exact nature of the phonological deficit and its underlying cognitive/neural causes remain unclear.

Indeed, the main symptoms of the "phonological deficit in dyslexia" are poor phonological awareness (the ability to pay attention to and explicitly manipulate speech sounds), poor verbal short-term memory, and slow lexical retrieval (evidenced in rapid naming tasks where subjects must name series of objects, colors, or digits in quick succession). This diversity of impairments has led many researchers to hypothesise that dyslexics' phonological representations are somewhat degraded, fuzzy or noisy, lacking either in temporal or spectral resolution, or insufficiently attuned to the categories of the native language. This degradation is assumed either to be specific to the speech-processing system (Adlard & Hazan, 1998; Serniclaes, Van Heghe, Mousty, Carré, & Sprenger-Charolles, 2004; Snowling, 2000), or to follow from a lower-level auditory deficit (Goswami et al., 2002; Tallal, 1980). The latter view has been much challenged in recent years (Ramus, 2003; S. Rosen,

[4] A minority of cases of dyslexia are likely due to disorders in the visual modality. They are not further discussed here, as they are less well understood and they are of course not relevant for language genetics. Regarding theories of the phonological deficit as part of a pan-sensory disorder, we refer the reader to earlier discussions .

2003; S. White, U. Frith et al., 2006; S. White, E. Milne et al., 2006). As will become apparent below, the neurobiological and genetic data are consistent with the view that an auditory disorder is not necessary to engender a phonological deficit in people with dyslexia (Ramus, 2004). An alternative view is that phonological representations in dyslexia are intrinsically normal, and that the observed difficulties in certain (but not all) phonological tasks arise from a deficit in the access to these representations, that is particularly recruited for short-term memory and conscious manipulations (Marshall, Tang, Rosen, Ramus, & van der Lely, submitted; Ramus & Szenkovits, 2008; Szenkovits, Darma, Darcy, & Ramus, submitted). The elucidation of the precise nature of the phonological deficit will therefore determine whether dyslexia can inform us on the links between genes and phonology per se, or rather between genes and some cognitive processes operating on phonological representations.

In the late seventies, Galaburda and colleagues began to dissect human brains whose medical records indicated a diagnosis of developmental dyslexia (Galaburda & Kemper, 1979). After dissecting four consecutive brains, and finding evidence for abnormalities of neuronal migration in all four, they hypothesised that this was unlikely to occur by chance, and that such brain development aberrations might provide an explanation of dyslexia (Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985). Most interestingly, neuronal migration disruptions were found predominantly in left peri-sylvian areas traditionally associated with language[5]. Galaburda et al. subsequently confirmed these findings in three more brains (Humphreys, Kaufmann, & Galaburda, 1990), as well as the rarity of such abnormalities in control brains (Kaufmann & Galaburda, 1989). Unfortunately, no attempt at an independent replication was ever published, so the dyslexia research community came to consider these findings as intriguing, but inconclusive. Nevertheless, brain imaging studies have largely confirmed structural and functional abnormalities in dyslexics' left perisylvian areas, although at a different level of description. Findings from MRI studies typically consist of reduced gray matter density, reduced anisotropy of the underlying white matter, and hypo- or hyper-activations (Démonet, Taylor, & Chaix, 2004; Eckert, 2004; Temple, 2002). At the moment it is impossible to establish their relationship with putative perturbations of neuronal migration, which are not visible in MRI scans. Quite strikingly, new results emerging from genetic studies suggest a reappraisal of the old neuronal migration hypothesis.

Until recently, linkage studies had provided at least six reliable chromosomal loci suspected to harbour genes associated with dyslexia, on chromosomes 1, 2, 3, 6, 15 and 18 (Fisher & DeFries, 2002; Grigorenko, 2003). Now six genes showing association with dyslexia have been identified in some of these loci: DYX1C1 on 15q21 (Taipale et al., 2003), KIAA0319 on

[5] More specifically, these areas are the left inferior frontal, posterior superior temporal, supra-marginal and angular gyri.

6p22 (Cope et al., 2005; Paracchini et al., 2006), DCDC2 a nearby gene also on 6p22 (Meng et al., 2005), ROBO1 on 3p12 (Hannula-Jouppi et al., 2005), and MRPL19 and C2ORF3 on 2p12 (Anthoni et al., 2007). The association of variants in KIAA0319 and DCDC2 with dyslexia has been replicated in at least some independent studies (Harold et al., 2006; Schumacher et al., 2005).

For two of these genes (DYX1C1 and ROBO1), mutations, chromosomal rearrangements, or at least rare patterns of alleles (haplotypes) have been found in the dyslexic members of some isolated families, but these changes are too rare to play a significant role in explaining dyslexia in general. As yet, there is little evidence that more common variants of these genes modulate the susceptibility to dyslexia in the general population (Bellini et al., 2005; Brkanac et al., 2007; Marino et al., 2005; Meng et al., 2005; Scerri et al., 2004; Wigg et al., 2004). As far as the other genes are concerned, the associated variants are alleles that are relatively frequent in the population. Thus, the mere possession of such a susceptibility allele is not a necessary and sufficient condition to cause dyslexia. Rather, it increases the probability of developing the disorder. Therefore, as predicted by earlier research (Fisher & DeFries, 2002), it seems that the most common cases of dyslexia belong to the family of "complex genetic diseases" (like diabetes, heart disease and certain cancers), where multiple genetic factors intervene, interact with each other and with environmental factors, thereby modulating the susceptibility to the disorder. Rather than altering the amino-acid sequence of the protein, such susceptibility alleles typically produce more subtle effects, altering quantitatively the expression of the protein (Hannula-Jouppi et al., 2005; Meng et al., 2005) or the way that this is regulated. Follow-up investigations are necessary to pin down the precise functional role of putative risk alleles by studying more directly the structure of the encoded protein and its sub-domains (Tapia-Paez, Tammimies, Massinen, Roy, & Kere, 2008; Velayos-Baeza, Toma, da Roza, Paracchini, & Monaco, 2007; Velayos-Baeza, Toma, Paracchini, & Monaco, 2008), as well as its expression patterns across the cortex and at different stages of brain development. It turns out that genes associated with dyslexia are highly (although not exclusively) expressed in the brain, in the cerebral cortex, and particularly so during fetal development (Fisher & Francks, 2006; Meng et al., 2005; Paracchini, Scerri, & Monaco, 2007).

