LETTERS TO THE EDITOR

Expanded CAG trinucleotide repeat of Huntington's disease gene in a patient with schizophrenia and normal striatal histology

Symptoms of schizophrenia including auditory hallucinations, paranoid delusions, and thought disorder occur in 5 to 10% of patients with Huntington's disease (HD).[1] Both disorders have pharmacological features of hyperdopaminergic activity and a reduction in the normal link between D1 and D2 receptor action.[2] In view of these similarities and because allelic variation can produce unexpected phenotypic diversity in neuropsychiatric disorders, we decided to examine a group of schizophrenics for mutations in the recently cloned gene for Huntington's disease,[3] starting with the unstable CAG trinucleotide repeat that is expanded in Huntington's disease. Although the original report suggested that normal subjects have 11 to 34 copies of the repeat and those with HD 42 to 100 copies,[3 4] more recent studies using an improved PCR assay that measures the precise size of the CAG repeat[5] show that the copy number in normal persons extends from 8 to 33, while the lower end of the HD range starts at 35.[6] Indeed no one, to date, outside an HD family has been identified with a copy number of 35 or more repeats. Using this latter PCR assay we have examined a group of unrelated schizophrenics and compared repeat size with those of Huntington's and control groups, previously reported.[6]

Materials and methods

Blood or brain DNA from 221 random schizophrenics who met Research Diagnostic Criteria[7] were examined for the CAG repeat expansion using the PCR assay as described[4] with the modification that one primer was fluorescent end labelled and repeat size was measured using ALF technology (Pharmacia).

The distribution of the repeat sizes in the three groups is shown in the figure. There is no overlap between the controls and the Huntington's group. The size distribution among the schizophrenics also closely resembles the controls. One case, however, has a repeat copy number unequivocally within the Huntington's range (36 repeats). Not only was this confirmed on a second independently collected DNA sample, but amplifications and sizing were repeated several times with DNA from an HD family with 36 repeats as a size marker. No variation in size was observed.

The patient had a clinical diagnosis of chronic schizophrenia. She died aged 88 in a mental hospital. DNA from necropsy brain tissue, courtesy of Cambridge Brain Bank, was examined. The patient had a normal childhood, schooling, and early adult life. There was no family history of insanity. She became severely psychiatrically disturbed aged 37 and remained in a mental hospital until her death. Symptoms included multiple paranoid delusions, auditory hallucinations, emotional blunting, and social withdrawal. These persisted into old age. For a year in her early 50s she had occasional strange shaking attacks which she claimed were due to vibrations being "put" upon her. These did not persist, however, and no other neurological symptoms were observed at any period in her life. She remained neat, tidy, and mobile until shortly before death. Brain weight at necropsy was 1121 g. There was moderate patchy atherosclerosis of large and middle size cerebral arteries and slight narrowing of the gyri on both cerebral hemispheres. Coronal sections showed moderate enlargement of the lateral ventricles with stretching of the septum. The basal ganglia including caudate, putamen, and globus pallidus were normal on both macroscopic and microscopic examination by a consultant neuropathologist. Final diagnosis was restricted to chronic schizophrenia with moderate cerebrovascular atherosclerosis. Huntington's disease was never suspected.

