



Genetic testing for Huntington's disease in South Africa

Huntington's disease (HD) is a late-onset inherited progressive neurodegenerative disorder characterised by motor impairment, chorea, dementia and psychiatric disturbances associated with selective neuronal death in the striatum and cortex. Onset of the disease is usually in midlife, with most cases being diagnosed between 35 and 50 years of age, with a range from 2 to 90 years. Death usually occurs 15 - 20 years after clinical onset of the disorder. There is marked clinical variability between patients, with about two-thirds of affected individuals initially presenting with neurological manifestations and a third with psychiatric changes. In the early stages following diagnosis, manifestations include subtle changes in eye movements, deteriorating co-ordination, minor involuntary movements, difficulty in mental planning, and often a depressed or irritable mood. In the next stage, chorea becomes more prominent, voluntary activity becomes increasingly difficult, and dysarthria and dysphagia increase. Impairment is usually considerable, sometimes with intermittent outbursts of aggressive behaviour and social disinhibition. In the late stages of HD, motor disability becomes severe and the individual is often totally dependent, mute, and incontinent.¹

HD is inherited as an autosomal dominant disease. Therefore, an affected individual is likely to have inherited the disease from an affected parent, and every child of an affected parent is at 50% risk of developing the disease. The affected individual's siblings would also be at 50% risk of inheriting the gene and developing the disease.

HD has a worldwide distribution. In European populations, it affects approximately 4 - 8/100 000 individuals. A high frequency has been reported in South African white Afrikaners owing to a founder effect.^{2,3} In South Africans of mixed ancestry (coloureds), frequencies comparable to other world populations have been reported, but with an increased proportion of juvenile cases.⁴

The disease has been thought to be less common in black African populations, with a frequency of 0.1/million.^{5,6} However, under-ascertainment of cases seems to explain at least part of the previously reported low frequency, and a number of cases have now been documented from countries in Africa, including South Africa,^{7,8} and by Magazi *et al.*⁹ in this issue of *SAMJ*.

The HD phenotype is usually caused by a polyglutamine-coding CAG repeat expansion in the HD gene on chromosome 4. A CAG repeat expanded to over 40 copies is predictive of disease.¹⁰ Mutations in this gene are considered to be the cause of HD in the great majority of families worldwide. A number of families have now been reported with a Huntington disease-like phenotype but with no mutations in the HD

gene. This led to the discovery of a Huntington disease-like 2 (HDL2) disorder. The disease-causing mutation of HDL2 is a CAG/CTG repeat expansion in the junctophilin-3 (JPH3) on chromosome 16.¹¹ The disease was reported to be clinically and pathologically virtually indistinguishable from HD, although parkinsonian features may predominate in some families, and the disease spectrum may be wider. Magnetic resonance imaging (MRI) findings may also be atypical of HD.¹²⁻¹⁴ Outside South Africa, HDL2 has been identified in as few as 1% of individuals with clinically or pathologically defined HD who do not have an HD-causing mutation. All individuals with HDL2 have black African ancestry.¹³

To date, the diagnosis of HD has been confirmed in over 200 white and coloured, and 50 black, South African families in the molecular genetics diagnostic laboratories at Wits National Health Laboratory Service (NHLS) and UCT NHLS. Over 1 000 DNA samples from HD family members are stored in these laboratories.

The South African HD genetic situation is unique in that individuals with an HD-like phenotype of black African ethnicity are almost as likely to have HDL2 as HD.¹⁵ More than half of the cases of HDL2 described worldwide are from South Africa. The relatively high proportion of HDL2 cases in black patients is further supported by the article by Magazi *et al.*⁹ where half of the 12 reported cases are positive for HD and half for HDL2. In addition, the HDL2 mutation is also found in individuals of mixed ancestry, 3 families tested at Wits NHLS and 1 family tested at UCT NHLS being positive for HDL2. It is possible that a founder effect for HDL2 exists in South Africa, particularly in the northern part of the country, as suggested by Magazi *et al.* and supported by unpublished studies of Krause *et al.*

It is therefore important that diagnostic testing in South Africa for both HD and HDL2 is carried out in patients with suggestive black African ancestry. Both academic laboratories in South Africa offering HD testing, namely the Divisions of Human Genetics at UCT NHLS and Wits NHLS, now test for both the HD and HDL2 genetic mutations. Furthermore, as suggested by the family of Bardien *et al.*¹⁴ and the letter by Greenberg *et al.*¹⁶ in this issue, HDL2 should be considered in a wider spectrum of patients with neuropsychiatric and movement disorder presentations, so that the full spectrum of the disease can be defined.

As HD is an inherited late-onset neurodegenerative disease, a predictive testing (PT) programme was set up in Johannesburg in 1989¹⁷ and in the Western Cape in 1996,¹⁸ with similar HD PT programmes now offered in Durban and at Tygerberg Hospital. The SA HD PT services are established in line with international testing protocols and include



pretest consultations with a team consisting of a neurologist, genetic counsellor, genetic nursing sister, psychiatrist and psychologist, and at least one post-test consultation at which results are given personally by a member of the PT team. The aim of these programmes is to ensure that the individuals are adequately prepared to make an informed decision about the test options and the potential results. The aim is to reduce the possibility of adverse emotional events occurring after testing. No predictive testing should in fact be undertaken without the presymptomatic individual having gone through a structured PT programme. Predictive testing requires the exact genetic fault to be defined in a family; it is therefore critical in the South African context that HD and HDL2 families are distinguished so that accurate predictive testing can be offered.

In conclusion, as illustrated by Magazi *et al.* and Greenberg *et al.* in this issue, HD in South Africa is a genetically and clinically heterogeneous disease, in contrast to its homogeneity elsewhere in the world. For this reason, both diagnostic and predictive testing need to include testing for mutations in both the HD and HDL2 genes, supported by appropriate genetic counselling and clinical referral. It is therefore vital that cases continue to be identified so that the unique nature of this disease in South Africa can be fully defined at both the clinical and molecular genetic level.

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