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VARIATIONS IN GENES REGULATING NEURONAL MIGRATION PREDICT REDUCED PREFRONTAL COGNITION IN SCHIZOPHRENIA AND BIPOLAR SUBJECTS FROM MEDITERRANEAN SPAIN: A PRELIMINARY STUDY

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Abstract—Both neural development and prefrontal cortex function are known to be abnormal in schizophrenia and bipolar disorder. In order to test the hypothesis that these features may be related with genes that regulate neuronal migration, we analyzed two genomic regions: the lissencephaly critical region (chromosome 17p) encompassing the LIS1 gene and which is involved in human lissencephaly; and the genes related to the platelet-activating-factor, functionally related to LIS1, in 52 schizophrenic patients, 36 bipolar I patients and 65 normal control subjects. In addition, all patients and the 25 control subjects completed a neuropsychological battery. Thirteen (14.8%) patients showed genetic variations in either two markers related with lissencephaly or in the platelet-activating-factor receptor gene. These patients performed significantly worse in the Wisconsin Card Sorting Test–Perseverative Errors in comparison with patients with no lissencephaly critical region/platelet-activating-factor receptor variations. The presence of lissencephaly critical region/platelet-activating-factor receptor variations was parametrically related to perseverative errors, and this accounted for 17% of the variance (P=0.0001). Finally, logistic regression showed that poor Wisconsin Card Sorting Test–Perseverative Errors performance was the only predictor of belonging to the positive lissencephaly critical region/platelet-activating-factor receptor group. These preliminary findings suggest that the variations in genes involved in neuronal migration predict the severity of the prefrontal cognitive deficits in both disorders.

Key words: neuronal migration, prefrontal cognition, LIS1, platelet activating factor receptor, endophenotype, lissencephaly.

Over several decades, numerous family, twin and adoption studies have indicated that genetic factors play a major role in predisposing individuals for schizophrenia and bipolar disorder (Berrettini, 2002; Riley et al., 2003). Several of the susceptibility loci and genes associated with schizophrenia play a principal role in neuronal migration, connectivity and in the maintenance of the neural microcircuits (Harrison and Weinberger, 2005). Nowadays, schizophrenia could therefore be considered a genetic neurodevelopmental disorder (Rapoport et al., 2005). Although literature on neurodevelopmental alterations in bipolar disorders is less extensive, recent findings suggest anomalies in neuronal migration and connectivity (Harwood, 2003). In general, genes that regulate the migration of neurons could therefore be possible candidate-risk genes to be investigated in both disorders (Merikangas et al., 2002; Harrison and Weinberger, 2005).

Interestingly, the similarities between schizophrenia and bipolar disorder in genetic and developmental findings, neuropsychological abnormalities (Daban et al., 2006) and in other epidemiological features (Torrey, 1999), are part of a heuristic pattern of coincidences which implies that at least some cases of both disorders have common etiological antecedents, and supports a continuum (Crow, 1998) vs. a categorical (Kendler et al., 1998) view of psychotic illness.

Various studies on postmortem human brains provide evidence of a significant alteration of cell migration in the both prefrontal cortex and dentate gyrus from subjects with schizophrenia and bipolar disorder (Fatemi et al., 2000; Guidotti et al., 2000; Knable et al., 2001, 2004). Moreover, alterations in the neural migration in the cortex have been observed in lissencephaly, a severe brain malformation with tragic consequences (epilepsy, mental retardation and premature death; the association of lissencephaly with craniofacial malformations is known as Miller-Dieker syndrome) (Hong et al., 2000). In addition, the occurrence of schizophrenia-like symptoms and secondary-affective symptoms has been demonstrated in patients with epi-

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Abbreviations: ANCOVA, covariance analysis; CARS-M, Clinician-Administered Rating Scale for Mania Factor 1; HRSD, Hamilton Rating Scale for Depression; IQ, intelligence quotient; LCR, lissencephaly critical region; PANSS, Positive and Negative Syndrome ScalePCR, polymerase chain reaction; WAIS-R, Wechsler Adult Intelligence Scale–Revised; WCST, Wisconsin Card Sorting Test; WCST-PE, Wisconsin Card Sorting Test-Perseverative Errors.

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lepsy (Hyde and Lewis, 2003). Even more interestingly, the family history of epilepsy is a significant risk factor for schizophrenia (Qin et al., 2005); thus, the same genetic factor might induce schizophrenia as well as epilepsy. Furthermore, the current pharmacological treatment of many patients with schizophrenia or bipolar disorder includes the combinations of anticonvulsants and antipsychotics (Citrome et al., 2005). Therefore, a certain etiopathogenic overlap may exist among lissencephaly, schizophrenia and bipolar disorder.