On top of these relatively classic functional studies, LoTurco and colleagues have used a particularly innovative technique to study the role of three of these genes in brain development (Bai et al., 2003). They have produced "functional knock-out" rats using in vivo RNA interference. This technique allowed them to specifically block the translation of the gene of interest, *in vivo*, locally, and at a chosen stage of development (indeed, *in utero* during neuronal migration). Using this technique, they showed that DYX1C1 is involved in radial neuronal migration, and that the part of the protein that is truncated in a Finnish dyslexic family (Taipale et al., 2003) is necessary and sufficient for normal neuronal migration (Wang et al., 2006).

They have further shown that cortical ectopias (like the ones observed in dyslexic brains) sometimes occur as a result of the DYX1C1-induced disruption of neuronal migration, and that more generally the laminar organisation is locally disrupted, with a distribution of neurons skewed in favour of layers I and II as well as towards the white matter (G. D. Rosen et al., 2007). The same team has been able to conduct similar studies on both DCDC2 (Burbridge et al., 2008; Meng et al., 2005) and KIAA0319 (Paracchini et al., 2006), again concluding that these genes are likely to be crucial for neuronal migration and the laminar organisation of the cortex. Finally, ROBO1 is a homologue of a well-known drosophila gene that is involved in inter-hemispheric axon guidance and in the migration of cortical inter-neurons (Andrews et al., 2008; Lopez-Bendito et al., 2007).

A gene will often play multiple roles depending on cellular/developmental context and can be involved in many different processes, but it is striking that functional links to neuronal migration have been uncovered for each of the candidate genes described above. It would seem a priori highly unlikely that the first four genes associated with developmental dyslexia should all be implicated in this particular aspect of neurodevelopment. The fact that they are suggests that there is indeed a real link between disturbances of neuronal migration and dyslexia, at least in a significant proportion of cases. Thus, 20 years after the first post-mortem studies, the emerging genetic findings are remarkably consistent with Galaburda et al.'s original hypothesis (Ramus, 2006a), suggesting a relatively coherent account of the aetiology of dyslexia, that can be summarised as follows. Certain variants (alleles or mutations) of particular genes increase the susceptibility to disruptions of neuronal migration, sometimes engendering ectopias or microgyri, but most importantly locally disrupting the laminar organisation of the cortex. Through mechanisms that are not yet understood, these disruptions may, in certain individuals, accumulate in left perisylvian areas, that are involved in speech processing and phonology, and that are later recruited for reading acquisition. The disruption of these areas also surfaces more macroscopically in the MRI in the form of reduced gray matter density and reduced anisotropy of the underlying white matter. It engenders subtle deficits of phonological abilities that may have little consequence on the acquisition of oral language, but manifest most remarkably during the acquisition of written language, which recruits particularly intensively those abilities (Galaburda, LoTurco, Ramus, Fitch, & Rosen, 2006; Ramus, 2004). There may be alternative neurogenetic pathways which lead to dyslexia, and which remain to be uncovered. However, the convergence of data from multiple lines of investigation makes this neuronal migration model particularly compelling as at least one highly testable account of dyslexia aetiology.

Specific language impairment

Specific language impairment (SLI) is a disorder of language acquisition that can be attributed neither to mental retardation, nor to other known pathologies (autism, brain lesion, epilepsy, deafness…), nor to environmental deprivation or disadvantage. Children with SLI show heterogeneous profiles, but typically have their language development delayed, with reduced vocabulary, reduced expression and/or comprehension abilities, reduced verbal short-term memory, and persistent production of ungrammatical patterns affecting both syntax (sentence structure) and morphology (e.g., verb inflections, gender, plural or case marking) (Leonard, 1998).

At a cognitive level, the most straightforward hypothesis is that children with SLI have deficits in one or several components of language, including syntax, morphology, phonology, the lexicon, and their interfaces (van der Lely, 2005). The precise combination of deficits in a given child, plus the interaction between different language abilities throughout development, would produce the particular cognitive profile presented by the child. An alternative view is that linguistic deficits arise either from a perceptual (auditory) deficit (Tallal & Gaab, 2006; Tallal & Piercy, 1973) or from a more general cognitive deficit (Leonard, 1998; Tomblin & Pandich, 1999). Again, this debate is quite controversial and goes well beyond the present chapter, so we refer the reader to the appropriate literature (Bishop, Adams, Nation, & Rosen, 2005; Ramus, 2004; S. Rosen, 2003; Tallal, 2004; Tallal & Gaab, 2006; van der Lely, 2005; van der Lely, Rosen, & Adlard, 2004; van der Lely, Rosen, & McClelland, 1998). For the purpose of the present discussion, while leaving the precise nature of impairments open, we assume that deficits can have differential impacts on aspects of language. As we will see, this view is at least consistent with the available neurobiological and genetic data.

