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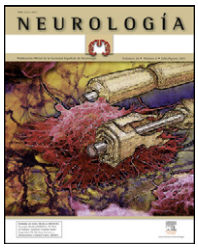

REVIEW ARTICLE

Problematic aspects of the genetic analysis of the specific disorders of the language: *FOXP2* as paradigm☆

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Aetiology;
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Abstract
Introduction: Genetic analysis of specific language disorders is of major interest for both clinical research and linguistic theory. However, the results of this analysis almost always do not show any univocal and compulsory relationships between particular gene mutations and particular disorders or a causal link between the genotype and the phenotype.
Objectives: This paper will review this type of evidence (referring to the ''language gene'' *FOXP2* as a leading example, where possible), try to suggest plausible reasons for such a perplexing output, and ultimately discuss if such reasons really explain the genuine aetiology of these conditions.
Results: The key to disentangle and understand the puzzling scenario emerging from the genetic analysis of specific language disorders is to pay attention to the actual role played by genes during ontogeny and, in particular, to the way in which developmental processes are actually regulated: genes are not direct causal agents regarding the emergence of impaired or wild phenotypes, but just one among the diverse types of regulatory factors involved.
Conclusions: When such a complex role as well as development models less focused on the genes are considered, the way in which genetic mutations really contribute to the emergence of these cognitive disorders is quite satisfactorily explained.

PALABRAS CLAVE
Correlaciones genotipo-fenotipo;
Etiología;
FOXP2;

Aspectos problemáticos del análisis genético de los trastornos específicos del lenguaje: FOXP2 como paradigma

Resumen
Introducción: El análisis genético de los trastornos específicos del lenguaje resulta del máximo interés, tanto para la práctica clínica como para la teoría lingüística. No obstante, un

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Genes;
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resultado casi universal de dicho análisis es que no parece existir una relación unívoca y obligada entre la mutación de determinados genes y la aparición de patologías concretas al término del desarrollo, ni por consiguiente, una relación causal directa entre el genotipo y el fenotipo.
Objetivos: El presente trabajo se plantea evaluar esta clase de evidencias (utilizando como modelo, allí donde resulte ilustrativo, el gen *FOXP2*, considerado habitualmente como el «gen del lenguaje» por excelencia), proponer posibles causas que expliquen su recurrencia y discutir si tales explicaciones contribuyen realmente a esclarecer la genuina etiología de estos trastornos.
Resultados: La clave para entender el intrincado (y a primera vista desconcertante) escenario resultante del análisis genético de los trastornos específicos del lenguaje radica en atender al verdadero papel que desempeñan los genes durante la ontogenia y, especialmente, al modo en que se regulan los procesos de desarrollo: lejos de erigirse en los agentes causales directos responsables en exclusividad de la aparición de los fenotipos, los genes constituyen uno más de los múltiples factores implicados.
Conclusiones: La asunción de la complejidad de dicho papel, así como la conveniencia de considerar modelos alternativos del desarrollo, menos centrados en los genes (por paradójico que pueda parecer), permite explicar satisfactoriamente el modo en que las alteraciones génicas contribuyen a la aparición de este tipo de trastornos de la cognición.

Introduction

The possibility of identifying the structural and functional nature of language-related genes—genes whose products presumably play an important role in regulating the development and function of the neural centres involved in processing linguistic stimuli—is a matter of utmost interest for two key reasons. On the one hand, it may serve to corroborate certain hypotheses put forth by linguistic experts who state that grammatical competence acquired by the individual at the end of the developmental stage (that is, acquired knowledge of his or her first language) cannot be regarded as the mere result of an inductive learning process based on exposure to information constituting linguistic input.[1,2] In fact, those who support such innateness hypotheses, including Chomsky himself,[1] have postulated that there may be a linguistic genotype consisting of all information necessary for language acquisition and not acquired by experience. This essentially refers to the building blocks of Universal Grammar.[3] According to this model, language is acquired because linguistic input in the presence of that genotype promotes the appearance of the phenotype representing competence.[3] On the other hand, the fact that many language disorders are hereditary[4–6] seems to suggest that in order to reveal a disorder's true aetiology, we must first identify and characterise the mutations that have presumably affected one of the genes making up the genotype in question. With that in mind, a common working hypothesis in this field is that the anomalous and hereditary linguistic action pattern present in some subjects must be the result of mutations in specific genes. It goes on to state that these genes affect a specific area of competence and leave other cognitive capacities unaltered (although some may be involved in the action). This scenario is ultimately possible because the mutation of the genes in question creates structural and/or functional changes in the brain centres involved in language processing.

In recent years, researchers have identified and drawn up clinical profiles for a variety of syndromes, ailments, disorders and illnesses that are hereditary and only seem to affect language. These include specific language impairment (SLI: OMIM 602081); dyslexia (OMIM 127700), and speech sound disorder (SSD: OMIM 608445). They may also include a number of other disorders with much lower prevalence rates, such as Landau—Kleffner syndrome (OMIM 245570), rolandic epilepsy/sylvian seizures with verbal dyspraxia (OMIM 601085), and 22q13.3 deletion syndrome (OMIM 606232). Likewise, a number of genes have been identified as possible candidates or risk factors for the appearance of such disorders. Additionally, certain loci (physical sites on a chromosome) are linked to or associated with these disorders.[4–6] Although it may seem paradoxical at first, the truth is that performing genetic analyses for language disorders has not contributed significantly to identifying their true aetiology. At the same time, this fact seems to suggest that genotype—phenotype relationships are not as direct as one might imagine.

In this study, we discuss some of the evidence supporting the above statement, providing data derived from the analysis of *FOXP2* as our principal examples. The *FOXP2* gene is normally considered to be one of the causal factors for specific language impairment, and also the predominant ''language gene''.[7–12] In light of this evidence, we will discuss whether or not re-examining the genotype—phenotype relationship is necessary in order to understand the true role of genes in the appearance of neurodevelopmental disorders. In the end, this will require us to relinquish overly gene-centric concepts of cerebral ontogeny.