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GUEST EDITORIAL

Schizophrenia genetics: expansion of knowledge?

Finding the genes for psychiatric illness by linkage approaches has turned out to be difficult. Therefore investigators have also turned to a variety of candidate gene approaches based on genetic or pathophysiologic hypotheses. Observations that anticipation may be present in some pedigrees with schizophrenia as well as affective disorder have suggested that expanding triplet repeats may play a role in some pedigrees with these disorders.[1,2]

Direct identification of pathogenic triplet repeat expansions in genomic DNA is complicated by the fact that many individuals have expansions of non-pathogenic repeats. An alternative is to screen proteins for the consequences of an expanded triplet in the coding region of a gene. Expansion of CAG coding for polyglutamine causes a class of neurodegenerative disorders, including Huntington's disease and the spinocerebellar ataxias, whose members are themselves rapidly expanding.[3–5] The fortuitous discovery of an antibody (termed 1C2) which preferentially detects expanded polyglutamine stretches[6,7] makes the screening for polyglutamine expansions feasible.

Two groups[8,9] now report that Western blots of protein extracts of cells from a small number of patients with schizophrenia have a band detected by this antibody. These data suggest the possibility that expansion of a polyglutamine tract in a protein whose identity is yet unknown may cause a subset of cases of schizophrenia and possibly bipolar disorder.

The group led by Christian Neri at CEPH studied childhood onset schizophrenics collected by Judith Rapoport and colleagues at the National Institute of Mental Health. Two out of 32 unrelated childhood onset schizophrenia patients had a band in the 52–55 kDa range which reacted strongly with the 1C2 antibody. Since both of these were African–American in ethnic origin, African–American controls were tested (a total of 38), and none of them had the strongly reacting band. The authors then used two-dimensional protein gel electrophoresis to identify this band as an acidic protein, with a pI of approximately 4. They tested a number of known CAG repeats for expansions and did not find any, indicating that this protein is likely to be novel.

The group of Guy Rouleau found two patients out of 57 adult onset schizophrenic patients with a band of approximately 50 kDa reactive with the 1C2 antibody. A total of 73 normal controls were used as a comparison group and no reactive bands were detected. A small number of affected and unaffected family members were tested in the two studies, with one affected individual in each study having a positive band (though in one case the affected individual had affective disorder not schizophrenia).

These data raise the possibility that polyglutamine expansions may contribute to a small percentage of cases of schizophrenia and possibly affective disorder. The size of the reactive bands was similar enough in the two studies that they could well represent the same protein. This could easily be tested by performing two-dimensional electrophoresis on the samples in the Canadian study.

The antibody does not permit the determination of the size of the expanded repeat in this putative novel protein. It is quite possible that it is a relatively short expanded polyglutamine tract, and thus would not have been detected by DNA-based methods for screening for expanded repeats.[10]

While these data are provocative they clearly need to be replicated with much larger samples. One difficulty with allele association studies is that the frequency of alleles can vary greatly among populations from different ethnic groups. The 1C2 antibody detects a number of bands in normal individuals, one of which is the TATA-binding protein, which commonly has 38 glutamines.[6] There may be other proteins which in some individuals have glutamine repeats long enough to be recognized by the 1C2 antibody, but not long enough to cause disease. It will be important to screen other samples of patients with schizophrenia and controls before accepting that this alteration is truly related to schizophrenia. It would be useful to test for expansions in larger family studies in which affected and unaffected individuals from the same pedigrees could be compared in more detail.

If the results can be confirmed they would have a number of implications for schizophrenia. First, this expansion is present in a very small proportion of individuals with schizophrenia. This is consistent with the idea of genetic heterogeneity in this disorder. Second, the reactive band was seen in an individual with affective disorder. This is consistent with recent findings suggesting that schizophrenia and affective disorder may share some components of genetic vulnerability.[11] Third, these results would be consistent with the hypothesis that anticipation is present in schizophrenia and affective disorder. However, the expanded band was not found in all families in which there was anticipation (and in fact childhood onset schizophrenia is usually sporadic). Thus, there could still be

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other triplet repeat loci contributing to the etiology of schizophrenia and affective disorder.