There are several explanations of our findings. It is possible that in spite of the apparent clear cut separation using the improved PCR assay of the CAG repeat, a small overlap exists in repeat copy number between normal persons and Huntington's disease patients, and we have identified a subject at the extreme end of the normal range, who by chance also happens to have chronic schizophrenia. Until larger numbers of normal controls are examined, this explanation cannot be discounted. Alternatively, the case described may have had mild Huntington's disease masked by schizophrenia with cognitive deficits or minor movement disorders passing unnoticed. The natural history of the illness, 50 years of psychiatric symptoms without supervening dementia or chorea, argues against this, as does normal striatal histology at necropsy. A final and more intriguing explanation is that, for poorly understood reasons, the effects of disturbed huntingtin gene function in the above case are less pronounced than expected, and are restricted to schizophrenic symptoms without the characteristic clinicopathological hallmarks of Huntington's disease. At present the data are insufficient to decide among these various explanations.
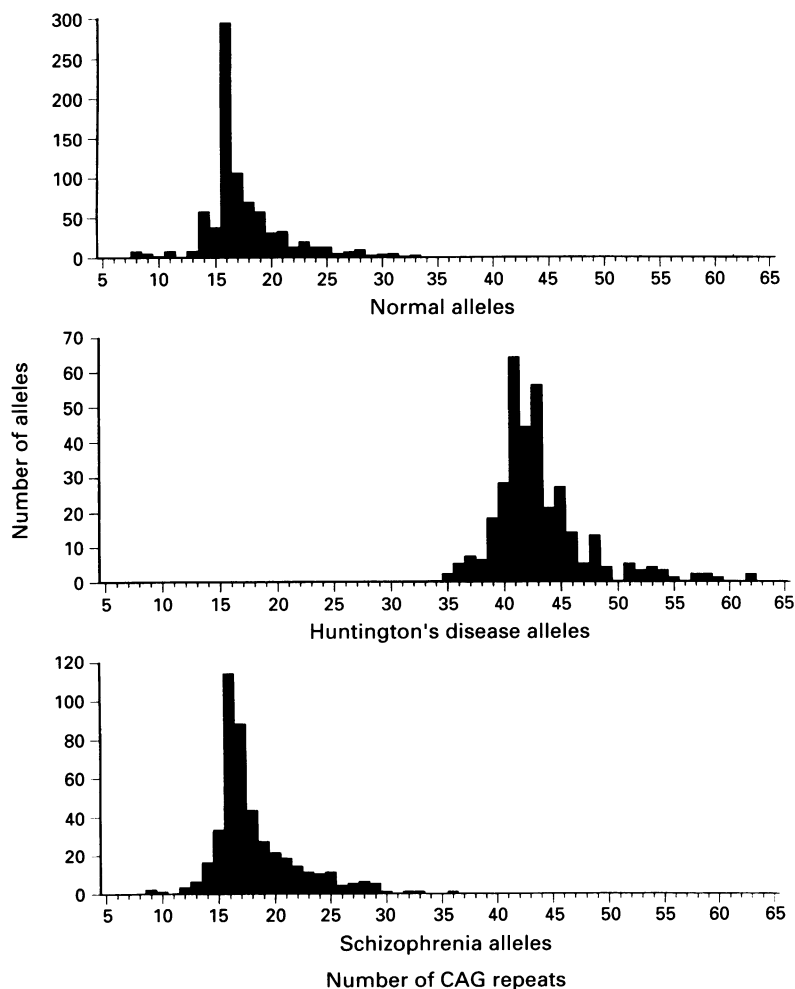
CAG trinucleotide repeat allele sizes and distribution frequency in 221 schizophrenics, 397 normal controls, and 337 cases from 145 Huntington's disease families.

approval for screening random schizophrenics for mutations was granted by Lothian Area Health Authority before the initiation of this study.

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Further family with autosomal dominant patent ductus arteriosus

Occasionally, families have been reported with apparent autosomal dominant inheritance of a patent ductus arteriosus (PDA), although the condition usually appears to be sporadic.[1-6] We report a further family with eight affected members in two generations.

The pedigree is shown in the figure. The grandfather (I·1) died suddenly after a tooth extraction at the age of 40; his wife died of old age. II·1 was diagnosed and operated upon for a PDA at the age of 35 years. Despite having a sister with a PDA and two children requiring PDA ligations, it was not until she brought her third affected child into hospital that she herself was examined. Mild right

Family pedigree.

ventricular hypertrophy was found and a small PDA was closed. She also had coeliac disease. II·2 has been in good health all his life. Because of the family history of patent ductus arteriosus he sought a cardiology opinion at the age of 54 years. A PDA was found with moderate biventricular dilatation and he was operated on successfully. II·4 had been a sickly child throughout her life but became progressively less well in her teenage years. At the age of 18 years bacterial endocarditis and a PDA were diagnosed. Both were eventually successfully treated. In later life she developed myasthenia gravis, scleroderma, and Reynaud's phenomenon. III·2 was referred to a cardiologist at the age of 7 years with an asymptomatic murmur. After two years of follow up, ventriculomegaly began to develop and the PDA was ligated. III·4 was diagnosed as having a PDA at the age of 5 years, had always been mildly exercise restricted, had ventriculomegaly, and was operated on at 6 years. III·5 was found to have an asymptomatic murmur at the age of 6 years and her PDA was tied at 6½ years. She also had coeliac disease. III·6 had frequent upper respiratory tract infections as a young child and was exercise restricted. At the age of 4 years he was referred to a cardiologist who found a typical PDA murmur. He was operated on at the age of 4½ years. His karyotype is normal. III·17 was referred to a cardiologist at the age of 3 years for an asymptomatic murmur. A PDA was diagnosed and ligated forthwith.