The overall picture provided by neurobiological data, although far from being clear and consistent, is that loosely-defined language-related brain areas are disrupted or differently organised in children with SLI. The most frequent MRI findings have concerned asymmetries between left and right perisylvian areas. The inferior frontal gyrus (IFG: Broca's area) and the planum temporale, generally found to be larger on the left than on the right, show a reduced or reversed asymmetry in people with SLI (De Fossé et al., 2004; Gauger, Lombardino, & Leonard, 1997; Plante, Swisher, Vance, & Rapcsak, 1991). An extra sulcus in the left IFG has also been reported in some individuals with SLI (Clark & Plante, 1998). In addition, it has been suggested that children with SLI present a broader pattern of deviant asymmetries, again in favour of the right hemisphere on average (Herbert et al., 2005). Affected children have also been shown to have a larger total brain volume, due to a substantial increase in white matter volume, while the cerebral cortex and the caudate nucleus are relatively smaller (Herbert et al., 2003). Finally, it should be noted that in Galaburda's dissection studies, three to four of the seven

patients showed, on top of dyslexia, some form of language delay or disorder (Galaburda et al., 1985; Humphreys et al., 1990). Therefore, it is not impossible that the same set of neuronal migration disruptions, perhaps located slightly differently, might lie at the heart of SLI as well as of dyslexia (Ramus, 2004, 2006b). However there is no direct evidence for that in the case of SLI.

At the genetic level, thus far the search for genes associated with SLI has been less successful than for dyslexia. Nevertheless there are quite a few interesting results to mention. Familial transmission of language disorders is widely reported, and one study has also reported that atypical perisylvian asymmetry patterns can be found in the relatives of children with SLI (Plante, 1991), suggesting that the transmission of neuroanatomical phenotypes underlies that of behavioural phenotypes. Twin studies also have applications beyond simple heritability estimations. Analysing correlations between the performance of one twin in a given test and the other twin in a different test allows one to estimate whether the same sources of genetic variance underlie both capacities. One study thus found that syntactic and morphological abilities[6] share some of their genetic variance, but phonological short-term memory and morphological abilities do not (Bishop et al., 2006). This suggests that some genetic factors may have differential effects on distinct aspects of language. In a similar vein, another study of children with SLI found that deficits in phonological tests (nonword repetition) are highly heritable, while impairments on a popular auditory processing test do not show significant evidence of genetic influence (Bishop et al., 1999). This casts further doubt on the idea that language and phonological deficits necessarily originate from low-level perception.

Finally, genome-wide linkage studies of SLI have converged on three main linkage sites: one named SLI1 on chromosome 16, another named SLI2 on chromosome 19 (SLI Consortium, 2002, 2004), and a third one on chromosome 13 (Bartlett et al., 2003; Bartlett et al., 2002). So far no candidate gene has been localised in any of these regions, and further mapping studies are underway. However, one recent investigation employed an alternative strategy to traditional mapping, using functional genetic analyses of a monogenic speech and language disorder (described further below) to identify novel candidates for involvement in SLI. This approach enabled successful identification of the first gene to be significantly associated with language deficits in children with SLI (Vernes et al., 2008). The gene, called CNTNAP2, (located on chromosome 7q35) is strongly downregulated by the FOXP2 transcription factor in neurons (see below) and is a member of the neurexin family, a set of proteins implicated in synaptic adhesion (Dean & Dresbach, 2006). Its association with SLI remains to be replicated. It is worth noting that none of the known SLI linkage sites overlap with those reported for dyslexia, despite frequent comorbidity and similar neurological findings.

[6] Typically measured, in English, by the ability to form the past tense of verbs.

However there is notable overlap with autism linkage sites. Furthermore, CNTNAP2 has been associated with autism in several studies (Alarcon et al., 2008; Arking et al., 2008; Bakkaloglu et al., 2008). This issue will be further discussed in the Comorbidity subsection below.

Speech sound disorder

Although most children make speech errors when they begin to speak, children with speech sound disorder (SSD) present with persistent difficulties in the accurate and intelligible production of speech sounds within words. Their prevalence is estimated to be around 15% of 3-year-old children and 3.8% of 6-year-olds (Shriberg, Tomblin, & McSweeny, 1999). Typically some speech sounds are omitted or mapped to other sounds (this is different from stuttering). The definition of SSD does not commit to a particular locus for the underlying deficit (phonological or articulatory), and it is likely that the population is heterogeneous in this respect. Unfortunately cognitive studies of SSD are currently insufficient to provide a clear typology and shed more light on the precise nature of the deficits. It should be noted that the field of (normal) child language is itself plagued by the issue of whether deviant speech productions should be attributed to constraints in articulatory skills or to stages of phonological acquisition (Ramus et al., in press).

The brain basis of SSD has to our knowledge not been investigated independently from that of SLI or dyslexia. There have been, however, genetic linkage studies. Investigations have tended to focus on the chromosomal regions implicated in dyslexia, and, intriguingly, have thereby uncovered SSD linkages on the dyslexia-related sites of chromosomes 3, 6, and 15 (Stein et al., 2006; Stein et al., 2004). One possible reason for this is that there is comorbidity between dyslexia and SSD, so that a fair proportion of pre-school children who are diagnosed with SSD grow up to become dyslexic. Thus, cohorts of children with SSD participating in genetic studies may well be largely composed of dyslexic children. Another more interesting potential explanation is that, beyond actual comorbidity, common biological factors may participate in the aetiology of different cognitive deficits. Confirmation of the latter awaits identification of particular allelic variants that play functional roles in both SSD and dyslexia. Curiously, at this point there is less evidence of genetic risk factors that are shared between SSD and SLI, although there may well be functional pathways that are common to both (see below).