One possible consequence of these results is that a small subset of patients with schizophrenia may have a neurodegenerative process. All of the glutamine repeat expansion disorders known so far, with Huntington's disease being the prototype, are neurodegenerative disorders. It has been proposed that a small subset of patients with schizophrenia, including some childhood onset cases,[12,13] has progressive brain atrophy consistent with neurodegeneration. Such patients might be a first priority for testing with the 1C2 antibody. However, it is conceivable that polyglutamine expansions may not always lead to a neurodegenerative phenotype. The pathogenesis of the polyglutamine diseases studied so far all appear to involve formation of intranuclear neuronal inclusions and aggregation of the polyglutamine-containing proteins in other locations in the cell. Recent mouse models of Huntington's disease have suggested that these intranuclear inclusions can be present without massive neuronal cell death.[14] Thus, it is conceivable that polyglutamine expansions in some cases may cause neuronal dysfunction without neuronal cell death.

The first priority to extend the current findings will be the identification of the gene which codes for this protein. The results of the two-dimensional gel analysis suggest that the protein is abundant enough to be seen by silver stain techniques. It has a distinctive molecular weight and acidic pH, which should make it possible to purify the protein using biochemical methods. Once peptide sequence is available, the gene which codes for it can be identified and studied. Patients with schizophrenia can then be screened directly using PCR. The identification of a gene which causes even a small subset of cases of schizophrenia and affective disorder would be of tremendous importance and would make possible the use of all the modern techniques of cell biology and biochemistry to study the pathogenesis of these disorders. In addition, it would permit a direct genetic test for the mutation.

However, it is necessary that enough individuals be tested to make sure that this genetic lesion really relates to the phenotype of schizophrenia. The importance of studies of many individuals with schizophrenia and many more controls cannot be overstressed. It is critical to show that psychiatric disorder is really associated with this expansion of polyglutamine. If this can be done, the potential for psychiatric genetics is for an expansion of knowledge.

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References

1 Ross CA, McInnis MG, Marigolds RL, Li S-H. Genes with triplet repeats: candidate mediators of neuropsychiatric disorders. *Trends Neurosci* 1993; **16**: 254–260.
2 McInnis MG. Anticipation: an old idea in new genes. *Am J Hum Genet* 1996; **59**: 973–979.
3 Ross CA. When more is less: pathogenesis of glutamine repeat neurodegenerative diseases. *Neuron* 1995; **15**; 493–496.
4 Warren ST, Nelson DL. Trinucleotide repeat expansions in neurological disease. *Curr Opin Neurobiol* 1993; **3**: 752–759.
5 Zoghbi HY. The expanding world of ataxins. *Nature Genet* 1996; **14**: 237–238.
6 Trottier Y, Lutz Y, Stevanin G, Imbert G, Devys D, Cancel G *et al*. Polyglutamine expansion as a pathological epitope in Huntington's disease and four dominant cerebellar ataxias. *Nature* 1995; **378**: 403–406.
7 Stevanin G, Trottier Y, Cancel G, Dürr A, David G, Didierjean O *et al*. Screening for proteins with polyglutamine expansions in autosomal dominant cerebellar ataxias. *Hum Mol Genet* 1996; **5**: 1887–1892.
8 Morinière S, Saada C, Holbert S, Sidransky E, Galat A, Ginns EI *et al*. Detection of polyglutamine expansion in a new acidic protein: a candidate for childhood onset schizophrenia? *Mol Psychiatry* 1999; **4**: 58–63.
9 Joober R, Benkelfat C, Jannatipour M, Turecki G, Lal S, Mandel J-L *et al*. Polyglutamine containing proteins in schizophrenia. *Mol Psychiatry* 1999; **4**: 53–57.
10 Margolis RL, Ross CA. Detection of unstable trinucleotide repeat loci: genome and cDNA screening. In: Wells RD, Warren ST (eds). *Genetic Instabilities and Hereditary Neurological Diseases*. Academic Press: San Diego, CA, 1998, pp 431–438.
11 Blouin J-L, Dombroski B, Nath SK, Lasseter VK, Wolyniec PS, Nestadt G *et al*. Schizophrenia susceptibility loci on chromosome 13q32 and 8p21. *Nature Genet* 1998; **20**: 70–73.
12 DeLisi LE. Is there progressive morphological brain and cognitive change in schizophrenia? In: Fog R, Gerlach J, Hemmingsen R (eds). *Schizophrenia*, Alfred Banzon Symposium 38. Munksgaard: Copenhagen, 1995, pp 162–176.
13 Rapoport JL, Giedd J, Kumra S, Jacobsen L, Smith A, Lee P *et al*. Childhood-onset schizophrenia: progressive ventricular change during adolescence. *Arch Gen Psychiatry* 1997; **54**: 897–903.
14 Davies SW, Turmaine M, Cozens BA, DiFiglia M, Sharp AH, Ross CA *et al*. Formation of neuronal intranuclear inclusions underlies the neurological dysfunction in mice transgenic for the HD mutation. *Cell* 1997; **90**: 537–548.