Commentary

Identification of a Common Genetic Risk Variant (LRRK2 Gly2385Arg) in Parkinson’s Disease
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Abstract

The recent identification of a common genetic variant (LRRK2 G2385R) which is associated with a two-fold increased risk of sporadic Parkinson’s Disease (PD) in two independent Chinese populations in Singapore and Taiwan has generated considerable excitement. Thus far, this variant appears specific for the Asian population, emphasising further that ethnic-specific effects should be considered in genetic association studies. Cautious optimism is advised as we await more scientific studies and clarification if this risk variant is specific to ethnic Chinese race. Our in-vitro studies suggest the Gly2385Arg variant is biologically relevant and it might act through pro-apoptotic mechanisms, especially under cellular stresses. This may provide a partial explanation why some carriers develop the disease while others do not. The presence of other epigenetic factors, gene-gene and gene-environmental interaction could modulate the phenotype expression. Further validation of these findings would be needed to confirm this variant as the single most important common genetic risk factor in ethnic Chinese and/or Asian PD patients. The identification of the LRRK2 Gly2385Arg variant could potentially facilitate the development of clinical, bioimaging, genetic and biological biomarkers, useful in the monitoring and neuroprotective therapy in asymptomatic individuals.

Key words: Chinese, Gene, Mutation

For diseases with complex inheritance, the age-old debate regarding the relative contribution of gene-environment interaction never fails to generate interest, discussion and hypothesis within the scientific community. The unraveling of the human genome project brings hope and great optimism that a verdict on such debates may be in the near horizon. However, hope and reality are frequent distant lovers who might require spirit and persistence to bring their supposedly destined marriage into fruition. The twists and turns of medical science research and discovery never fail to amaze, and the recent discovery that a common genetic variant (LRRK2 G2385R) increases the risk of Parkinson’s Disease (PD) makes one good illustrative example. I will take you through a quick journey of the roller roster ride in this field and share our personal experience and our contribution in uncovering this genetic variant that is beginning to attract worldwide attention.

Parkinson’s disease (PD) is the second most common neurodegenerative disease globally and is characterised clinically by rest tremor, rigidity, bradykinesia and postural instability.1-2 It is a significant cause of morbidity amongst the elderly population and while medical and surgical treatment is effective, no cure is currently available.3-8 Since the description by James Parkinson more than two centuries ago, it has always been a widely held view that PD is of “idiopathic” in origin. The first twist accompanies the discovery of MPTP (methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-induced Parkinsonism in intravenous drug users in 1983 which led many to initially speculate that environmental factors could be the primary aetiology.9 However, numerous epidemiologic studies evaluating potential environmental causative agents have not conclusively identified any specific environmental agent. Then came an unexpected genetic turn in 1997 when a missense mutation in the alpha-synuclein gene was found to be associated with the disease in some families with autosomal dominant (AD) mode of inheritance of parkinsonism.10 This “genetic revolution” continues unabated in recent years, largely due to the enterprising spirit of investigators worldwide who have a determined
effort to map and identify putative pathogenic gene variants in different ethnic populations. Supporters of PD as a genetic disease must now be pleasantly delighted as currently 13 genetic loci have been ascribed and 6 disease-causing genes have been uncovered.11 Two significant genes, Parkin (PARK2) and LRRK2 are worth mentioning as the former accounts for up to 50% and 15% to 20% of autosomal recessive and young onset sporadic PD.12 Mutations in the leucine-rich repeat kinase 2 (LRRK2, PARK8) are the most frequent known cause of familial autosomal dominant PD.13-16 The common G2019S mutation accounts for 3% to 7% of familial PD and 1% to 3% in sporadic PD in several ethnic populations, with the highest prevalence (up to 40%) in North Africans and Ashkanezi Jews.11 The striking absence of the common G2019S mutations in three independent Chinese populations involving 2000 study subjects suggests the possibility that ethnicity specific differences may exist for other LRRK2 mutations.17-20 The lack of differentiating features between carriers and non-carriers of these gene mutations and the alarmingly high frequency of mutations in sporadic cases in certain populations certainly challenge a previously held view by some that the genetic forms are different from the common garden variety and should be termed separately as “familial parkinsonism” and not PD. The nosology of “idiopathic” PD is being questioned as a clear defined genetic cause has been found even amongst the typical PD cases.

