



NEW & VIEWS

News about disturbances of neuronal migration bring views to bipolar disorder

Recently, Fox *et al* from the Harvard Institute of Medicine, identified the bilateral periventricular nodular heterotopia (BPNH) gene correspondent to filamin 1 (FLN1), which encodes an actin-crosslinking phosphoprotein that transduces ligand-receptor binding into actin reorganization, and which is required for locomotion of many cell types. High-level expression of FLN1 in the developing cortex is required for neuronal migration to the cortex, and is essential for embryogenesis.¹

Currently there exist data on the molecular mechanisms involving Filamin 1. Ohta *et al* have studied the action of the small GTPase RA1A inducing filopodia using filamin in this pathway.²

BPNH is a neuronal migration disorder (NMD) in which nodular masses of gray matter line the walls of the lateral ventricles. Individuals with periventricular heterotopia are at high risk for epilepsy, usually presenting with sporadic or familial epilepsy with normal intelligence, primarily in females. Usually hemizygous males die as embryos, although one group has evaluated two boys with BPNH and severe mental retardation.^{3–5}

In the X-linked dominant BPNH, many neurons fail to migrate and persist as nodules lining the ventricular surface. The gene for BPNH has been mapped to chromosome Xq28 based on linkage studies in multiplex families and observation of a subtle structural abnormality in one of the boys with BPNH and severe mental retardation.^{6,7}

Other malformations of neuronal migration, such as lissencephaly (agyria-pachygyria spectrum), are causes of mental retardation and epilepsy which are often genetic. X-linked lissencephaly and subcortical band heterotopia (XLIS) present with sporadic or familial mental retardation and epilepsy. The XLIS gene is located on chromosome Xq22.3 based on the breakpoint of an X-autosomal translocation.⁶

Interestingly, in a study of an extended Finnish pedigree of bipolar disorder (BD) patients, Pekkarinen *et al*

examined 25 markers spanning the Xq24–q28 region near the BPNH gene region, demonstrating linkage between BD and a distinct chromosomal haplotype on Xq24–q27.1. The largest lod score was ($\theta = 0.0$) at the DXS994 locus. Positive, though more modest, lod values were observed at nearby loci. Analysis with markers outside the Xq24–27.1 region resulted in negative lod scores. When haplotypes were constructed for Xq24–q27.1 markers, all family members with the narrowly defined phenotype were found to carry the same haplotype, reducing the possibility of false linkage due to undetected recombinants. The largest lod scores were obtained under a stringent phenotype definition (bipolar I, II and not otherwise specified, and schizoaffective-manic⁸).

Later, the review of previously published data on Xq26–27 markers in bipolar pedigrees using uniform diagnostic criteria and inheritance models found suggestive evidence for linkage in combined analysis: the maximum polylocus lod scores for markers DXS51, F9a and F9b were 2.78, 1.51 and 1.77, respectively. They conclude that the combined data support that linkage diminishes in regions distal to F9.⁹

Bipolar disorder (BD) is a psychiatric disturbance which has serious implications for patients' lives and is an important risk of suicide attempts and chaotic patterns of mood variation. The genetics of BD are complex, but there is strong evidence that genetic factors are involved in the pathogenesis of these disorders provided by studies of twins, and adopted subjects.¹⁰ Linkage analysis suggests molecular evidence of association with chromosomes X, 18, 21, 4, 6, 13 and 15 in different pedigrees.^{10–14}

This relative proximity of the genetic region involved in these two diseases may suggest an overlapping of many haplotypes, eventually indicating a common genetic mechanism as the major primary cause of disturbances of neuronal migration and/or alterations in the electric stability in areas of neural tissue.

Epilepsy and BD have different clinical manifestations, but some similar drugs are used in their treatment, and both diseases, if not well treated, worsen over time, evolving to more frequent and severe crises. The pharmacological treatment of BD includes the current use of lithium carbonate and, more recently, the

association with the anticonvulsants carbamazepine and valproic acid. The anticonvulsant medications were first used only to control and prevent different forms of epilepsy.

Previous studies show evidence of considerable overlap between some forms of epilepsy and BD. These suggestions come from the studies of comorbidity between temporal lobe epilepsies, BD and schizoaffective features. Some studies suggest the mood changes associated with temporal lobe disorders as existing on a spectrum with rapid-cycling affective illness.¹⁵

Studies of the personality traits of patients with temporal lobe epilepsy show decreases in sexual interest and increases in social aggressiveness. The patients are also found to be intensely emotional, ardently religious, extremely moralistic, and lacking in humor. In contrast, patients with epileptic foci outside the temporal lobe do not generally show abnormalities in emotion and behaviour.¹⁶

BD patients with rapid-cycling develop more than four episodes of pathological mood switches per year and are a group of patients with the best therapeutic responses to the association of lithium with carbamazepine and/or valproic acid.¹⁵

The clinical and genetic region 'proximities' between these two groups of diseases may suggest that some form of NMD can be involved in the pathogenesis of BD. This kind of approach, by relating two different disorders based on some organic and clinical similarities, is frequently used to begin studies of disturbances which have partial common biological pathways. The best example is the finding of the first mutations of familial forms of Alzheimer's disease in the 21 chromosome based on the presence of senile plaques (amyloid deposits) in patients with Down's syndrome.¹⁷

One way to study this hypothesis is to compare the gene and regulatory regions of the filamin-1 in case-control studies of BD. The use of neuroimaging techniques and histopathological studies are other possible approaches.

Magnetic resonance imaging (MRI) has enabled the identification of NMD in living subjects which represents an important achievement in the diagnosis of patients with these anomalies. The severity of the patients' clinical symptoms was clearly related to MRI findings.⁵

The first analysis of affectively disordered patients using magnetic resonance imaging (MRI) has recently shown that the ratio of temporal lobe to hemisphere area was significantly smaller when compared with controls, but no differences were found in BD patients.¹⁵ The use of techniques with better resolution can enhance the possibility of positive findings. Pathological studies should look for similar alterations compatible with NMD in the temporal lobe or other regions better studied in the BD, such as the limbic system.

The search for similar pathological alterations in BD and NMD based on these overlapping characteristics can give some answer as to the organic basis of BD manifestation. This is essential because it can partially

explain the mechanisms involved in the mood swings found in BD. It is possible that the alterations in BD are mild when compared to those of epileptic subjects since the installation of the depressive or manic states is not usually as acute as the epileptic symptoms.

A separate analysis by subgroups of BD patients seems to be important to an accurate study with this kind of approach since BD has clinical variants which include BD type I and II. Within these two groups there exist episodes of major depression, but in type II, a hypomanic state occurs which presents as a mild form of manic episode. Each one of these subgroups may have different biological particularities above a same partial pathological base. This hypothesis could possibly explain some of these patients, since X linkage to BD accounts for only a minority of cases. This is an important clinical aspect which reinforces the start of these studies with rapid cycling patients as they also have a good response to carbamazepine as a maintenance therapy and more episodes when compared with other BD subgroups. They present a profile of higher clinical resemblance to the epileptic subjects, since their illness episodes are more frequent.

Several other differences between BD and epilepsy may be explained by a polygenic model controlling the clinical variations of manifestation in this affective illness.

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