Entrega de l'Abstract

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Títol de la recerca: **Genetic screening of the 1q21-23 region confirms the association between UHMK1 gene and schizophrenia spectrum psychoses in a family-based association study.**
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Abstract (màxim 500 paraules):

INTRODUCTION

Schizophrenia (SZ) is a chronic, severe and disabling brain disorder estimated to affect 1% of the population worldwide. Family, twin and adoption studies indicate that SZ has an important genetic component, although the mode of inheritance is complex. This complexity is not only obvious from its non-mendelian inheritance but it is also because the illness is clinically heterogeneous and has no single-pathognomonic phenotype or biological characteristic.

Linkage studies have implicated a number of genomic regions potentially involved in disease susceptibility, including 1q21-23 (e.g. Brzustowicz et al. 2000, 2002 and 2004). Several association studies have also reported associations with candidate genes positioned in this region (Puri et al. 2007, Kremeyer et al. 2008, Prasad et al. 2009).

In a previous original association study by our team (Rosa et al. 2002) we analyzed 6 microsatellites in the 1q21-q22 region in a sample of 80 families with psychosis. Our findings pointed out a positive allelic association with marker D1S1679 which lies between two candidate genes for schizophrenia UHMK1 and CAPON.

The aim of our study was to thoroughly explore for disease-associated SNPs along the candidate region described in our previous work (chromosome 1 region 1q21-23) with a larger sample of families.

METHODOLOGY

Participants:
The sample comprised 615 individuals of Caucasian origin from 183 nuclear Spanish families affected by schizophrenia spectrum disorders (DSM-IV criteria) (parents-proband trios and parents-

proband healthy sib quadruplets).

Method:

We genotyped 25 Single Nucleotide Polymorphisms (SNPs) in the 1q21-23 region in chromosome 1. The markers span together approximately 940 kb and harbour four candidate genes for schizophrenia: CAPON, EAT, UHMK1 and RGS4. The genetic markers were genotyped using the Sequenom iPLEX MassARRAY® technology following standard protocols.

The Transmission Disequilibrium Test (TDT) for single markers was carried out as implemented in the SNPator program (Morcillo-Suárez et al. 2008) and was used to study preferential transmission of alleles from parents to the affected offspring.

RESULTS

In a first approach, the broad definition of cases including all the categorical DSM-IV schizophrenia spectrum disorders was used. When we examined the transmission of the alleles from the parents to the affected offspring, we found a significant association for rs6694863 (p=0.0280), within the UHMK1 gene. No preferential transmission was found for the other markers analyzed.

In view of the psychopathological heterogeneity of schizophrenia we also used a narrow categorical definition of the phenotype of cases (DSM-IV schizophrenia or schizoaffective disorder). The TDT analysis still showed the previously reported association.

DISCUSSION

Our results suggest a positive association between schizophrenia and the SNP rs6694863 in the gene UHMK1. The UHMK1 gene encodes a serine/threonine protein kinase that is highly expressed in regions of the brain implicated in psychoses such as the amygdala (Bieche et al. 2003). Different previous association studies have also reported an association between UHMK1 gene and schizophrenia (Puri et al. 2007, 2008).

We are currently working in the haplotypic analysis of the markers. Haplotype-based methods offer a powerful approach to disease gene mapping, complementary and more efficient, than separate analyses of individual markers (Gabriel et al. 2002).

Additionally, further analysis will be done to explore possible associations with more specific intermediate phenotypes or endophenotypes of the disease. Its use in complex disorders such as psychosis has been suggested as a powerful tool with recent interesting results (Gottesman and Gould, 2003).

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AUTHORSHIP

The author has contributed to the design and selection of the markers included in this study. She has conducted all the analyses of the data and is involved in the writing of the paper.