Neurología. 2014;29(9):560—566

NEUROLOGÍA

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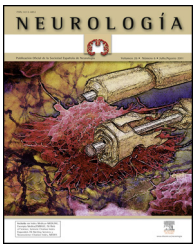

REVIEW ARTICLE

Exploring the genetic basis of stroke. Spanish stroke genetics consortium☆

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Received 28 December 2012; accepted 21 April 2013
Available online 22 October 2014

KEYWORDS
Stroke;
Genetics;
Association;
Genetic risk factors;
Prediction;
Consortium

Abstract This article provides an overview of stroke genetics studies ranging from the candidate gene approach to more recent studies by the genome wide association. It highlights the complexity of stroke owing to its different aetiopathogenic mechanisms, the difficulties in studying its genetic component, and the solutions provided to date. The study emphasises the importance of cooperation between the different centres, whether this takes place occasionally or through the creation of lasting consortiums. This strategy is currently essential to the completion of high-quality scientific studies that allow researchers to gain a better knowledge of the genetic component of stroke as it relates to aetiology, treatment, and prevention.

PALABRAS CLAVE
Ictus;
Genética;
Asociación;
Factores de riesgo genético;
Predicción;
Consorcio

Aproximación al conocimiento de las bases genéticas del ictus. Consorcio español de genética del ictus

Resumen El presente artículo revisa la evolución de los estudios en genética del ictus desde la aproximación por gen candidato hasta los recientes estudios de *genome wide association*. Se destaca la complejidad de esta afección por sus muy variados mecanismos etiopatogénicos, las dificultades que comporta el estudio de su componente genético y las soluciones que se han aportado. Se subraya en especial el valor de las colaboraciones entre distintos centros, ya sea

☆ Please cite this article as: Giralt-Steinhauer E, Jiménez-Conde J, Soriano Tárraga C, Mola M, Rodríguez-Campello A, Cuadrado-Godia E, et al. Aproximación al conocimiento de las bases genéticas del ictus. Consorcio español de genética del ictus. Neurología. 2014;29:560—566.

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2173-5808/$ - see front matter

de manera puntual o sobre todo a través de la creación de consorcios estables. Esta estrategia actualmente se hace imprescindible a la hora de realizar estudios de alta calidad científica que permitan seguir avanzando en el conocimiento de las bases genéticas del ictus tanto en etiología, como en tratamiento y prevención.

Introduction

In Spain, stroke is currently the second most frequent cause of death in the general population, as well as the leading cause of death in women (http://www.ine.es/prensa/np703.pdf). It is also the leading cause of disability in adults and the second most common cause of dementia.[1]

However, despite important advances in stroke prevention, diagnosis, and treatment in the past 2 decades, the World Health Organisation estimates that the incidence of this entity will increase by 27% by the year 2025.[2] Researchers have described numerous risk factors associated with stroke, although in order to understand its causes it seems necessary to consider both external factors and the predisposition of each individual.[3] The disease has been shown to have a hereditary component, and genetic load plays a very important role in its development.[4] Technological advances in recent years have promoted genome-wide association studies (GWAS), which let researchers perform non-biased genetic analyses and discover new genes and metabolic pathways associated with stroke.

The purpose of this study is to review the current status and future perspectives of genetics in the field of cerebrovascular disease.

Evidence

Genetic factors in stroke

Unlike monogenic disorders, complex diseases are characterised by their considerable aetiological and pathological diversity. Family history is recognised as one of the most important risk factors for many complex disorders; this is also the case for cardiovascular disease, cancer, or autoimmune disorders.[5] In conclusion, even though these disorders are not monogenic or oligogenic, inherited genetic variations are apparent. Scientists believe that co-presence of different low-risk allelic variants whose combined risk is additive or multiplicative, and interaction of those variants with the environment, may play a crucial role in the development of complex disorders.[5,6]

Heritability rates between 30% and 50% have been described for ischaemic stroke.[4] Because of its multiple causes, the numerous risk factors involved, and its array of different forms of presentation, stroke may be considered the final manifestation of any of a number of complex diseases. Apart from the simplest stroke classification scheme that distinguishes between ischaemic and haemorrhagic events, we can also identify several distinct aetiopathogenic subtypes. Several recently published studies have shown differences between the genetic heritability of lacunar, cardioembolic, and atherosclerotic strokes; the latter are the most strongly associated with family history.[4,7,8]

This also occurs in intracerebral haemorrhages (ICH), which account for 15% of all strokes. Pathogenic pathways involved in lobar haemorrhage, which is closely linked to cerebral amyloid angiopathy (CAA), may differ substantially from those involved in hypertensive haemorrhages.[9,10]

Therefore, genetic studies having to do with stroke should be designed so as to examine these particularities and accommodate the difficulties inherent to investigating heterogeneous diseases.

Genetic association studies in complex disorders: techniques and approaches

Research on most genetic causes of stroke, excluding those that follow classic Mendelian inheritance patterns, are generally based on case-control genetic association studies. These studies analyse the different frequencies of genetic variants in patients and healthy controls. Studying common variants or single nucleotide polymorphisms (SNPs) largely involves candidate-gene and genome-wide association, whereas the recently developed technique of complete exome sequencing lets scientists examine uncommon variants. Other techniques, such as analysis of copy-number variation or epigenome studies, will also be discussed below.

Candidate-gene studies

For several decades, and until recently, the most common technique was the candidate-gene study. This approach consists of selecting genes that may be associated with a disease based on the pathophysiology of that disease and the pathways believed to be involved. Scientists identify previously described SNPs located near the candidate genes and select the most representative ones (tag SNPs) which will typically display linkage disequilibrium.[11] These candidate tag SNPs are genotyped within a population and statistical analysis is used to determine if there are associations between genetic variants and the clinical spectrum.

These studies present several problems. On the one hand, the fact that these genes are selected based on a priori hypotheses may mean that some researchers look for spurious differences based on preconceived notions. Meanwhile, they may fail to analyse genes that are potentially involved in the disease.