

The 'genes of language' and the language of genes

Os "genes da linguagem" e a linguagem dos genes

Antonio Benítez-Burraco*

University of Huelva (Spain)

1. Inherited language disorders and the Faculty of Language

There are many cognitive disorders where language seems to be impaired and which are also of an inherited nature. Among other conditions, one needs to point out dyslexia, SLI (an acronym for *specific language disorder*), SSD (an acronym for *speech-sound disorder*), and some other rare (i.e. of low prevalence) conditions, such as Landau-Kleffner syndrome, rolandic (or sylvian) epilepsy and speech dyspraxia, or chromosome 22q13 deletion syndrome (for a review see Benítez-Burraco, 2009a: 83-227). After many decades of intensive (and sometimes controversial) phenotypical (i.e. symptomatic) analyses, recent neurobiological and genetic analyses are increasingly being carried out in an effort to obtain a more accurate characterization of these conditions from a clinical point of view, but also for disentangling their genuine aetiology. Nowadays, it seems progressively clearer that such disorders are caused by the mutation of particular genes, giving rise to structural and/or functional anomalies in diverse areas of the brain, which ultimately origin the underlying deficit(s), traditionally linked to these conditions. Therefore, a common working hypothesis in the field has customarily been the following: a specific language impairment or disorder (namely, dyslexia or SLD), whether of an inherited nature, must be a consequence of a gene dysfunction which, affecting a (specific) component of linguistic competence (i.e. the internal knowledge that every speaker has about his own language), would nevertheless leave unaffected the remaining cognitive capacities/abilities. It is thus conventionally assumed that a univocal and casual relationship exists between certain genes and certain

specific linguistic disorders. At a higher level of biological complexity, it is also usually assumed that such genes will be univocally and specifically involved in the regulation of the development (and function) of the so-called brain 'language areas', i.e., neural structures exclusively devoted to processing linguistic stimuli. Although these are controversial issues, which will be briefly but critically discussed in this paper, it also seems clear that clinical practice should benefit to some extent from the identification and functional characterization of genes that, when mutated, contribute to the emergence of this kind of conditions.

On the other hand, the possibility that there might be genes that, when mutated, will impair linguistic competence is of major interest for linguists and for linguistic theory. Since Chomsky's work (Chomsky, 1959; 1980: 34), there is an ample consensus regarding the hypothesis that competence cannot be uniquely (and properly) acquired by just inductive learning, hence the well-known corollary that some linguistic knowledge must be innate (Chomsky, 1959; 1980: 34). Following Chomsky (1980: 75-76), Anderson and Lightfoot (1999) have postulated the existence of both a linguistic genotype and a linguistic phenotype. Anyway, it is worth bearing in mind that what can be biologically regarded as "innate" necessarily transcends what can be considered "genetic". In fact, epigenetic factors and maternal inheritance also seem to play a relevant role in this context, whereas part of the information which determines the features and the functional properties of the neural substrate of language could plausibly be generated by the developmental process itself (Oyama, 2000; Oyama *et al.*, 2001) or would depend on general laws which regulate the self-organization of biological systems (Kauffman, 1995;

* abenitez@uc.c5

2000). Moreover, innatism (or nativism) is compatible with substantially different forms of regulation of the development and organization of brain structures. These issues will be examined again in §6 and §8.

2. How to identify and characterize genes related to language

Due to ethical concerns we cannot deliberately mutate human DNA sequences of interest in order to establish and evaluate the consequences such mutations may have in language. Hence, the search for genes related to language must necessarily depart from people exhibiting a dysfunctional or afunctional linguistic competence. In turn, any experimental analysis of competence must necessarily depart from an assessment of performance. The way in which individuals presumably affected by (specific) language impairments and disorders are clinically characterized and categorized at the phenotypic level, conditions the relevance and the significance of their genetic (and neurobiological) analysis. Thus, genetic analyses will establish statistically significant correlations between certain chromosomal fragments and certain phenotypes no matter how (and how precisely) such phenotypes are defined, categorised, and delimited. An imprecise phenotypic definition, categorization or delimitation of one particular disorder can give rise to results that could be interpreted as indicating the involvement of the same gene (or the same brain area) in the emergence of more than one impairment, whereas this common aetiology would be actually apparent. At this level, special attention should be given to (i) the kind of cognitive abilities the resolution of the experimental tasks routinely employed for the diagnosis demands (merely linguistic competence?); (ii) whether there is more than one different test for the diagnosis of the same disorder (perhaps based on dissimilar criteria?), and (iii) the way in which test results are homogenized (how many different groups = clinical categories are postulated?).

The latter are not trivial concerns. In fact, the numerous difficulties which arise when trying to properly distinguish, at the phenotypic level, different conditions (both specifically linguistic or of a broader cognitive profile), to correctly assign affected people to the diverse clinical categories that these disorders represent (diagnosis), and to accurately discriminate among different types of disorders or even of subtypes of the same disorder, ultimately point to the possibility that specific language impairments could not be as

(strictly) specific as they are normally assumed to be. On the contrary, it is a common finding that these conditions are symptomatically heterogeneous and frequently comorbid with other cognitive impairments, both linguistically specific or not (for a review, see Benítez-Burraco, 2009b), whereas in most cases linguistic competence dysfunction in affected people impairs rather general aspects of language, but not necessarily and exclusively any of the linguistic components which are nuclear for the different theoretical models of language developed by linguists (Newmeyer, 1997). It has consequently been suggested that in these disorders other (cognitive) abilities besides linguistic competence could be simultaneously impaired, or alternatively, that they could be caused by a broader (cognitive) impairment (Nobre and Plunkett, 1997). This apparent lack of specificity of specific language disorders also extends to the neuroanatomical and neurophysiological levels (i.e. structurally and/or functionally anomalous brain areas in affected people give rise in other subjects to different deficits and/or different [including non-linguistic] disorders), but also to the genetic level, as we will discuss below (see §3). While some of these difficulties for satisfactorily characterizing these conditions as specifically linguistic (at all those levels of biological complexity) are of a methodological nature (see below and §4), in other cases they are actually pointing to the genuine way in which cognition is structured and organized, but above all to the true nature of the neural substrate of language and the genuine way in which genes (among other molecular factors) contribute to the regulation of its development (see §4 and §6).

Whatever the case, when trying to discover genetic factors related to (specific) language disorders, a second but crucial step is to evaluate the heritability of the latter. Different methodological tools allow us to properly do so: studies of familial aggregation, analyses of identical and nonidentical twins, studies of adopted individuals, studies of kinship, etc. (Bishop, 2001; Stromswold, 2001). We can now make use of diverse cloning strategies to identify and physically isolate the gene (or genes) presumably mutated in the affected probands. The most productive of such tools is known as *positional cloning*. It allows to correlate, in the absence of significant evidences about the aetiology of the disorder, the anomalous phenotype with a particular chromosomal fragment, by just measuring the coheredarity of the trait with a suitable number (in statistical terms) of known polymorphic genetic markers. Depending on whether

the kin relationships among the experimental subjects are known or unknown (a circumstance that crucially conditions the number of markers to be used), the correlation analysis is known as linkage or association analysis, respectively. The analytical yield of positional cloning has become implemented by the recent development of the so-called *genome-wide association studies* (GWASs), which make use of the whole genome and consequently not only turn unnecessary linkage analyses, but also allow to simultaneously establish the presence and the localization of multiple *loci* of susceptibility to a certain disorder (Zondervan and Cardon, 2007; Potkin *et al.*, 2009). Moreover, the categorization of language disorders as continuous variables (thus going beyond the traditional but simplifying dichotomy *affected vs. nonaffected*) has allowed us to identify the so-called QTLs (quantitative trait *loci*) (Lander and Kruglyak, 1995; Risch and Merikangas, 1996), and ultimately permitted the detection of multiple genes which exert a relatively small effect on a particular trait (Bishop, 2002). Finally, the employment of endophenotypes (i.e. cognitive, neuroanatomical, neurophysiological, endocrine or biochemical quantifiable components of the different levels of biological complexity between the linguistic phenotype and the genes [Gould and Gottesman, 2006]) as the starting point for linkage and association analyses allows us to obtain more direct evidences of the links which plausibly exist between certain genes and certain cognitive (dys)functions, as they refer to more concrete (and more physiological) aspects of brain activity (Gottesman and Gould, 2003). In addition, as these endophenotypes have uncontroversial homologous in other species, they also justify the use of animal models when cloning genes related to language and analysing their structural and functional features (it is worth remembering here that language is a trait that, as Chomsky [1972; 1980] but also many others have repeatedly pointed out, exhibits a fundamental discontinuity at the phenotypic level with the communicative devices employed by the remaining animal species).

