

A putative founder effect for Parkinson's disease in South African Afrikaners



Neurodegenerative diseases are important causes of disability and death, with prominent examples including Alzheimer's disease, Parkinson's disease (PD) and motor neuron disease. Although familial clustering of these illnesses was well known before the advent of modern molecular genetics, meaningful strides in identifying the origin of neurodegenerative diseases have really only begun to be made in the past two decades. All these disorders are characterised by a small percentage of affected patients whose disease is clearly the result of Mendelian inherited genetic illness, either recessive or dominant. In particular, dominant disease is exemplified in the case of Alzheimer's disease by presenilin 2 mutations that arose in German immigrants from the Volga river region in the 17th century,^[1] and in PD by mutations in the LRRK2 protein that are linked to a founder effect dating back to the 2nd century, probably in Ashkenazi Jews.^[2]

Such autosomal dominant families enable a crucial aspect of neurodegenerative disease to be addressed, namely the identification of biomarkers that can serve to identify the earliest features of the onset of disease. These biomarkers range from proteins in cerebrospinal fluid, such as amyloid and tau, to magnetic resonance imaging scans of the brain volumes of cortex and temporal lobe

structures, and positron emission tomography scans of markers of neurodegeneration, such as amyloid.^[3,4]

It is clear, certainly in the case of Alzheimer's disease, that by the time even mild memory impairment has developed there is widespread pathological change that is highly likely to be irreversible.^[5] Similarly, although tremor may be the best-appreciated manifestation of dopaminergic cell loss in PD, it is clearly preceded by a slowly progressive process that gradually ascends up the brainstem and may produce features of brainstem dysfunction as long as 25 years before the onset of classic PD.^[6,7] In general, it would probably be most useful to identify individuals who are genetically at risk for developing neurodegenerative illness, and monitor particular biomarkers, in the event that successful therapies become available.

After the initial euphoria when the first genes associated with Alzheimer's disease and PD were identified, a major issue has been the extrapolation of these findings to the much more common situation of sporadic disease in individuals who lack a clear-cut family history. So far, although genome-wide association studies (GWASs) have shown much promise, they have failed to deliver many significant advances with regard to the genetic cause of neurodegenerative disease. In particular, the power of such studies has been limited, and not uncommonly GWASs have only served

to confirm genetic targets already identified by other methods.^[8] It could be argued that a sporadic case is more likely to have an environmental cause, but the evidence for the environment playing an important role in the causation of neurodegenerative disease is not particularly strong.

A major advantage of genetic studies is not only that they identify the cause of illness, but also that they shed light on the various molecular pathways implicated in the causation of neurodegenerative disease.^[9] This clearly has significant implications for the development of treatments that would potentially be of benefit for patients harbouring preclinical or manifest mutations, as well as for patients with sporadic disease.

To reiterate, the identification of mutations has profound implications for understanding the cause of disease, and it is likely that it will only be through the understanding of the mechanisms of cell injury and death in neurodegenerative disease that advances will be made in therapeutics.

One major issue regarding the utility of genetics when applied to neurodegenerative disease is that age is a major risk factor, and many patients may not develop illness simply because they die before the disease manifests. Confirmation of a family history of an illness being inherited in a particular pattern may therefore be difficult. Over and above mutation analysis, genealogical studies can be very useful in populations where there are common founder effects and church records. Such is the case for the original Dutch population that settled in the Cape from the mid-1600s, and with the admixture largely of German and French immigrants, ultimately developed into the South African (SA) Afrikaner population. As is well known, this population has well-established founder effects for a wide range of conditions, of which the best-known examples are familial hypercholesterolaemia and variegate porphyria. Furthermore, the Afrikaner population has genealogies that range from the 1600s through the early 1800s and later, and are well documented and recorded.^[10]

Interestingly, with respect to neurodegenerative disease, there is some evidence for a founder effect for Huntington's disease in SA, possibly arising from an early Dutch settler, since there is a common haplotype indicative of a European origin.^[11,12] In the study by Geldenhuys *et al.*^[13] published in this issue of the *SAMJ*, genealogies of 12 Afrikaner families were investigated in detail using the records of the Genealogical Institute of South Africa in Stellenbosch and other sources. The genealogical research concentrated on those with a family history suggestive of either dominant or recessive inheritance of PD. The 12 families were shown to be linked to a single ancestral couple, and this finding was further supported by confirmation of ancestral lines to the putative founder couple in an additional 28 families, also of Afrikaner origin and with a history of PD. The affected family members had a mean age of onset of PD of only 52 years, which is considerably less than that in typical idiopathic disease and suggests a genetic origin for the illness.^[14] The

founder couple was of Dutch and German ancestry and married in the Cape in 1668.

This finding is of importance for two reasons. Firstly, given that established genetic causes of PD have not been identified in the Afrikaner population, it appears likely that this population carries unique mutations that remain to be identified by genome-wide screening.^[15,16] Secondly, in the event that effective treatments are developed, particularly for presymptomatic patients, the Afrikaner population may be considered to be at risk and requiring careful assessment with accurate biomarkers.

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S Afr Med J 2014;104(6):411-412. DOI:10.7196/SAMJ.8390