In conclusion, speech sound disorder has the potential to reveal important information about the genetic bases of phonology and speech articulation. Unfortunately, the findings on SSD in general are rather scarce, so this disorder warrants more investigation. However, one particular form of SSD, namely developmental verbal dyspraxia, is currently at the centre of a very fruitful line of research, which is detailed in the next section.

Developmental verbal dyspraxia

Developmental verbal dyspraxia (DVD) — also referred to as childhood apraxia of speech (American Speech-Language-Hearing Association, 2007) — is a speech-sound disorder that leans clearly on the articulation side, involving problems with co-ordinating and sequencing movements of the tongue, lips, jaw and palate, which cannot be explained by muscle weakness, paralysis, or other overt neurological or physical factors. A diagnosis of DVD can encompass a range of severities and impairments, and there may also be some degree of impairment in performing non-speech orofacial movements on command, such as puffing out cheeks or licking lips (oral dyspraxia). In recent years substantial advances have been made in understanding one particular genetically-mediated subtype of DVD, a rare form of the disorder showing monogenic inheritance (Fisher, Vargha-Khadem, Watkins, Monaco, & Pembrey, 1998; Lai, Fisher, Hurst, Vargha-Khadem, & Monaco, 2001). In the following sections we focus on the behavioural, cognitive and neural features of this well-studied subtype, given that its genetic basis has now been firmly established.

Much of our understanding of links between genes and DVD stems from intensive studies of one multigenerational pedigree, known as the "KE family", first reported in the early 1990s (Hurst, Baraitser, Auger, Graham, & Norell, 1990). Around half of the members of this family — fifteen individuals across three successive generations — display a severe speech and language disorder, inherited as a Mendelian trait with an autosomal dominant mode of transmission. While some linguists initially characterised the KE family's disorder as one primarily affecting certain features of grammatical processing (Gopnik, 1990; Gopnik & Crago, 1991), other researchers noted that the most profound problems were impaired speech articulation reminiscent of DVD (Hurst et al., 1990). Indeed, subsequent reports showed that word and non-word repetition tasks provided the most robust diagnostic marker of the disorder (Vargha-Khadem et al., 1998). Consistent with a diagnosis of DVD, the deficits of affected members are already evident when repeating shorter utterances, but become more dramatic with increases in syllable number and complexity (Watkins, Dronkers, & Vargha-Khadem, 2002). Tests of non-speech praxis in the KE family indicate reduced performance when making simultaneous and sequential oral movements on command (Alcock, Passingham, Watkins, & Vargha-Khadem, 2000; Vargha-Khadem et al., 1998). This is again reminiscent of other cases of DVD which (as noted above) often show evidence of oral dyspraxia affecting non-speech movements. Notably, affected members of the KE family are not significantly impaired in making single simple oral movements or in limb praxis, and do not show gross oromotor dysfunction, for example, in feeding or swallowing (Alcock et al., 2000).

The speech difficulties of the KE family are accompanied by linguistic impairments which are not confined to spoken language or to the expressive

domain. For example, affected members perform worse than unaffected members on written tests of verbal fluency and non-word spelling, as well as in lexical decision tasks assessing receptive vocabulary, and they display significant deficits in reception and production of grammar (Watkins, Dronkers et al., 2002), albeit not as selectively as proposed in initial linguistic studies (Gopnik, 1990). They show difficulties in generating word inflections and derivations but tests of past-tense production indicate similar levels of deficits for both regular and irregular words, and their receptive impairments extend to syntax at the word-order level (Gopnik & Crago, 1991; Watkins, Dronkers et al., 2002). The relationship between the motoric and linguistic aspects of the disorder in the KE family is the subject of continuing debate. One hypothesis is that a primary deficit in articulation could lead to more general impoverishment in language representation at many other levels (Watkins, Dronkers et al., 2002). However, it is not clear why accurate speech articulation would be necessary to acquire all the other dimensions of language, and indeed it has been shown that it is not (Fourcin, 1975a, 1975b; Lenneberg, 1962; Ramus, Pidgeon, & Frith, 2003). A plausible alternative is that multiple components of language (articulation, phonology, the lexicon, morphology and syntax) are concurrently affected, without one deficit being responsible for all the others.

The brains of affected people from the KE family appear overtly normal in structure on standard evaluation of MRI scans (Vargha-Khadem et al., 1998). However, statistical comparisons to unaffected members using voxel-based morphometry revealed subtle anomalies affecting multiple brain regions (Belton, Salmond, Watkins, Vargha-Khadem, & Gadian, 2003; Vargha-Khadem et al., 1998; Watkins, Vargha-Khadem et al., 2002). These include putative abnormalities in cortical language-related regions, with decreased grey matter density in the inferior frontal gyrus (containing Broca's area) and increased density in the posterior portion of the superior temporal gyrus (Wernicke's area). Notably, the sites of pathology suggested by such analyses were not limited to the cerebral cortex, but extended to the cerebellum and the striatum, where there were significant reductions in grey matter density in the caudate nucleus accompanied by increases in the putamen. Functional neuroimaging of the KE family during language tasks identified abnormal patterns of neural activation in the affected members, even under covert (silent) conditions when there was no requirement for spoken output (Liegeois et al., 2003). Broca's area, other cortical language-related regions, and the putamen were significantly underactivated in affected individuals, who showed a more posterior and bilateral pattern of activation than unaffected members of the family. Sites of abnormalities include both areas associated with motor control and areas associated with language, mirroring the co-occurrence of motor and linguistic symptoms at the cognitive level. It has been suggested that abnormalities in development and function of distributed frontostriatal and/or frontocerebellar circuits are responsible for the

DVD and accompanying linguistic impairments of the family (Vargha-Khadem, Gadian, Copp, & Mishkin, 2005).