Anyway, all those otherwise productive techniques cannot be merely regarded as a panacea. This can be justified by the fact that, on the one hand, the search for QTLs cannot properly detect highly polymorphic *loci*, as it leaves unidentified other non-genetic factors plausibly involved in the emergence of a disorder, such as epigenetic, maternal, or ontogenetic factors (in fact, molecular tools for the analysis of such factors are underdeveloped compared to

those devoted to the analysis of genes and their direct products [ARN and proteins]). On the other hand, it is also because positional cloning merely establishes statistical correlations, not compulsory casual relationships, between certain genes and certain phenotypes why its validity is restricted as well to concrete populations and particular environmental conditions (Hofmann, 2003; Fisher, 2006). In other words, functional analyses of the cloned genes are a must (see below).

On the contrary, the identification of genes related to language (and which mutation gives rise to different language disorders) becomes simplified when there are evidences of chromosomal rearrangements in the karyotype of affected individuals, since these anomalies can be easily detected by different techniques such as fluorescence *in situ* hybridization (FISH) (Volpi and Bridger, 2008). Moreover, this kind of genes does not seem to be randomly localized in the genome, (Ramsay, 2000; Benítez Burraco, 2009a: 197-205). Likewise, when the impaired linguistic phenotype specifically entails the atypical presence, accumulation or degradation of one particular biochemical product, it is possible to identify the affected gene by *functional cloning*, if the identity and the biological activity of the enzyme involved in its biosynthesis or catabolism are previously known (Brzustowicz, 1998). Additionally, *comparative cloning* also simplifies the identification of the affected genes (Brzustowicz, 1998). In this case we usually know the sequences and the functional properties of homologous genes that, when mutated, give rise to similar disorders in other species, i.e., disorders characterized by similar structural and/or functional brain anomalies or which phenotypic profiles resemble those observed in our own species at the cognitive level.

Once the relevant chromosomal fragments are cloned, they should be sequenced to settle on the identity and nature of the gene (or genes) they comprise (Brzustowicz, 1998). DNA sequences are routinely subject to intensive computational analyses, in order to obtain as much relevant information as possible about structural features of the genes, the nature and function of the biochemical products presumably encoded by them, and even the phylogenetic relationships that they maintained with homologous genes from other species. Candidate genes are subsequently subject to functional analyses (*in vitro* and *in vivo*), in order to fully and properly characterise their transcriptional and translational profiles, the biochemical properties of the products

they encode and, ultimately, the physiological role carried out by such products, and basically the way in which their mutation contributes to the emergence of the disorder (Gibson and Gruen, 2008).

Functional analyses are commonly implemented by recurring to animal models of the disorders (typically the rat and the mouse, but also different songbirds). As it was previously pointed out, continuity (i.e. homology) regarding the Faculty of Language (henceforth, FL) quickly arises when molecular, neurobiological, and even cognitive levels are considered. In addition, homologous genes in particular can be deliberately disturbed in these organisms (by *knocking* them *down* or *out*) to clarify the physiological role of the products encoded by such candidate genes. We are especially interested in finding neural anomalies and/or articulatory, perceptive, or cognitive deficits which can be regarded as similar to those detected in humans. Dyslexia notably exemplifies how the analysis of such animal models can contribute to reinforce the feasibility of the causal link between the mutation of certain genes and the emergence of a particular language disorder previously suggested by positional cloning. Hence, in rats and mice, an induced decrease of mRNA levels (*knockdown*) of the candidate genes *DYX1C1* and *DCDC2* gives rise to brain structural changes (plausibly as a consequence of the disruption of the normal pattern of neural migration and interconnection) which are similar to those observed in dyslexic people (Paracchini *et al.*, 2006; Rosen *et al.*, 2007; Burbridge *et al.*, 2008), and significantly also to auditive and cognitive deficits which resemble those detected in dyslexics (Galaburda *et al.*, 2006; Threlkeld *et al.*, 2007).

Last but not least, special attention must be given to the elucidation of the functional value of the different variants of a candidate gene naturally arisen in different human populations. These variants can indistinctly be functional, dysfunctional or afunctional compared to the wild type. Consequently, different alleles and protein polymorphisms can be ideally correlated to different linguistic deficits (this test is known as allelic association analysis) (Wahlsten, 1999).

3. Structural and functional characterization of genes related to specific language impairments

In recent years different genes, that have been regarded as casual or risks factors for the emergence

of hereditary conditions in which only language seems to be impaired, have been cloned and characterised. A well-known case, popularly regarded as 'the language gene' *par excellence*, is *FOXP2*. This gene encodes a transcriptional repressor and its mutation gives rise to a plausible subtype of SLI, though this is still a controversial claim (for a symptomatic profile of the affected people, see Gopnik, 1990; Vargha-Khadem *et al.*, 1995; Watkins *et al.*, 2002; Vargha-Khadem *et al.*, 2005; Shriberg *et al.*, 2006). Either way, there are ample evidences supporting the relevant role of this gene in modulating the development of brain areas involved in language processing. Firstly, the primary pathology of the disorder associated to the gene's mutation is located in the caudate nucleus, a subcortical structure which seems to play a key role in the computation of the sequential tasks involved in phonation and syntax (but not only in these) (Ullman, 2001; Lieberman, 2002). Secondly, the *FOXP2* protein seems to be involved in the regulation of the neural differentiation (and plausibly in establishing the cellular identity and/or function) needed for the correct organization and/or development of cortico-thalamic-striatal circuits associated to motor planning, sequential tasks, and procedural learning (for a review, see Marcus and Fisher, 2003; Vargha-Khadem *et al.*, 2005; Fisher and Scharff, 2009). Thirdly, the mutation of some of its physiological targets gives also rise to (different) language disorders, as the case of *CNTNAP2* clearly shows regarding SLI and autism (Vernes *et al.*, 2008). Finally, *Foxp 2* mutations in mice bring about characteristic structural anomalies in the cerebellum, but also reduce the long-term plasticity related to learning tasks in which basal ganglia play a relevant role (Yin *et al.*, 2006). Simultaneously, mice carrying the human (nonmutated) sequence exhibit physiological responses which are substantially opposed to the former (Enard *et al.*, 2009). Besides, at the phenotypic level, the *knockout* of *Foxp2* typically leads to a decrease in the frequency of the ultrasonic vocalizations in the pups (Shu *et al.*, 2005), probably resembling the deficit in the capacity for discriminating brief auditive stimuli, (and plausibly certain sound frequencies) which is found in SLI (McArthur and Bishop, 2001). On the other hand, it is also significant that the *knockdown* of *FoxP2* in zebra finch mainly affects neurons of the X-area of the song circuit, a structure homologous to the basal ganglia. As a consequence, a significant shortening of the critical period for song learning is observed, but also a reduction in the accuracy of the song itself

(Haesler *et al.*, 2007), also resembling the reduced capacity for repeating words and pseudowords, but also complete sentences, which is characteristic of affected people carrying a mutation in *FOXP2* (Watkins *et al.*, 2002). In the whole, it seems quite plausible that, if *FOXP2* has played a prominent role in the evolution of language (as it seems), this role would, to a certain extent, not only be confined to mechanisms involved in the regulation of the development (and the structural and functional patterning) of certain brain regions, but also to those involved in the modulation of neural plasticity needed for the learning of motor tasks (Fisher and Scharff, 2009; White, 2009). To date, several other QTLs linked or associated to SLI have been identified (Bartlett *et al.*, 2002; SLI Consortium, 2002; Fisher *et al.*, 2003; SLI Consortium, 2004), though the only other risk factor for SLI, plausibly attested to, seems to be *ATP13A4*, which encodes a cation-transporting P5-type ATPase (Kwasnicka-Crawford *et al.*, 2005).

