Genetic testing for spinal muscular atrophy (SMA) in South Africa

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To the Editor: Spinal muscular atrophy (SMA) is an autosomal-recessive neuromuscular disorder that results in progressive muscle weakness and atrophy due to the degeneration of the anterior horn cells of the spinal cord. SMA occurs at a rate of 1/5 000 - 1/10 000 live births in most European countries, a figure that translates into an approximate carrier frequency of 1/40 individuals, making it the most common autosomal-recessive disorder after cystic fibrosis, the second most common neuromuscular disease after Duchenne muscular dystrophy, and a significant cause of infantile hypotonia. SMA has traditionally been classified into three clinical subgroups based on age of onset and clinical severity.

The gene for SMA, the survival motor neuron (SMN) gene, is found on chromosome 5q13, in a region harbouring a 500 kb duplication, resulting in two copies (a telomeric and a centromeric copy) of each of the genes found within the duplication (Fig. 1).

SMN is homozgyously deleted in 90 - 95% of patients worldwide. The clinical presentation and molecular basis of SMA in the South African white population appears to be similar to that in most European populations, but it appears that SMA in the SA black population differs both in clinical presentation and underlying molecular basis.

Frequent involvement of the facial muscles in black children with SMA was first reported by Moosa and Dawood. In addition, Stevens et al. showed that the deletion frequency of the SMNt gene was significantly lower in SA black patients (65%) than in SA white patients (90 - 95%). The deletions present also appeared to be smaller in the black patients. These findings were significantly different from the results of other studies performed worldwide.

On the basis of these findings, a study to determine the molecular basis of SMA in SA black patients was undertaken by the Department of Human Genetics, National Health Laboratory Services (NHLS) and University of the Witwatersrand together with the Department of Paediatrics at Chris Hani Baragwanath Hospital. Results showed that only 51% (47/92) of SA black SMA patients have homozygous deletions of the SMNt gene, confirming the results of the previous study. In addition, a newly developed dosage assay enabling the detection of SMNt gene deletion carriers confirmed that in at least 70% of black ‘non-deletion’ SMA patients, one copy of the SMNt gene was missing, strongly supporting the diagnosis of SMA. It is believed that this deletion together with a second disease-causing mutation, as yet unidentified, causes SMA in these patients. Further studies are required in order to define the molecular basis of SMA in the SA black population. The elucidation of this molecular basis may in turn explain the different clinical presentation of SMA in the SA black population.

A diagnostic service can now be offered to all SA SMA patients and their families and can be performed on approximately 10 ml of EDTA blood. A muscle biopsy is therefore no longer required to confirm the clinical diagnosis in the majority of cases. Prenatal and preclinical diagnosis can also be offered to the families. If the proband has died it is also possible to perform testing on paraffin-embedded tissue. In addition, development of the SMNt dosage assay has increased the percentage of cases in which diagnosis of SMA can be confirmed. It also makes carrier detection possible for ‘at-risk’ individuals.

Fig. 1. Proposed arrangement of genes in the SMA region on chromosome 5 (adapted from Burghes’).