Genome-wide scanning of the KE family identified a region of chromosome 7q31 showing highly significant linkage to the disorder (Fisher et al., 1998), which was found to contain at least 70 genes (Lai et al., 2000). The search was cut short by the serendipitous discovery of another child affected with DVD (unrelated to the KE family) who had a gross chromosomal abnormality mapping within the region of interest (Lai et al., 2000; Lai et al., 2001). The child, known as CS, carried a balanced translocation involving exchange of material between chromosomes 5 and 7, with a breakage in the 7q31 band. It was shown that the chromosome 7 breakpoint of this child directly interrupted a novel gene, known as FOXP2 (Lai et al., 2001). Analysis of the gene in the KE family uncovered a heterozygous single-base change in all fifteen affected members, which was not found in any unaffected members or in several hundred independent controls (Lai et al., 2001). This mutation was predicted to disrupt the function of the protein encoded by FOXP2 (see below), a hypothesis that has since been robustly confirmed (Groszer et al., 2008; Vernes et al., 2006).

FOXP2 encodes a protein belonging to the "Forkhead bOX" (or FOX) family of transcription factors, which act to regulate the expression of suites of genes during embryogenesis, development and in adulthood (Carlsson & Mahlapuu, 2002). The single-base missense mutation in the FOXP2 gene of affected KE family members alters one amino acid residue at a crucial part of the DNA-binding domain of the encoded protein (Lai et al., 2001). Functional experiments show that the substitution impedes the DNA-binding ability of the mutated FOXP2 protein, dramatically disturbing its capacity to regulate transcription of downstream targets (Vernes et al., 2006).

Targeted screening of FOXP2 in different disorders has indicated that disruption of this gene is not unique to the KE family and CS case, but still represents only a rare cause of speech and language deficits in the wider population. Initially, comprehensive mutation searches were carried out across all known FOXP2 exons in groups of children with SLI and autism (Newbury et al., 2002; Wassink et al., 2002), syndromes which typically occur in absence of DVD. These studies concluded that FOXP2 is not a major genetic risk factor for SLI or autism, a finding that has been generally borne out by subsequent work. MacDermot et al. (2005) reported the first specific assessment of FOXP2 contribution in a cohort of children diagnosed with DVD. The study screened 49 unrelated probands with a primary diagnosis of DVD, and identified three distinct coding changes. One was a heterozygous nonsense mutation predicted to severely truncate the encoded FOXP2 protein, such that it would lack crucial functional domains, including the DNA-binding motif. The nonsense mutation was also found in the proband's affected sister and mother, and was absent from normal controls (MacDermot et al., 2005). Functional analyses suggest that the truncated product is unstable, mislocalised within the cell, and lacks transcription factor function (Groszer et

al., 2008; Vernes et al., 2006). In recent years, cases of gross chromosome abnormalities in which FOXP2 is disrupted or deleted have also been reported, with speech articulation difficulties emerging as a common symptom (Feuk et al., 2006; Shriberg et al., 2006; Zeesman et al., 2006).

Since FOXP2 encodes a transcription factor, functional genomic methods are now being used to successfully identify the downstream target genes that it regulates in neurons (Spiteri et al., 2007; Vernes et al., 2007). Exciting new data from these screening efforts indicate that pathways downstream of this regulatory factor may have broader relevance for language-related disorders, even in absence of mutations of FOXP2 itself. Vernes et al. (2008)identified a novel direct target that is strongly downregulated by FOXP2 in neurons (the CNTNAP2 gene, described above), and went on to show that the allelic variants of this target were significantly associated with language impairments in a large cohort of children with typical SLI. Not only do these findings establish a functional genetic link between rare monogenic forms of DVD and common forms of SLI, but similar allelic variants in the target gene are also associated with language deficits in autistic disorder (Alarcon et al., 2008).

FOXP2 is expressed in the brain during embryogenesis and early development, both in humans and in mice (Lai, Gerrelli, Monaco, Fisher, & Copp, 2003). It is not expressed ubiquitously throughout the brain, but localized to a number of structures, including the deep layers of the cerebral cortex, the striatum, the thalamus, the Purkinje cells of the cerebellum and the inferior olives. Most notably, FOXP2 expression in the caudate nucleus and in the cerebellum coincides with known sites of neuroanatomical anomalies in the KE family. Beyond sensorimotor processing and motor-skill learning, the contribution of these brain regions to language function is becoming more and more appreciated (Booth, Wood, Lu, Houk, & Bitan, 2007; Friederici & Kotz, 2003; Justus, 2004; Marien, Engelborghs, Fabbro, & De Deyn, 2001; Teichmann, Dupoux, Kouider, & Bachoud-Levi, 2006; Ullman, 2001).