Up to nine different *loci* for dyslexia have also been identified so far (DYX1 to DYX9) (Williams and O'Donovan, 2006; Gibson and Gruen, 2008). Nevertheless, there seem to be many additional *loci* which confer susceptibility to the disorder and which would consequently correspond to genes that can be regarded as risk factors for reading disability (Smith, 2007). From three of these *loci* (DYX1, DYX2 and DYX5) a total of four different genes have been cloned. *ROBO1*, which corresponds to *locus* DYX5, encodes a protein which seems to be involved in the regulation of axonal growth (Hannula-Jouppi *et al.*, 2005; McGrath *et al.*, 2006), possibly of nerve fibres which conform the so-called thalamo-cortical projections, as has been attested in mice (Bagri *et al.*, 2002). The remaining three genes (*DYX1C1*, which corresponds to *locus* DYX1, and *DCDC2* and a close counterpart, *KIAA0319*, which both correspond to *locus* DYX2) encode proteins which contribute to the regulation of the radial migration of cortical neurons (Taipale *et al.*, 2003; Meng *et al.*, 2005; Paracchini *et al.*, 2006; Velayos-Baeza *et al.*, 2008). The analysis of chromosome rearrangements detected in different dyslexic individuals has made feasible the identification of other candidate genes for this condition, or at least of genes which can be considered as risk factors for the disorder in certain subjects or certain populations. One of the most promising is *DIP2A* (Poelmans *et al.*, 2009), which encodes a protein that plays a key role in the regulation of synaptic plasticity (Yu *et al.*, 2001; Collingridge and Isaac, 2003), and which mutation

impairs diverse cognitive processes which depend on hippocampal activity, such as learning and memory (Collingridge and Isaac, 2003), which are also impaired in dyslexics (Swanson *et al.*, 2006).

Finally, speech-sound disorder (SSD) is another, purportedly, specific language impairment with a genetic basis. Significantly, one of the *loci* related to this disorder (3p12-q13) corresponds to *ROBO1*, which is also associated to dyslexia (Nopola-Hemmi *et al.*, 2001; see above). The existence of a remarkable linkage has been documented as well between SSD and the 15q14 region (Stein *et al.*, 2006). It is worth mentioning that the duplication of the 15q11-13 region has been associated to autism (Cook *et al.*, 1997; Schroer *et al.*, 1998; Filipek *et al.*, 2003; Shao *et al.*, 2003), while its deletion gives rise to both Angelman and Prader-Willi syndromes (Magenis *et al.*, 1990; Kishino *et al.*, 1997). For a review of the genetic basis of other rare infrequent language disorders (including those mentioned in §1), see Benítez-Burraco, 2008 or Benítez-Burraco, 2009a: 83-227.

4. Some remarks about brain organization as a way of justifying why the scope of our research should be extended

As was previously pointed out (see §2), the exhaustive analysis of these allegedly specific language disorders at different levels of biological complexity (phenotypic/clinical, cognitive, neuroanatomical, neurophysiological and genetic) has given rise to an increasing body of evidences which suggest that they could be not (strictly) specific at all those levels of complexity, in the sense that it could be unfeasible to always correlate them with (just) (i) language impairments (but not simultaneously with other cognitive disturbances); (ii) underlying deficits which can be characterised as strictly linguistic (but not with broader cognitive deficits); (iii) structural alterations and/or functional anomalies of particular brain regions which are specialized in the processing of linguistic stimuli (i.e. 'language areas'); or (iv) the mutation of genes that ideally merely affect the development and functioning of such regions (i.e. 'language genes'). What we actually observe is perhaps unexpected. At the symptomatic level, (i) there frequently is a (certain) comorbidity among different language (and cognitive) disorders, while at the same time (ii) these disorders do not show unvarying symptomatic profiles, but represent heterogeneous clinical categories. At the cognitive

level, (i) these disorders usually entail other (cognitive) dysfunctions besides those which can be regarded as specifically linguistic, and/or (ii) they seem to arise as a result of a broader cognitive dysfunction; consequently, (iii) the same disorder can be caused by several different underlying deficits, while (iv) the same underlying deficit can give rise to diverse linguistic (and cognitive) disorders. At the neural level, (i) brain regions which seem to be structurally or functionally disturbed in affected people are also frequently involved in computational tasks not directly related to language processing, while (ii) the identity and extension of such areas is variable (as it is also in the normal population); hence, (iii) the impairment of these purportedly 'language areas' commonly gives rise in other subjects to different deficits and/or different (including nonlinguistic) disorders. At this level an illustrative example is the ventral portion of the occipito-temporal region, a classic area for dyslexia (Horwitz *et al.*, 1998; Shaywitz *et al.*, 1998; Paulesu *et al.*, 2001), whose dysfunction gives rise as well to a nonlinguistic disorder known as prosopagnosia (Sorger *et al.*, 2007; Dricot *et al.*, 2008). Finally, at the genetic level, the real scenario could appear at first glance as even more puzzling as (i) genes which are mutated in individuals who exhibit this kind of specific language disorders are also expressed in brain regions not related to language processing in healthy people, but even in diverse tissues outside the nervous system. Consequently, it sometimes occurs that (ii) these supposed 'language genes' are mutated in people affected by other cognitive (i.e., nonspecifically linguistic) disorders, or (iii) are simultaneously linked or associated to diverse language impairments. It also frequently happens that (iv) in some of the individuals affected by a particular language disorder the sequence of these candidate 'language genes' is normal (phenocopy) or (v) the linguistic competence of some of the individuals who are endowed with an anomalous variant of one of such 'language genes' is not impaired at all (null penetrance) or is just mildly impaired (reduced penetrance). Moreover (vi) the identity of such genes differs (to a certain extent) from one population to another and/or depending on the subtype of the disorder; it is clear that for each language disorder there are numerous candidate genes and multiple genes that can be considered as risk factors for its emergence. Ultimately, (vii) most genes related to language have been identified in individuals who not only exhibited a (partially or totally) impaired competence, but in whom other

cognitive abilities were also disturbed (for a review, see Benítez-Burraco, 2009a: 88-94, 168-172, and 177-227).

It is true that, to a certain extent, the difficulties which arise for achieving a precise characterization of (specific) language impairments and a distinctive separation (at all biological levels previously discussed) between them and other language impairments – both specific or linked to a broad cognitive dysfunction – are of a methodological nature. We have already discussed main shortcomings concerning the clinical characterization and categorization of the disorders, as well as major caveats regarding the conventional tools employed for the genetic (and molecular) analysis of language disorders (see §2). At this point, those concerning the analysis of the neural substrate of the FL should also be considered. A controversial issue at this level is the concrete way in which we tend to correlate the structural anomalies detected by the assorted neuroimaging techniques employed for testing the performance (but especially the visual representations corresponding to the anomalous computational tasks specifically generated by the experimental tests used in functional/clinical studies) with the diverse linguistic dysfunctions or dysfunctional components of language. In brief: why do we systematically tend to interpret such (anomalous) visual representations as (impaired) homogeneous linguistic functions/categories and to isolate them from other functions/categories of dissimilar nature when neural systems are not, in fact, (so) discrete in functional terms? (see Kosik, 2003 for an interesting discussion on this issue). Of course, a crucial caveat at this level is also the limited resolution of most noninvasive neuroimaging techniques (usually they do not go beyond 0.1 mm) (Koizumi, 2004), which can lead us to wrongly conclude that brain areas implicated in language processing (and which are anatomically and/or functionally impaired in affected people) are multifunctional, when there being some kind of histological and/or functions dissociation among different (but very closely located) neural populations in such (apparently) multifunctional areas could actually be the case.

