Progress Report

Storey Elsdon - A New Genetic Form of Parkinson's Disease

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Title of Project: Delineation of a new form of Parkinson's disease due to mutation in the FMR1 gene.

Summary:

Mutations in the Fragile-X gene with an abnormally long genetic code triplet sequence (more than 200 repeats) are the commonest cause of mental retardation in boys. This mutation impairs synthesis of the protein coded for by this gene. In recent years it has become apparent that this mutation becomes more severe across three generations, such that if an affected boy inherited the mutation from his maternal grandfather, the grandfather would have a smaller mutation (55 to 200 repeats). This smaller mutation size (termed a "premutation") allows normal amounts of the corresponding protein to be synthesized, but the messenger RNA, which carries the genetic code from the DNA to the protein synthesis mechanism,is increased and is itself toxic. This can produce a completely different disorder - Fragile X Tremor/Ataxia syndrome, or FXTAS. Even smaller mutations (41 to 54 repeats) - termed "grey zone (GZ) mutations" do not expand sufficiently across three generations to cause neurological problems in grandchildren, and so can only be identified by testing the general population. We and others have recently found that GZ mutations are about twice to three times as common in both men and women already diagnosed with Parkinson's disease as in the general population (about 2.5% versus 1%), suggesting that such mutations are either causative or a risk factor in a proportion of Parkinson's patients.

We aim to determine whether GZ mutation-positive Parkinson's is clinically separable from regular Parkinson's, using validated clinical scales for tremor, coordination, stiffness/slowness of movement and cognitive impairment, and recording premonitory symptoms of Parkinson's using a standard questionnaire. We are also performing MRI scans of brain, where possible, as our initial work shows that GZ Parkinson's patients have more abnormalities in the deep parts of the brain than do controls. As well as this clinical study, we are also studying the oxygen consumption/energy producing pathways of blood cells, and one of their key regulators - an enzyme named AMPK. A raised AMPK is an adaptive response to sudden (acute) cell stress, but chronically raised levels can be harmful. (It has been known for a long time that there is a disturbance in the oxygen consumption/energy-producing pathways in Parkinson's, and our preliminary work shows a significant

difference in this pathway in GZ compared with regular Parkinson's disease. Our findings of a derangement in AMPK are novel, however.) The control patients we are using for this study have GZ-negative Parkinson's, and are being matched for age, sex and disease duration (but not severity, as this seems likely to be a point of difference).

The importance of this study is two-fold: firstly, if our hypothesis that GZ Parkinson's can indeed be identified clinically and on MRI is correct, this will guide clinicians as to who requires genetic testing for GZ mutations. This itself will enable cascade testing of other family members. Efficient diagnosis of GZ Parkinson's will also enable more accurate prognostication, as our preliminary data suggests that GZ Parkinson's is more aggressive that ordinary Parkinson's. Secondly, our study to date suggests that the metabolic derangement in regular and GZ Parkinson's are similar in pattern but different in extent. AMPK can be regulated with currently available drugs or chemicals, and knowledge of its activity in regular and GZ Parkinson's disease may identify it as a therapeutic target.

We proposed to study twenty such GZ Parkinson's patients, already identified from the Griffith University Parkinson's cohort DNA bank. Unfortunately, most were unable to be tested clinically, due to death or advanced disease, change of location/lost to follow-up, remote addresses, etc. Ultimately, we could only test eight. We therefore sought to search for GZ mutations in other Parkinson's cohorts. We have tested another five newly identified from Prof. Malcolm Horne's Victorian cohort for a total to date of thirteen, and anticipate that a further one or two will be available from the NSW component of his cohort and a further three or four from the WA component. We contacted Prof Simon Lewis about his NSW cohort of 250 Parkinson's patients and are in the process of having GZ mutations tested for in these by our collaborators in the USA. This should yield about 6 or 7 GZ Parkinson's individuals, of whom perhaps half will be available for, and agree to, clinical assessment. We have also approached Prof Tim Anderson in Christchurch, whose cohort should include five or six GZ patients at currently known prevalence rates, and this collaboration looks promising.

This more widespread recruitment process, and necessity to test for GZ mutations first in these other cohorts has obviously slowed progress, and we are seeking an extension of time for this study until June 2018.

Hypothesis vs Findings
Not yet available

Unanswered Questions
Not yet available

What these research outcomes mean

Not yet available

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