More insights into human FOXP2 function have come from animal models. Heterozygous mice carrying the same missense mutation as that found in the human KE family display abnormal synaptic plasticity in neural circuits where Foxp2 is expressed, including loss of long-term-depression in parts of the striatum (Groszer et al., 2008). In addition they show subtle but significant motor-skill learning deficits during species-typical behaviours. Homozygous mouse pups that have no functional Foxp2 have severe motor dysfunction, general developmental delays, and delayed maturation of the cerebellum, and they do not emit innately specified ultrasonic calls on isolation from their mother (Groszer et al., 2008; Shu et al., 2005). They do not survive beyond a month of life. Whether the homozygous mouse phenotype is relevant for understanding the syndrome observed in heterozygous humans remains a controversial question. More convincing evidence of a role for FoxP2 in vocalization skills of non-linguistic species comes from studies of vocal learning in songbirds (White, Fisher, Geschwind, Scharff, & Holy, 2006). In

particular, zebrafinches show changes in FoxP2 expression levels in a key striatal nucleus (called Area X) which appear to correlate with vocal plasticity (Haesler et al., 2004; Teramitsu & White, 2006). Haesler and colleagues (2007) used RNA interference to selectively knock down expression of FoxP2 in Area X of juvenile zebrafinches during song learning. This treatment yielded inaccurate and incomplete copying of the tutor's song, which was suggested to show parallels to DVD in humans (Haesler et al., 2007).

Finally, analyses of the evolution of FOXP2 in primates indicated that two amino-acid substitutions occurred on the human lineage after splitting from the chimpanzee, and found evidence of recent Darwinian selection (Enard et al., 2002; Zhang, Webb, & Podlaha, 2002). Although initial studies suggested this accelerated evolution may have occurred within the last 200,000 years of human history (Enard et al., 2002; Zhang et al., 2002), investigations of the gene in bone samples from Neanderthals indicate that they also carried the human amino-acid substitutions, which would suggest a more ancient origin (at least 3-400,000 years) for the changes (Krause et al., 2007). At the moment, nothing is known about the functional consequences of these two amino-acid changes, but this raises the possibility that FOXP2 might have acquired new functional roles in humans.

In summary, FOXP2 may simultaneously contribute to human language pathways via at least two routes. First, through an evolutionarily conserved role related to motor sequencing and vocal learning, as observed in non-linguistic species (studies of birds and mice). Deficits in these processes are likely to mediate parts of the DVD phenotype associated with FOXP2 disruption. Second, the human version may have putative novel functions which remain to be understood, but which might conceivably contribute to more human-specific aspects of language.

Perspectives for language genetics

Comorbidity and pleiotropy

Until now we have largely described the different forms of language disorders as if they were distinct entities, however this is an oversimplification. Many children with SLI, although not all of them, grow up to become dyslexic (Bishop & Snowling, 2004; Flax et al., 2003; Marshall et al., submitted; McArthur, Hogben, Edwards, Heath, & Mengler, 2000). Some children with dyslexia or SLI also present some form of speech sound disorder, if only in early development (Bishop & Adams, 1990; Shriberg et al., 1999). This pattern of multiple comorbidities is hardly surprising if one considers that the different components of language, albeit functionally independent, may partly depend on each other in the course of development. But beyond this observation, it is likely that comorbidity can be largely ascribed to common underlying biological factors. This is indeed suggested by several lines of converging evidence:

- As we have noted above, the neural bases of dyslexia and SLI partly overlap.
- Familial aggregation studies have found that in families having one member with SLI or SSD, the likelihood of other members to show another form of language impairment (whether dyslexia, SLI or SSD) was increased (Flax et al., 2003; Lewis, 1992).
- Genetic linkage sites seem to overlap between dyslexia and SSD. Two caveats, however. Firstly, the fact that linkage sites overlap does not guarantee that a single gene is associated with both disorders: linkage sites may contain many genes, including two affecting different disorders. And indeed none of the genes associated with dyslexia has been associated with SLI or SSD so far. Secondly, there is no hint as yet of any overlap between dyslexia and SLI linkage sites, which may seem puzzling. However, this is not all that surprising, given the statistical power of most linkage analyses (Marlow et al., 2003), and this may well change sooner or later.
- Genetic linkage sites also overlap between SLI and autism. Furthermore, the CNTNAP2 gene, identified as a downstream target of FOXP2, also appears to be associated with common cases of SLI (Vernes et al., 2008), as well as with autistic spectrum disorder (Arking et al., 2008; Bakkaloglu et al., 2008). One study further suggested the association between CNTNAP2 and language abilities in autism, as measured by age at first word (Alarcon et al., 2008). This suggests aetiological overlaps between SLI and autism.

The possibility that some gene variants might increase the susceptibility to several disorders makes sense in functional terms. For instance, there is no reason to expect that dyslexia is the only disorder arising from slight disturbances in neuronal migration (indeed, others are known, such as nodular periventricular heterotopia). Therefore genes involved in neuronal migration and associated with dyslexia could plausibly be expected to be associated with other disorders such as SLI. Furthermore, genes typically have more than one function, and therefore can have effects on multiple phenotypes: this is known as pleiotropy. For instance, all the genes discussed in this chapter are expressed not only in the developing brain, but also in other organs at various stages of life, showing that they have multiple functions, some as remote from cognition as digestion or reproduction.