Nevertheless, our main point regarding this controversy will be precisely the opposite one: the pertinacious problem which universally arises when trying to completely discriminate among these disorders at all these levels of biological complexity, and to distinctively separate them as well from other cognitive disorders, is not (only)

due to methodological caveats, but (also) to an inaccurate conception of the genuine structure and organization of cognition, and above all, of the true nature of the neural substrate of language and the genuine way in which genetic factors (among other molecular factors) contribute to the regulation of its development.

The existence of (i) complete dissociations between language and other cognitive abilities, and even among the different functional components of language (at the phenotypic/clinical level), (ii) 'language areas' which are clearly delimited in anatomical and functional terms (at the neural level), and (iii) specific 'language genes' involved in the regulation of the development and functioning of such areas (at the molecular level), ultimately points to a strictly modular hypothesis concerning the biological nature of both cognition and language, and particularly, the anatomical and functional organization of the brain. According to this view, modules are encapsulated and autonomous computational devices, innately specified, which exhibit a domain specificity and which evolved independently to satisfy particular functions (*cf.* Fodor, 1983; Coltheart, 1999), supporting the idea that the mutation of a particular (language) gene can give rise to the dysfunction of a particular brain (language) area, which in turn will give rise to just an impairment of the linguistic competence (and performance), while keeping intact the remaining cognitive capacities. Nevertheless, this kind of hypothesis cannot properly explain (i) the aforementioned unexpected difficulties for achieving an effective separation (at all levels of biological complexity) between the diverse afunctional or dysfunctional phenotypes of the competence and those corresponding to the impairment of other cognitive capacities, not to mention (ii) the very dynamic followed by the development of the brain during ontogeny (Karmiloff-Smith, 1998) or, consequently, (iii) the effect exerted by experience on the structuring and functioning of the FL, and ultimately (iv) the characteristic discrepancy which can also be adverted during development between the ontogenetic itineraries followed by linguistic competence and the remaining cognitive abilities in people affected by language disorders (see (Shaywitz *et al.*, 1995; Shaywitz and Shaywitz, 2005 on dyslexia, for instance).

On the contrary, as Marcus (2006) has pertinently pointed out, two cognitive modules, being functionally distinct (in fact, they have to be if they are to be considered modules), are never

completely independent in genetic, neurobiological and evolutionary terms. Thus, most genes which contribute to regulate the development (and to some extent, the functioning) of the neural structures involved in language processing are shared, in fact, with other cognitive capacities (or modules), as it is also the case with most of such neural structures. But at the same time, both the genetic program (in the loose sense of a set of functionally related genes) as a whole and the neural substrate of the FL (also in the loose sense of a set of functionally related neural structures) as a whole are idiosyncratic (though simultaneously having a prolonged evolutionary history), so warranting the functional autonomy and specificity which characterise the FL from a cognitive/phenotypic perspective. Collaterally, this alternative view of the biological nature of the FL seems to legitimate (and also to demand) the consideration of general cognitive (i.e. nonspecifically linguistic) disorders if genes involved in the regulation of the development and functioning of the neural structures implicated in language processing are to be identified and characterised. In §8 we will further suggest that this kind of genes are principally related to what we will label as the Faculty of Language in a Broad Sense (FLB).

5. Structural and functional characterization of genes related to broad language impairments

When also considering cognitive disorders which cannot be regarded as specifically linguistic, but which simultaneously exhibit a characteristic impairment of the linguistic competence, the number of genes related to language substantially increases (for a review see Benítez-Burraco, 2009: 88-94, 168-172, and 177-227). Consequently, the biochemical nature and function of the products encoded by them are diverse, as they include (i) enzymes involved in basic brain metabolic reactions, (ii) membrane transporters (or proteins associated to them), (iii) enzymes involved in basic cellular metabolic reactions or essential cellular structural proteins (including, significantly, those related to the functioning of the cellular cytoskeleton); (iv) proteins implicated in cell-to-cell interactions (including, notably, those responsible for adhesion and recognition processes between neurons); (v) extracellular signalling proteins, (vi) membrane receptors and proteins integrated in signal transduction pathways, and (vii) transcriptional and translational factors, and other regulators of gene

expression (including, ncRNAs and proteins which interact with the DNA).

At the same time, these products mediate diverse physiological processes at the brain level. While some of them are (i) regulators of the basic brain metabolism, others regulate (ii) basic cellular processes (such as cell-to-cell interactions and/or cellular adhesion; inwards and outwards cell vesicle trafficking; organelle morphology, location, and interaction; DNA replication and reparation; transcriptional/translational activity and mRNA processing; or cell cycle related processes, including the stabilization and remodelling of the cellular cytoskeleton and the cell size, shape, and movement); (iii) neuron specific cellular processes (comprising diverse events related to the generation of action potentials, the nerve impulse transmission, and the different steps encompassed by the synapses); (iv) neural proliferation and migration; (v) synaptogenesis and axonogenesis; (vi) neural identity and/or functionality (including the establishment of brain basic patterns and regions, and the [embryonic, perinatal, and postnatal] maturation of certain cerebral circuits), and (vii) basic brain processes (such as memory, long-term potentiation [LTP], neural plasticity and/or critical periods for synaptic development in response to experience).

By and large, a high percentage of genes related to language play an eminently modulatory role, as their products regulate the expression of other genes, or belong to cellular pathways involved in signal transduction. From a physiological perspective, these genes are mostly related, at the brain level, to the regulation of neural proliferation, migration, and specialization, or to the establishment of initial contacts among differentiated neurons (synaptogenesis, and axonogenesis).

6. How the development of the neural substrate of language is genetically (but not exclusively genetically) regulated

It would be a mistake to simply assume that all the wiring of the neural substrate of the FL is exclusively genetically determined. On the one hand, because genes represent just one among diverse biological factors (belonging to different levels of complexity) involved in the regulation of the development and functioning of such neural substrate. On the other hand, because neural connections are universally subject to plastic modifications crucially depending on activity if they are to generate operative devices;

in other words, they cannot be regarded as fully genetically prewired.

At this point it could be convenient to summarize (and properly delimit) the real contribution of genes to the regulation of the development (and functioning) of the neural substrate of the FL (for a more detailed discussion, see Benítez-Burraco, 2009: 355-364): (i) genes do not directly determine language, but just synthesize biochemical products, which will be engaged in particular physiological functions; (ii) ordinarily, the same gene plays different roles (i.e. contribute to different physiological functions) in diverse moments and body tissues during ontogeny (pleiotropy); simultaneously, (iii) many genes usually contribute (each to a different extent) to the same biological process (polygenism); and (iv) the extent to which a particular gene product contributes to such a biological process heavily depends on the precise balance it keeps, in a particular moment and place, with the biochemical products encoded by the remaining involved genes (gene products are normally arranged in gradients or specific combinations of signalling molecules).