Family members are of normal appearance and intelligence and have no symptoms suggestive of a prostaglandin metabolic defect, such as atopy or difficulties during labour. Although all occurrences of PDA have been inherited from an affected mother in this family, paternal-offspring transmission has been described previously.[1,3,4,6] The PDAs found in this family were not unusual in their position and varied greatly in the symptomatology they caused.

The empirical recurrence risk for a PDA is 3% whether it is a parent or a sib that is affected.[7] Most cases are thought to be the result of polygenic/multifactorial inheritance. In families such as this, where so many members are affected, autosomal dominant inheritance seems likely and the recurrence risk is probably 50%. In order to give realistic recurrence risks to a family where a child has a PDA, the facial phenotype described by Davidson[6] should be sought, and both parent's cardiovascular systems should be examined. Referral to a cardiologist of any children born to a family with possible auto-

somal dominant PDA seems sensible whether or not they have a detectable murmur.

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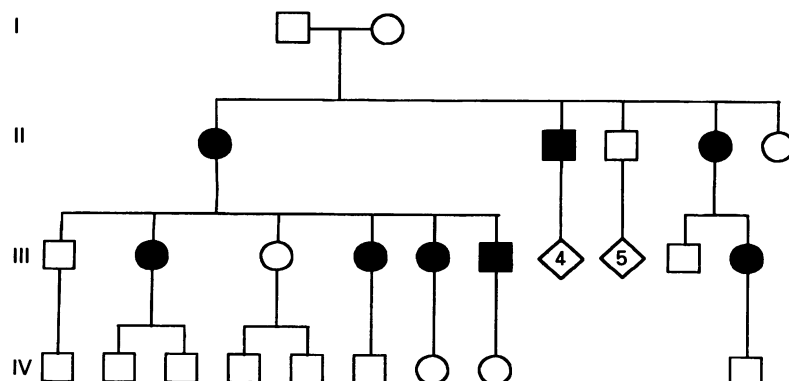Flemington Road, Parkville, Victoria 3052,
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Molecular basis of the common electrophoretic polymorphism (Fu1/Fu2) in human α-L-fucosidase

α-L-fucosidase (EC.3.2.1.51) is a lysosomal hydrolase involved in the catabolism of fucose-containing glycolipids and glycoproteins. A deficiency of this enzyme leads to the lysosomal storage disease, fucosidosis.[1,2] α-L-fucosidase exists as multiple molecular forms, which can be separated by various procedures.[3,4] The precise molecular basis of this heterogeneity is not understood but it is probably post-translational. All the forms are encoded by a single locus on the short arm of chromosome 1 at 1p34.1-1p36.1 which encodes the structural gene for the enzyme, FUCA1[5,6] The enzyme shows a genetically determined, common, electrophoretic polymorphism (Fu1/Fu2), which can be detected in blood and tissues[7] and maps to the structural gene locus (FUCA1).[8] The minor allele, Fu2, produces more cathodal forms of the enzyme.

The structural gene for α-L-fucosidase has been isolated and sequenced.[9,10] It is 23 kb in length and has eight exons. Two common RFLPs obtained with PvuII and BglI are in almost complete linkage disequilibrium and can be used to haplotype subjects.[11] Several disease-causing mutations have been identified in patients with fucosidosis.[2,12-14] In addition, an A to G transition in exon 5 causing substitution of an arginine for glutamine, Q281R, has been found homozygously in both patients and controls, indicating it is a polymorphism rather than a disease-causing mutation.[14] All homozygotes for this substitution showed the RFLP PvuII-BglI haplotype, 2-2, 2-2. It was postulated that Q281R might be the molecular basis of the Fu1/Fu2 electrophoretic polymorphism.[14] Evidence to support that suggestion is presented in this paper.

The Q281R polymorphism creates a new site for the restriction enzymes DsaI and BsaJI in exon 5. It can be readily detected by amplifying exon 5 with the two primers used for mutation analysis (F42 and F43 in reference 14), followed by digestion with DsaI or BsaJI (fig 1). Analysis of the BsaJI digestion products by electrophoresis in 3% agarose (BRL)/