These considerations have led Kovas and Plomin (2006) to hypothesise that genes affecting cognition are "generalist genes" affecting most cognitive functions and disorders, and indeed that they produce their effects relatively uniformly on a "generalist brain". It is certainly true that many genes affect many brain areas and many cognitive functions, yet the "generalist genes" hypothesis is likely to be an over-generalisation. Some twin studies find that certain cognitive functions share little genetic variance, for instance phonological and morphosyntactic abilities (Bishop et al., 2006). And although many genes seem to be expressed more or less uniformly across the

cortex, few studies have actually compared the expression of the genes of interest across different cortical areas. FOXP2 is a good case in point. It may well have multiple effects on development, but it certainly does not have uniform effects throughout the brain. As we have seen above, it is expressed in particular brain areas that turn out to bear a clear relationship with the neurological and cognitive phenotypes associated with a FOXP2 mutation. This kind of neuroanatomical specificity is not uncommon among transcription factors. Performing a systematic search over more than 1000 known transcription factors, Gray and colleagues (2004) have found 349 whose expression pattern is restricted to specific areas of the mouse brain, and are together sufficient to explain its architecture. Far from being generalist genes, their expression is rather specific and has equally specific functional consequences. Similar considerations hold for CNTNAP2, the only gene so far suggested to be associated with SLI (Vernes et al., 2008), which turns out to demonstrate particularly enriched fetal expression in human frontal cortex (including inferior and middle frontal gyri) as well as in subcortical areas (including the caudate nucleus) (Abrahams et al., 2007).

In the case of genes associated with dyslexia, while expression patterns in human foetal brains are available (Paracchini et al., 2006), comparisons between neocortical areas have been carried out in adult brains only, and with a relatively rough cortical parcellation (lobe by lobe, without distinguishing left from right hemisphere). Yet they do not turn out to be particularly uniform (Meng et al., 2005; Paracchini et al., 2007). Most importantly the sites of brain disturbance themselves are clearly not uniform, whether one looks at histological studies, brain morphometry, or diffusion tensor imaging. The relationship between genes and neuropathological sites remains to be fully understood. More detailed studies might reveal that genes associated with dyslexia are expressed more in left perisylvian areas, but this can be considered unlikely for genes generally involved in neuronal migration. Then, why do the disruptions occur precisely there? One reason could be just chance: in many individuals with the same gene variants, they may by chance occur elsewhere, and produce other effects (SLI, SSD, or any other cognitive deficit for that matter). We would see them in left perisylvian areas because we look only at dyslexic individuals. Yet, if chance was the only factor at play, one would predict complete cross-transmission between disorders: dyslexic parents would be as likely to beget SLI as dyslexic children. However this is not the case (Flax et al., 2003; Lewis, 1992). Another possibility would be that left perisylvian areas are, for unrelated (say, vascular) reasons, more vulnerable to all forms of insult, including disturbances of neuronal migration (Geschwind & Galaburda, 1985; McBride & Kemper, 1982). One way or another, neuroanatomical location matters, more than anything else, for determining the precise nature of a cognitive phenotype.

Another alternative would be that genes implicated in neuronal migration interact with other genes, which do have more specific expression patterns (Ramus, 2004). The combination of certain alleles in these different

genes could result in disruptions of neuronal migration confined to certain cortical areas. For instance, a number of genes have been found whose expression is asymmetric between left and right hemispheres in early embryonic development, and could thus explain the predominance of certain anomalies on one side or the other. Furthermore, one of these genes (LMO4) is expressed more specifically in perisylvian regions, and more so in the right than in the left hemisphere (Sun et al., 2005). Other genes have been found with expression enriched (or specifically impoverished) in language-relevant areas in midgestation (Abrahams et al., 2007). Alleles of these or similar genes, interacting with alleles of genes associated with neuronal migration, could potentially explain the occurrence of neuronal migration anomalies specifically in left perisylvian regions such as in dyslexia.

In light of the above discussion on comorbidity and pleiotropy, one does expect to find genes associated with dyslexia as well as SSD and/or SLI, and perhaps even with other developmental disorders. However this does not imply that all disorders are the same or that genes are "genes for everything". Not all dyslexic children have SSD or SLI, not all brain areas are involved in all language functions, not all genes impact on all brain areas and functions, and therefore it is also to be expected that some genes will be uniquely associated with one disorder, alongside other genes that will be more general susceptibility factors for a certain class of neurodevelopmental disorders.

A "gene for language"?

When the KE family was first investigated in the early 1990's, speculations about the existence of a "gene for grammar" flourished in the press. The story turned out to be much more complex, and when FOXP2 was discovered more than ten years later, it became clear that it was neither a gene for grammar, nor a gene for language, nor a gene for the brain, nor even a specifically human gene. It is a highly conserved transcription factor, found in similar form in many distantly related vertebrate species, where it is expressed in a range of tissues during embryonic development, postnatally and in the mature organism, including the lung, heart and intestines as well as the brain (Bonkowsky & Chien, 2005; Haesler et al., 2004; Lai et al., 2001; Lai et al., 2003). Genes associated with dyslexia and other language disorders are turning out to show similar characteristics. Thus, the very notion of a "gene for something", in particular a gene coding directly, specifically, and uniquely for a given cognitive function, is flawed (Fisher, 2006). But this does not mean that the notion of genetic bases of language is itself flawed. Rather it should be understood in less naive ways than it sometimes has.

The data reviewed in this chapter show that variations in many genes may cause variations in language abilities, and in particular language disorders. Rather than being "genes for language", these genes perform several different functions, in various organs at various stages of development. But they have in common that they have an influence on brain development, and that certain of their variations may alter the development and/or function of

particular brain areas, that in turn are useful for some aspects of language acquisition. Thus these genes are necessary for normal language acquisition, but they are of course not sufficient, and furthermore they have not necessarily evolved for the purpose of language acquisition. Some of them (like FOXP2) have indeed undergone some human-specific modifications, apparently under selection pressure, and within a timeframe that is compatible with the evolution of language in the human lineage. In such a case it is possible that these changes were one of the steps that made it possible for humans to develop language. Other known genes associated with language disorders also differ slightly between humans and other mammals, but so far there is no evidence that these differences are functionally significant and may have played a role in language evolution (Fisher & Francks, 2006). Nevertheless this does not make those genes uninteresting.