Moreover, as it was pointed out in §1, other innate factors besides genes themselves also contribute to the initial wiring of the neural substrate of the FL. Consequently, a special consideration should be also given to epigenetic elements (i.e. structural modifications of the DNA which, not affecting nucleotide sequences, do affect gene expression patterns), maternal factors (in essence, protein gradients inherited via the egg cytoplasm), and regulatory elements belonging to all levels of biological complexity located between genes (and their products) and brain areas (i.e. the metabolome, different subcellular organelles, diverse brain cells, synaptic activities, and diverse specific brain circuits) (Choudhary and Grant, 2004). What is more, it seems that part of the information which determines the features and functional properties of the neural substrate of language could plausibly be generated by developmental processes themselves (Oyama, 2000; Oyama *et al.*, 2001) or would depend on general laws which regulate the self-organization of biological systems (Kauffman, 1995; 2000).

Nevertheless, this complex (and only partially genetic) regulatory mechanism would essentially determine just the basic interconnection patterns among the diverse types of differentiated neurons involved (and hence, the basic histological organization of the main anatomic macrostructures which conform the neural substrate of language),

but without generating fully operative computational devices (Ramus, 2006). This fundamental brain pre-wiring, which consequently would be more relevant during the first stages of ontogeny, must be compulsorily implemented by the feedback effect exerted on brain structures by neural activity during language processing. This is an eminently physiological phenomenon, encompassing structural and functional changes in neurons as the result of the interactions which take place among different brain regions, but also (and crucially) between them and the environment. Only in such a way, the definitive cytoarchitecture of the neural substrate of the FL is achieved and fully operative neural structures are generated.

To sum up, as gene activity (and the activity of the products encoded by genes) is necessarily (and decisively) conditioned by such epigenetic, maternal, and ontogenetic factors, by the physiological factors derived from the remaining levels of biological complexity of the FL, and by the environmental factors (which, in addition, interact in a nonlinear way), a noteworthy corollary is that we cannot still regard genes as a primary cause regarding either the development of the FL, or the emergence of language disorders. On the contrary, they just represent one more among the diverse regulatory devices involved in the modulation of such processes, with the particularity (previously mentioned) that each of these levels regulates (and is regulated by) the activity of the remaining ones. Quoting Oyama (2000: 40), "a gene initiates a sequence of events only if one chooses to begin analysis at that point".

7. Inherited language disorders revisited

The concise depiction of the biological nature and the developmental itinerary of the FL previously sketched (see §6), and particularly, of the genuine relationships which exist between genes and language (see also §6), seems to allow us to satisfactorily explain many of the most remarkable and apparently paradoxical results of the analysis of (specific) language impairments and disorders at the phenotypic/clinical, cognitive, neuroanatomical, neurophysiological and genetic levels (see §2 and §4), which could not be exclusively imputed to just methodological caveats (see §4).

In a pleiotropic context the mutation of a particular gene can affect the normal development (and functioning) of two (or more) different brain areas, giving rise to structural and functional anomalies

which will in turn originate two (or more) diverse deficits; these deficits will subsequently give rise to different symptoms, susceptible of being clinically categorised as two (or more) dissimilar disorders (sometimes heterogeneous, sometimes comorbid). As the context is simultaneously polygenic, it frequently occurs that the mutation of two (or more) functionally related genes can give rise to similar structural and functional anomalies in the same brain area(s), and consequently to an equal deficit, and ultimately to akin symptoms susceptible of being clinically categorised as a unique (and the same) language disorder (which sometimes can be heterogeneous). What is more, as the contribution of each dysfunctional or afunctional product to the anomalous phenotype will always be subtly conditioned by the effect exerted by the remaining involved genes, and crucially, by the remaining involved modulatory factors (epigenetic, maternal, ontogenetic, environmental, etc.), it also frequently happens that (i) the mutation of the same gene gives rise, in different people or populations, to diverse levels of affectedness regarding the structural and functional integrity of a particular brain area (or even of different areas), and to diverse cognitive and symptomatic profiles of the affected individuals, which can be clinically categorised as two (or more) subtypes of the same disorder or even as two (or more) different disorders (which sometimes will be comorbid); or (ii) the mutation of two different genes gives rise, in different people or populations, to similar structural and functional anomalies in the same or different brain areas, which will in turn originate a common deficit, this deficit giving rise to akin symptoms susceptible of being clinically categorised as the same disorder or as different subtypes of a common condition.

Consequently, a remarkable corollary, of particular interest for clinical linguists, is that the actual contribution of genes to a final dysfunctional or afunctional phenotype is, in general, limited, difficult of prediction, and substantially conditioned by the effects exerted by the remaining involved factors. Anyhow, according to the consequences caused by their mutation, and basically following Winterer and Goldman (2003), some of these genes can be regarded as principal (i.e. their mutation constitutes a main causal factor in the emergence of a particular disorder in most affected people), while others can be considered as secondary (i.e., their mutation just represents a risk factor for the appearance of the condition in some individuals).

8. An appendix for linguists: genes and minimalism

In addition, the depiction of the biological nature and the developmental itinerary of the FL which has been outlined in this paper also nicely fits main Chomskyan recent intuitions about human language and about its distinctive (biological) properties. Over the last years, such intuitions have substantially moved from an eminently modular conception of the FL (and its components) to a less modular/more functional view of it, rooted in Minimalist Program (Chomsky, 1995; Chomsky, 2000). Thus, the hypothesis of the existence of an Universal Grammar (i.e. an autonomous system of knowledge based on idiosyncratic principles and categories which would not be shared with other cognitive systems) has been replaced by a conception of language as an interface between the cognitive systems responsible for thought and the sensorimotor systems involved in perception and motricity (usually known as “external”), thus language becoming reduced to just a lexicon and a computational system. Two further developments of such a hypothesis deserved to be analysed. On the one hand, Chomsky posits a crucial and productive distinction between a Faculty of Language in a Narrow sense (FLN) (i.e., computational system capable of recursive processing), and a Faculty of Language in a Broad sense (FLB) (i.e., all the aspects related to contents to be expressed and interpreted, and also to signals employed in their transmission) (Hauser *et al.*, 2002). While the former would be the main evolutionary innovation for human language in biological terms, the latter (in essence, the remaining components of the FL) would have a long-lasting evolutionary history. On the other hand, Chomsky thinks that the coupling between the conceptual system and the sensorimotor systems would be mandatory during development whenever growth takes place in presence of a threshold amount of linguistic stimuli (Hauser *et al.*, 2002). This essentially implies that the development and the functioning of the FL would also rely, to a certain extent, on those general laws which regulate the organization of biological systems (which Chomsky [2001: 1-2; 2005] famously categorizes as “the third factor”).

Different reasons seem to prove the claim that the language depiction derived from the Chomskyan Minimalist Program matches, better than others, his characterization of the FL emerging from the genetic (and in general, the [neuro]biological) analysis of

the FL. On the one hand, because a significant part of the genetic information needed for the constitution of the linguistic functional system would correspond to genes needed for the development and functioning of the “external” systems as well. This also implies that most ‘language genes’ would ultimately be related to the FLB, and hence, that their mutation, while not affecting the FLN itself, will impair the FL as a whole, though also plausibly giving rise to other diverse disorders in certain populations and/or environments. On the other hand, because a considerable amount of the innate information (in essence, information not derivable from experience) needed for the development of the FL would not be genetic, but either epigenetic, or biologically determined by the features of the ontogenetic environment in which development takes place (Vercelli, 2009), or even dependent on those aforementioned general laws which regulate the organization of biological systems, which are independent from the environment and from the genome (Chomsky 2001: 1-2). Finally, because it is still licit to understand the biological idiosyncrasy of the FL in terms of domain specificity, which would reside, as discussed in §4, in the particular way in which the diverse components related to it interact at different levels of biological complexity, and particularly, in the precise set of functionally interrelated genes involved in the regulation of the development of its neural substrate, and also in the particular interconnection pattern which gives (structural and functional) cohesion to that substrate.