Within the genomic region that is frequently deleted in lissencephaly (lissencephaly critical region, LCR in chromosome 17p13.3), the most well-known gene is *LIS1*, which interacts with dynein to mediate the coupling of the nucleus to the centrosome in neuronal migration. Furthermore, it binds both dynein and NUDEL (NDEL1) among many other interacting proteins (Shu et al., 2004). A most interesting point from the present study is that NUDEL1 has been shown to interact with the product of the *DISC1* gene (*Disrupted In Schizophrenia 1*; Morris et al., 2003; Ozeki et al., 2003). Interestingly, disruption of *DISC1* by a balanced chromosomal translocation (1;11)(q42;q14.3) was identified as a potential susceptibility factor for schizophrenia due to its co-segregation with this disease (St Clair et al., 1990; Millar et al., 2000; Blackwood et al., 2001). Moreover, other studies also described different *DISC1* variations related to schizoaffective and bipolar disorders (Hennah et al., 2003; Hodgkinson et al., 2004). The possibility of a direct role of *DISC1* in schizophrenia is further suggested by two recent studies. Callicott et al. (2005) showed that allelic variation within *DISC1* compromised hippocampal structure and function and, by virtue of this effect, would increase risk for schizophrenia. Finally, Sachs et al. (2005) detected a specific mutation in the *DISC1* in several members of a family. This mutation is predicted to cause a frame shift and truncated DISC1 protein.

There is considerable evidence that DISC1-NUDEL-LIS1 interaction plays an important role in neuronal migration, neurite architecture, and in intracellular transport (Ozeki et al., 2003; Brandon et al., 2004). Thus, functional alterations of this trimolecular complex could confer a variable degree of susceptibility for schizophrenia and other related disorders.

The *p53* gene (*TP53*) is also mapped into the LCR, and genetic variations of this gene have been related with a predisposition to develop schizophrenia and with its associated neurocognitive deficits (Chiu et al., 2001; Papiol et al., 2004; Ni et al., 2005).

Another set of interactions involved LIS1 and PAF (a phospholipid mediator, which acts by binding to a unique G-protein-coupled seven transmembrane receptor, PTAFR). LIS1 was identified as a subunit in the PAF–AH1B enzymatic complex. The PAF system (PAF, PAFAH and PTAFR) is functionally related to the *LIS1* gene within the molecular mechanisms involved in neuronal migration (Bix and Clark, 1998; Pahnke et al., 2004; Tokuoka et al., 2003; Yan et al., 2003).

On the other hand, converging lines of research suggest that an abnormal structure and function of the prefrontal cortex may be a cardinal feature of schizophrenia and bipolar disorder (Weinberger et al., 2001; Harrison, 2002). In this respect, cognitive and imaging endophenotype studies suggest that specific variations in genes could affect normal brain morphogenesis, prefrontal function, and subsequently, they could increase the risk of cognitive abnormalities, schizophrenia and bipolar disorder (Egan et al., 2001; Shifman et al., 2004; Harrison and Weinberger, 2005).

Consequently, we hypothesized (1) that patients with schizophrenia and bipolar disorder could show variations in some genes involved in neuronal migration, and (2) that these genetic variations could be functionally associated with a reduced prefrontal executive function. In order to test these hypotheses, we included the analyses of seven markers located in the critical region for lissencephaly (LCR), and those of the 13 markers of the PAF system-related genes (*PAFAH1B2*, *PAFH1B3* and *PTAFR*) in patients diagnosed with schizophrenia and bipolar type I disorder, compared with a group of normal control subjects. We also investigated eight cognitive domains.

EXPERIMENTAL PROCEDURES

Subjects

A written informed consent was obtained from all participants following an explanation of study procedures. The ethics committee of the University Clinic Hospital of Valencia (Spain) approved the research protocol. All subjects were aged between 18 and 60 years and were unrelated individuals of European ancestral birth, who were educated in Spain. Patients were recruited if they fulfilled the *Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition* (DSM-IV; American Psychiatric Association, 1994) criteria for either schizophrenia (n=52) or bipolar disorder type I (n=36), and if they had attended three different consecutive mental health units in the metropolitan area of Valencia over a 9-month period. Diagnoses were established with the Spanish version of the Schedules for Clinical Assessment in Neuropsychiatry (SCAN-CATEGO; Vázquez-Barquero, 1993) after a minimum of one year's progress of the illness. The exclusion criteria used were: electro-convulsive therapy during the previous year, substance use disorders in the previous six months, and epilepsy, medical illness or a known organic cause that may account for either psychosis or cognitive abnormalities. All control subjects (n=65) were interviewed with the Spanish adaptation (Leal et al., 1988) of the Family History-Research Diagnostic Criteria (FH-RDC; Endicott et al., 1978) interview, and with the psychotic screening questionnaire of Bebbington and Nayani (1995) to confirm the absence of any family and personal history of psychiatric disorders, respectively.

Neuropsychological and clinical assessment

This assessment was performed according to Tabarés-Seisdedos et al. (2003) and Balanzá-Martínez et al. (2005). Briefly, all patients and the 25 control subjects completed a battery of 11 tests measuring eight cognitive domains with the following sequence: executive functions-abstraction (Wisconsin Card Sorting Test, WCST with four separate scores: Categories, Perseverative Errors, Non-Perseverative Errors and Total Errors), semantic and phonologic verbal fluency (Category Instant Generation Test, CIG; FAS Test from the Controlled Oral Word Association Test), working memory (the backward part of Digit Span Test from the Wechsler Adult Intelligence Scale–Revised or WAIS-R), verbal memory (VM) (the Babcock Story Recall Test), visual memory (the Rey-Osterrieth Complex Figure Test), visual-motor processing/attention (the Trail Making Test, parts A and B; the Stroop Color and