The language faculty is very unlikely to be an entirely new organ that has appeared from scratch in the human brain (Fisher & Marcus, 2006). Rather, it should be seen as a product of ”descent with modification”, that is, a new combination of old and possibly new cognitive ingredients (Marcus, 2006). Old ingredients may include auditory perception, primate vocalisation, long-term, short-term, and working memory, sequence processing, a conceptual system, and many more. Of course each of these components must have to some extent evolved in human-specific ways in order to be harnessed for linguistic purposes, which implies that some of the genes that were already implicated in the construction of the corresponding brain areas either have undergone some functional changes, or have been triggered in new ways by upstream transcription factors and other regulatory elements. Thus, even a human gene identical to an ancestral primate version could nowadays be important for language, if for instance it is involved in the construction of a relevant brain area in virtue of being expressed in new ways by a transcription factor such as FOXP2. As for new cognitive ingredients, it is not entirely settled yet what (if anything) should fall into that category. An influential and controversial proposal is that a capacity for recursion is the unique new cognitive ingredient required for language, together with an adaptation of ”interfaces” between this new component and the old ones (Fitch, Hauser, & Chomsky, 2005; Hauser, Chomsky, & Fitch, 2002; but see Jackendoff & Pinker, 2005; Pinker & Jackendoff, 2005).

Taking this as a working hypothesis, it is unlikely that such a new cognitive capacity could have evolved overnight thanks to a single mutation. Even if it is truly new in a cognitive sense, it is likely to be much less novel in biological terms. For instance, a change in a single gene producing a signalling molecule (or a receptor, channel etc.), could lead to creating new connections between two existing brain areas. Even an altogether new brain area could evolve relatively simply by having a modified transcription factor prenatally define new boundaries on the cortex, push around previously existing areas, and create the molecular conditions for a novel form of cortex in Brodmann’s sense: still the basic six layers, but with different relative importance, different

patterns of internal and external connectivity, and different distributions of types of neurons across the layers. This would essentially be a new quantitative variation within a very general construction plan, requiring little new in terms of genetic material, but this area could nevertheless present novel input/output properties which, together with the adequate input and output connections, might perform an entirely novel information processing function of great importance to language. Even if the ultimate form of that brain area turns out to require many genetic changes, there is no necessity that all the changes co-evolved simultaneously. Once the area is delineated, further genetic changes could progressively shift its boundaries and refine its cellular makeup and thus its information-processing capabilities. Thus, even the creation of a new neuroanatomical and cognitive module is not as unlikely as one might imagine, and does not require improbable assumptions about dramatic genetic changes. Dramatic effects can be obtained by small changes in the way the construction plan is laid out.

In a nutshell, there is no need of a ”gene for language” to explain the genetic basis of language. Having said that, it is now known that some human genes (perhaps 150 to 300) really are human-specific, in the sense that they are entirely new concatenations of bits of other genes, that have no equivalent in other species (Bailey et al., 2002; Nahon, 2003). Very little is known about those genes, but it is of course possible that one or more of them could have been important in the evolution of the neural bases for language. The point is that even if this is not the case, more standard genetic changes in ancestral genes would still be adequate to explain the emergence of a new cognitive ability such as language.

Perspectives

The picture laid out in this chapter is of course very incomplete. Many more genes associated with language disorders remain to be found, and genes associated with normal variations in language abilities are only beginning to be searched for (Paracchini et al., in press). Nevertheless, the data that we have discussed are probably a reasonable illustration of what can be expected in the future. We can expect more genes involved in aspects of brain development (neuronal migration being just one possibility), and more transcription factors and other genes with a restricted cortical expression that may affect the development of more specific brain areas. Genes involved in neurotransmission, on the other hand, are currently out of the picture (although implicated in other disorders such as ADHD), but this is of course no guarantee that they will remain so.

One point that may change is that until now the genetic variations considered have been mostly deletions, insertions or substitutions of single nucleotides. This has led to a pattern where mutations (such as those in FOXP2 or DYX1C1) appear to be scarce, while most of the variation in language abilities seems to be explained by susceptibility alleles that simply modulate the probability of developing the disorder. However mutation

screening efforts are very preliminary; for instance the genes already known to be associated with dyslexia have typically not been systematically screened for mutations in most available dyslexia cohorts. Furthermore, a wider range of mutations is now going to be analysed, such as copy number variants, whereby entire stretches of DNA are sometimes deleted or duplicated, to an extent that previously has been vastly underestimated (Redon et al., 2006; Stranger et al., 2007). Thus, there may be etiological mutations in a much higher proportion of individuals with language disorders than has been appreciated before.

One final area where entirely novel results should be expected in the coming years is that of gene-environment interactions. All genetic studies of language disorders have until now focused on detecting main effects of gene variants. This is of course the first step necessary to the identification of candidate genes. However, the effects of genes sometimes differ as a function of other factors, some genetic, some environmental. Evidence for non-additive effects between genetic and environmental factors have begun to be investigated in the case of other disorders, such as conduct disorder (Caspi et al., 2002) or depression (Caspi et al., 2003). Does a susceptibility allele for a language disorder produce a different effect depending on the presence of other risk factors (such as mild hearing impairment)? Or on the familial linguistic environment? Or on the language itself? Or on schooling practices? Or symmetrically, does a given environmental factor produce a different effect depending on the genotype of the child? These fascinating questions are now within arm's reach.

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