In sum, the minimalist conception of the FL harmonize better than others (even the preminimalist Chomskyan conception itself) with the recent findings concerning the way in which evolutionary and developmental processes take place in living beings (with regard to which the FL should not represent any exception, notwithstanding its significant idiosyncrasy at the phenotypic level). At present, it seems clear that the enterprise of fractioning language into different biological components and of analysing the way in which such components interact (and particularly, how genes do that) will play a key role in our long-lasting challenge for satisfactorily answering the five central questions posited by Chomsky concerning the (biological) study of language (Chomsky and Lasnik, 1993): what constitutes knowledge of language, how this knowledge is acquired, how it is put in use, how it is implemented at the brain level, and how it has evolved in the species.

9. References

- Anderson, S. R. and Lightfoot, D. W. (1999). The human language faculty as an organ. *Annu Rev Physiol*, 62: 697-722.
- Bagri, A., Marin, O., Plump, A. S., Mak, J., Pleasure, S. J., Rubenstein, J. L. R. and Tessier-Lavigne, M. (2002). Slit proteins prevent midline crossing and determine the dorsoventral position of major axonal pathways in the mammalian forebrain. *Neuron*, 33: 233-248
- Bartlett, C. W., Flax, J. F., Logue, M. W., Vieland, V. J., Bassett, A. S., Tallal, P., Brzustowicz, L. M. (2002). A major susceptibility locus for specific language impairment is located on 13q21. *Am. J. Hum. Genet.*, 71: 45-55
- Benítez Burraco, A. (2008). Más allá del TEL y de la dislexia: otros trastornos lingüísticos de base genética [Beyond SLI and dyslexia: other language disorders with a genetic basis]. *Neurología, Neurocirugía y Psiquiatría*, 41: 21-36
- Benítez-Burraco, A. (2009). *Genes y lenguaje: aspectos ontogenéticos, filogenéticos y cognitivos* [Genes and language: ontogenetic, phylogenetic, and cognitive aspects]. Barcelona: Reverté.
- Benítez Burraco, A. (2009b). ¿Hasta qué punto son específicos los trastornos específicos del lenguaje? Implicaciones para una caracterización biológica de la facultad lingüística humana [How specific are actual specific language impairments? Implications for a biological characterization of the Faculty of Language]. *Ludus Vitalis XVI* (30): 101-134
- Bishop, D. V. M. (2001) Genetic and environmental risks for specific language impairment in children. *Philos. Trans. R. Soc. Lond., B, Biol. Sci.*, 356: 369-380.
- Bishop, D. V. M. (2002). The role of genes in the etiology of specific language impairment. *J. Commun. Disord.*, 35: 311-328.
- Brzustowicz, L. M. (1998). Molecular genetic approaches to the study of language. *Hum. Biol.*, 70: 325-345.
- Burbridge, T. J., Wang, Y., Volz, A. J., Peschansky, V. J., Lisann, L., Galaburda, A. M., LoTurco, J. J. and Rosen, G. D. (2008). Postnatal analysis of the effect of embryonic knockdown and overexpression of candidate dyslexia susceptibility gene homolog *Dcdc2* in the rat. *Neuroscience*, 152: 723-733.
- Chomsky, N. A. (1959). Review of *Verbal Behavior*, by B. F. Skinner. *Language*, 35: 26-57
- Chomsky, N. A. (1972). *Language and Mind*. New York: Harcourt, Brace & Jovanovich.
- Chomsky, N. A. (1980). *Rules and Representations*. Oxford: Basil Blackwell.
- Chomsky, N. A. (1995). *The Minimalist Program*. Cambridge: MIT Press.
- Chomsky, N. A. (2000). Minimalist inquiries: The Framework. In *Step by Step. Papers in Minimalist Syntax in Honor of Howard Lasnik* (R Martin, D Michaels, and J Uriagereka, eds.). Cambridge: MIT Press, pp. 89-155.
- Chomsky, N. A. (2001). *Beyond explanatory adequacy*. Cambridge: MIT Press.
- Chomsky, N. A. (2005). Three factors in language design. *Linguistic Inquiry*, 36: 1-22.
- Chomsky, N. A., and Lasnik, H. (1993). The theory of principles and parameters. In *Syntax. An International Handbook of Contemporary Research* (J. Jacobs, A. von Stechow, W. Sternefeld, and T. Vennemann, eds.). Berlin: Walter de Gruyter, pp. 506-569.
- Collingridge, G. L. and Isaac, J. T. R. (2003). Functional roles of protein interactions with AMPA and kainate receptors. *Neurosci. Res.*, 47: 3-15.
- Coltheart, M. (1999). Modularity and cognition. *Trends Cogn. Sci.*, 3: 115-120.
- Cook, E. H., Lindgren, V., Leventhal, B. L., Courchesne, R., Lincoln, A., Shulman, C., Lord, C., and Courchesne, E. (1997). Autism or atypical autism in maternally but not paternally derived proximal 15q duplication. *Am. J. Hum. Genet.*, 60: 928-934.
- Dricot, L., Sorger, B., Schiltz, C., Goebel, R. and Rossion, B. (2008). Evidence for individual face discrimination in non-face selective areas of the visual cortex in acquired prosopagnosia. *Behav. Neurol.*, 19: 75-79.
- Enard, W., Gehre, S., Hammerschmidt, K., Hölter, S. M., Blass, T., Somel, M., Brückner, M. K., Schreiweis, C., Winter, C., Sohr, R., Becker, L., Wiebe, V., Nickel, B., Giger, T., Müller, U., Groszer, M., Adler, T., Aguilar, A., Bolle, I., Calzada-Wack, J., Dalke, C., Ehrhardt, N., Favor, J., Fuchs, H., Gailus-Durner, V., Hans, W., Hölzlwimmer, G., Javaheri, A., Kalaydjiev, S., Kallnik, M., Kling, E., Kunder, S., Mossbrugger, I., Naton, B., Racz, I., Rathkolb, B., Rozman, J., Schrewe, A., Busch, D. H., Graw, J., Ivandic, B., Klingenspor, M., Klopstock, T., Ollert, M., Quintanilla-Martinez, L., Schulz, H., Wolf, E., Wurst, W., Zimmer, A., Fisher, S. E., Morgenstern, R., Arendt, T., de Angelis, M. H., Fischer, J., Schwarz, J. and Pääbo S. (2009). A humanized version of *Foxp2* affects cortico-basal ganglia circuits in mice. *Cell*, 137: 961-71.
- Filipek, P. A., Juranek, J., Smith, M., Mays, L. Z., Ramos, E. R., Bocian, M., Masser-Frye, D., Laulhere, T. M., Modahl, C., Spence, M. A. and Gargus, J. J. (2003). Mitochondrial dysfunction in autistic patients with 15q inverted duplication. *Ann. Neurol.*, 53: 801-804.
- Fisher, S. E. (2006). Tangled webs: tracing the connections between genes and cognition. *Cognition*, 101: 270-297.
- Fisher, S. E. and Scharff, C. (2009). *FOXP2* as a molecular window into speech and language. *Trends Genet.*, 25: 166-177
- Fisher, S. E., Lai, C. S. and Monaco, A. P. (2003). Deciphering the genetic basis of speech and language disorders. *Annu. Rev. Neurosci.*, 26: 57-80.
- Fodor, J. A. (1983). *The Modularity of Mind. An Essay on Faculty Psychology*. Cambridge: MIT Press.
- Galaburda, A. M., LoTurco, J., Ramus, F., Fitch, R. H. and Rosen, G. D. (2006). From genes to behavior in developmental dyslexia. *Nat Neurosci*. 9: 1213-1217.
- Gibson, C. J. and Gruen, J. R. (2008). The human lexinome: genes of language and reading. *J. Commun. Disord.*, 41: 409-420.
- Gopnik, M. (1990). Feature-blind grammar and dysphasia. *Nature*, 344: 715.
- Gottesman, I. I. and Gould, T. D. (2003). The endophenotype concept in psychiatry: etymology and strategic intentions. *Am. J. Psychiatry*, 160: 636-645.
- Gould, T. D. and Gottesman, I. I. (2006). Psychiatric endophenotypes and the development of valid animal models. *Genes Brain Behav.*, 5: 113-119.
- Haesler, S., Rochefort, C., Georgi, B., Licznarski, P., Osten, P. and Scharff, C. (2007). Incomplete and inaccurate vocal imitation after knockdown of *FoxP2* in songbird basal ganglia nucleus area X. *PLoS Biol.* 5: e321.
- Hannula-Jouppi, K., Kaminen-Ahola, N., Taipale, M., Eklund, R., Nopola-Hemmi, J., Kaariainen, H. and Kere J. (2005). The axon guidance receptor gene *ROBO1* is a candidate gene for developmental dyslexia. *PLoS Genet.* 1: e50.
- Hauser, M. D., Chomsky, N. and Fitch, W. T. (2002). The faculty of language: what is it, who has it, and how did it evolve? *Science*, 298: 1569-1579.
- Hofmann, H. A. (2003). Functional genomics of neural and behavioral plasticity. *J. Neurobiol.*, 54: 272-282.
- Horwitz, B., Rumsey, J. M. and Donohue, B. C. (1998). Functional connectivity of the angular gyrus in normal reading and dyslexia. *Proc. Natl. Acad. Sci. U.S.A.*, 95: 8939-8944.
- Kamiloff-Smith, A. (1998). Development itself is the key to understanding developmental disorders. *Trends Cogn. Sci.*, 2: 389-398.
- Kauffman, S. (1995). *At Home in the Universe: The Search for the Laws of Self-Organization and Complexity*. New York: Oxford University Press.
- Kauffman, S. (2000). *Investigations*. New York: Oxford University Press
- Kishino, T., Lalande, M. and Wagstaff, J. (1997). UBE3A/E6-AP mutations cause Angelman syndrome. *Nature Genet.*, 15: 70-73. *Erratum: Nature Genet.*, 15: 411.

43. Koizumi, H. (2004). The concept of 'developing the brain': a new natural science for learning and education. *Brain Dev.*, 26: 434-441
44. Kosik, K. S. (2003). Beyond phrenology, at last. *Nat. Rev. Neurosci.*, 4: 234-239.
45. Kwasnicka-Crawford, D. A., Carson, A. R., Roberts, W., Summers, A. M., Rehnstrom, K., Jarvela, I. and Scherer, S. W. (2005). Characterization of a novel cation transporter ATPase gene (*ATP13A4*) interrupted by 3q25-q29 inversion in an individual with language delay. *Genomics.*, 86: 182-194.
46. Lander, E. and Kruglyak, L. (1995). Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. *Nat. Genet.*, 11: 241-47.
47. Lieberman, P. (2002). On the nature and evolution of the neural bases of human language. *Am. J. Phys. Anthropol.*, 45: 36-62.
48. Magenis, R. E., Toth-Fejel, S., Allen, L. J., Black, M., Brown, M. G., Budden, S., Cohen, R., Friedman, J. M., Kalousek, D., Zonana, J., Lacy, D., LaFranchi, S., Lahr, M., Macfarlane, J. and Williams, C. P. S. (1990). Comparison of the 15q deletions in Prader-Willi and Angelman syndromes: specific regions, extent of deletions, parental origin, and clinical consequences. *Am. J. Med. Genet.*, 35: 333-349.
49. Marcus, G. F. (2006). Cognitive architecture and descent with modification. *Cognition*, 101: 443-465.
50. Marcus, G. F. y Fisher, S. E. (2003). FOXP2 in focus: what can genes tell us about speech and language? *Trends Cogn. Sci.*, 7: 257-262.
51. McArthur, G. M. and Bishop, D. V. M. (2001). Auditory perceptual processing in people with reading and oral language impairments: current issues and recommendations. *Dyslexia*, 7: 150-170.
52. McGrath, L. M., Smith, S. D. and Pennington, B. F. (2006). Breakthroughs in the search for dyslexia candidate genes. *Trends Mol. Med.*, 12: 333-341
53. Meng, H., Smith, S. D., Hager, K., Held, M., Liu, J., Olson, R. K., Pennington, B. F., DeFries, J. C., Gelernter, J., O'Reilly-Pol, T., Somlo, S., Skudlarski, P., Shaywitz, S. E., Shaywitz, B. A., Marchione, K., Wang, Y., Paramasivam, M., LoTurco, J. J., Page, G. P. and Gruen, J. R. (2005). DCDC2 is associated with reading disability and modulates neural development in the brain. *Proc. Nat. Acad. Sci. U.S.A.*, 102: 17053-17058
54. Newmeyer, F. J. (1997). Genetic dysphasia and linguistic theory. *J. Neurolinguistics*, 10: 47-73.
55. Nobre, A. C. and Plunkett, K. (1997). The neural system of language: structure and development. *Curr. Opin. Neurobiol.*, 7: 262-266.
56. Nopola-Hemmi, J., Myllyluoma, B., Haltia, T., Taipale, M., Ollikainen, V., Ahonen, T., Voutilainen, A., Kere, J. and Widen, E. (2001). A dominant gene for developmental dyslexia on chromosome 3. *J. Med. Genet.*, 38: 658-664.
57. Oyama, S. (2000). *The Ontogeny of Information. Developmental Systems and Evolution*. Durham: Duke University Press.
58. Oyama, S., Griffiths, P. E. and Gray, R. D. (eds.) (2001). *Cycles of Contingency. Developmental Systems and Evolution*. Cambridge: MIT Press.
59. Paracchini, S., Thomas, A., Castro, S., Lai, C., Paramasivam, M., Wang, Y., Keating, B. J., Taylor, J. M., Hacking, D. F., Scerri, T., Francks, C., Richardson, A. J., Wade-Martins, R., Stein, J. F., Knight, J. C., Copp, A. J., Loturco, J. and Monaco, A. P. (2006). The chromosome 6p22 haplotype associated with dyslexia reduces the expression of *KIAA0319*, a novel gene involved in neural migration. *Hum. Mol. Genet.*, 15: 1659-1666.
60. Paulesu, E., Demonet, J.-F., Fazio, F., McCrory, E., Chanoine, V., Brunswick, N., Cappa, S. F., Cossu, G., Habib, M., Frith, C. D. and Frith, U. (2001). Dyslexia: cultural diversity and biological unity. *Science*, 291: 2165-2167.
61. Poelmans, G., Engelen, J. J., Van Lent-Albrechts, J., Smeets, H. J., Schoenmakers, E., Franke, B., Buitelaar, J. K., Wuisman-Frerker, M., Erens, W., Steyaert, J. and Schrander-Stumpel C. (2009). Identification of novel dyslexia candidate genes through the analysis of a chromosomal deletion. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 150B: 140-147.
62. Potkin, S. G., Turner, J. A., Guffanti, G., Lakatos, A., Torri, F., Keator, D. B. and Macciardi, F. (2009). Genome-wide strategies for discovering genetic influences on cognition and cognitive disorders: methodological considerations. *Cogn. Neuropsychiatry* 14(4-5):391-418.
63. Ramsay, M. (2000). Communication genes clustered on 7q31. *Mol. Med. Today*, 6: 380-381.
64. Ramus, F. (2006). Genes, brain, and cognition: a roadmap for the cognitive scientist. *Cognition*, 101: 247-269.
65. Risch, N. and Merikangas, K. R. (1996). The future of genetic studies of complex human diseases. *Science*, 273: 1516-1517.
66. Shao, Y., Cuccaro, M. L., Hauser, E. R., Raiford, K. L., Menold, M. M., Wolpert, C. M., Ravan, S. A., Elston, L., Decena, K., Donnelly, S. L., Abramson, R. K., Wright, H. H., DeLong, G. R., Gilbert, J. R. and Pericak-Vance, M. A. (2003). Fine mapping of autistic disorder to chromosome 15q11-q13 by use of phenotypic subtypes. *Am. J. Hum. Genet.*, 72: 539-548.
67. Shaywitz, B. A., Fletcher, J. and Shaywitz, S. E. (1995). Defining and classifying learning disabilities and attention-deficit/hyperactivity disorder. *J. Child Neurol.* 10: S50-S57
68. Shaywitz, S. E. and Shaywitz, B. A. (2005). Dyslexia (Specific Reading Disability). *Biol. Psychiatry*, 57: 1301-1309
69. Shaywitz, S. E., Shaywitz, B. A., Pugh, K. R., Fulbright, R. K., Constable, R. T., Mencl, W. E., Shankweiler, D. P., Liberman, A. M., Skudlarski, P., Fletcher, J. M., Katz, L., Marchione, K. E., Lacadie, C., Gatenby, C. and Gore, J. C. (1998). Functional disruption in the organization of the brain for reading in dyslexia. *Proc. Nat. Acad. Sci. U.S.A.*, 95: 2636-2641.
70. Schroer, R. J., Phelan, M. C., Michaelis, R. C., Crawford, E. C., Skinner, S. A., Cuccaro, M., Simensen, R. J., Bishop, J., Skinner, C., Fender, D. and Stevenson, R. E. (1998). Autism and maternally derived aberrations of chromosome 15q. *Am. J. Med. Genet.*, 76: 327-336.
71. Shriberg, L. D., Ballard, K. J., Tomblin, J. B., Duffy, J. R., Odell, K. H. and Williams, C. A. (2006). Speech, prosody, and voice characteristics of a mother and daughter with a 7,13 translocation affecting *FOXP2*. *J. Speech Lang. Hear. Res.*, 49: 500-525.
72. Shu, W., Cho, J. Y., Jiang, Y., Zhang, M., Weisz, D., Elder, G. A., Schmeidler, J., De Gasperi, R., Sosa, M. A., Rabidou, D., Santucci, A. C., Perl, D., Morrissey, E. and Buxbaum, J. D. (2005). Altered ultrasonic vocalization in mice with a disruption in the *Foxp2* gene. *Proc. Natl. Acad. Sci. U.S.A.*, 102: 9643-9648
73. SLI Consortium (2002). A genomewide scan identifies two novel *loci* involved in specific language impairment. *Am. J. Hum. Genet.*, 70: 384-398.
74. SLI Consortium (2004). Highly significant linkage to the *SLI1 locus* in an expanded sample of individuals affected by specific language impairment. *Am. J. Hum. Genet.*, 74: 1225-1238.
75. Smith, S. D. (2007). Genes, language development, and language disorders. *Ment. Retard. Dev. Disabil. Res. Rev.*, 13: 96-105
76. Sorger, B., Goebel, R., Schiltz, C. and Rossion, B. (2007). Understanding the functional neuroanatomy of acquired prosopagnosia. *Neuroimage*, 35: 836-852.
77. Stein, C. M., Millard, C., Kluge, A., Miscimarra, L. E., Cartier, K. C., Freebairn, L. A., Hansen, A. J., Shriberg, L. D., Taylor, H. G., Lewis, B. A. and Iyengar, S. K. (2006). Speech sound disorder influenced by a *locus* in 15q14 region. *Behav. Genet.*, 36: 858-868.
78. Stromswold, K. (2001). The heritability of language: A review and metaanalysis of twin, adoption and linkage studies. *Language*, 77: 647-723.
79. Swanson, H. L., Howard, C. B. and Saez, L. (2006). Do different components of working memory underlie different subgroups of reading disabilities? *J. Learn. Disabil.*, 39: 252-269.
80. Taipale, M., Kaminen, N., Nopola-Hemmi, J., Haltia, T., Myllyluoma, B., Lyytinen, H., Muller, K., Kaaranen, M., Lindsberg, P. J., Hannula-Jouppi, K. and Kere, J. (2003). A candidate gene for developmental dyslexia encodes a nuclear tetratricopeptide repeat domain protein dynamically regulated in brain. *Proc. Natl. Acad. Sci. U.S.A.*, 100: 11553-11558.

81. Threlkeld, S. W., McClure, M. M., Bai, J., Wang, Y., LoTurco, J. J., Rosen, G. D. and Fitch, R. H. (2007). Developmental disruptions and behavioral impairments in rats following in utero RNAi of *Dyx1c1*. *Brain Res. Bull.*, 71: 508-514
82. Ullman, M. T. (2001). The declarative/procedural model of lexicon and grammar. *J. Psycholinguist Res.*, 30: 37-69
83. Vargha-Khadem, F., Watkins, K. E., Alcock, K. J., Fletcher, P. and Passingham, R. E. (1995). Praxic and nonverbal cognitive deficits in a large family with a genetically transmitted speech and language disorder. *Proc. Natl. Acad. Sci. U.S.A.*, 92: 930-933.
84. Vargha-Khadem, F., Gadian, D. G., Copp, A. and Mishkin, M. (2005). *FOXP2* and the neuroanatomy of speech and language. *Nat. Rev. Neurosci.*, 6: 131-138.
85. Velayos-Baeza, A., Toma, C., Paracchini, S. and Monaco, A. P. (2008). The dyslexia-associated gene KIAA0319 encodes highly N- and O-glycosylated plasma membrane and secreted isoforms. *Hum. Mol. Genet.*, 17: 859-871.
86. Vercelli, D. (2009). Language in an epigenetic framework. In *Of Minds and Language* (M. Piatelli-Palmarini, P. Salaburu, and J. Uriagereka, eds.). Oxford: Oxford University Press.
87. Vernes, S. C., Newbury, D. F., Abrahams, B. S., Winchester, L., Nicod, J., Groszer, M., Alarcón, M., Oliver, P. L., Davies, K. E., Geschwind, D. H., Monaco, A. P. and Fisher, S. E. (2008). A functional genetic link between distinct developmental language disorders. *N. Engl. J. Med.*, 359: 2337-45.
88. Volpi, E. V. and Bridger, J. M. (2008). FISH glossary: an overview of the fluorescence in situ hybridization technique. *Biotechniques*, 45: 385-386, 388, 390 *passim*.
89. Wahlsten, D. (1999). Single-gene influences on brain and behavior. *Annu. Rev. Psychol.*, 50: 599-624.
90. Watkins, K. E., Dronkers, N. F. and Vargha-Khadem, F. (2002). Behavioural analysis of an inherited speech and language disorder: comparison with acquired aphasia. *Brain*, 125: 452-64.
91. White, S. A. (2009). Genes and vocal learning. *Brain Lang.* doi:10.1016/j.bandl.200910.002
92. Williams, J. and O'Donovan, M. C. (2006). The genetics of developmental dyslexia. *Eur. J. Hum. Genet.*, 4: 681-689.
93. Winterer, G. and Goldman, D. (2003). Genetics of human prefrontal function. *Brain Res. Rev.*, 43: 134-163.
94. Yin, H. H., Davis, M. I., Ronesi, J. A. and Lovinger, D. M. (2006). The role of protein synthesis in striatal long-term depression. *J. Neurosci.*, 26: 11811-11820
95. Yu, G., Zerucha, T., Ekker, M. and Rubenstein, J. L. R. (2001). Evidence that GRIP, a PDZ-domain protein which is expressed in the embryonic forebrain, coactivates transcription with DLX homeodomain proteins. *Brain Res. Dev. Brain Res.*, 130: 217-230
96. Zondervan, K. T. and Cardon, L. R. (2007). Designing candidate gene and genome-wide case-control association studies. *Nature Protocols*, 2: 2492-2501.