The association of a disease with genetic mutations is frequently clear-cut in cases where co-segregation of the genotype and phenotype could be demonstrated in family and case control studies and a disruption of biological function from the mutation is evident. However, the role of genetic risk factors in disease is more debatable. For a long time, research into genetic susceptibility risk factors to diseases has been a common focus that cuts across the entire realm of medical illnesses. The rationale for genetic association studies is based on the hypothesis that there may be an association of a defined disease trait and specific genetic variants. The relationship between genetic variants of the candidate gene and disease status, and the pattern of linkage disequilibrium in the population and genomic region under study will influence the variability and validity of the findings. However, unlike investigations into clinical risk factors, such as hypertension and diabetes mellitus, association studies of genetic risk factors are limited by various methodological problems. Genetic association studies in PD have frequently given conflicting findings, likely because of inadequate sample size, bias in selecting only individual polymorphic loci of susceptibility genes so that background genetic variations are not systematically studied and population stratification.21 Various investigators have tried to partly overcome some of these problems through studies using sib-pairs, genetic isolates, whole genome amplification and multi-centre meta-analysis of pooled data.22 However, no single genetic risk variant has yet to be consistently replicated in PD.

It is in this back-drop that when we undertook the onerous task of conducting a detailed case control haplotype tagging analysis of the LRRK2 gene in our Chinese population in early 2005 shortly after the genetics mutations of this gene were reported, few would believe any useful data could be generated. We identified a haplotype that dramatically increases disease risk when present in two copies (OR = 5.5, 95% CI = 2.1-14.0, P = 0.0001).15 At the same time, we also found an association of a few individual polymorphic variants, including the LRRK2G2385R variant with an increased risk of PD. Conventional wisdom and many historic publications told us then that the chance of a false positive association with these individual variants is high, particularly if the frequency of these variants is low. We decided to publish only our haplotype data instead of these individual variants. At around the same time, three studies suggest little role of common LRRK2 variants in Caucasian PD populations,23-25 echoing a familiar tune in the futility of genetic association studies. A twist came in early 2006 when our Dutch collaborators informed us that they have found an association of the LRRK2 Gly2385Arg variant, (which was originally described in a PD family from Taiwan26) with an increased risk of PD in Taiwanese Chinese.27 Interestingly, this variant has yet to be detected in Caucasians. We went back to dig out our old LRRK2 G2385G data which we have shelved and were surprised to find a similar magnitude of risk in our Chinese patients. Our further in-vitro studies seemed to suggest that this variant is more toxic under stressful cellular conditions, reinforcing the clinical observation.28 The extent of the importance of this finding was subsequently highlighted at a recent conference (10th International Congress of Parkinson’s Disease and Movement Disorders, Kyoto, Japan) where poster presentations from other groups showed that the clinical association could be replicated in other Asians populations and the risk seems to be even higher in familial cases.

Cautious optimism is advised while we await more scientific studies and further clarification if this risk variant is specific to the ethnic Chinese race only. Our recent in-vitro studies suggest the Gly2385Arg variant is biologically relevant and it might act through pro-apoptotic mechanisms, especially under cellular stresses. In our initial experiments, the variant is associated with increased cell death compared to the wildtype only when exposed to an oxidative stress environment.29 This observation may provide a partial explanation why some carriers develop the disease while other do not. The presence of other epigenetic factors,
gene–gene and gene–environmental interaction could modulate the phenotype expression.

If indeed this risk variant turns out to be the most important common genetic risk factor specific to the Chinese populations or other Asian races globally, credit should be given to those investigators in the field who persisted and pursued optimistically their hopes in finding a biomarker in genetic association studies. The courage of the journals to publish these “non-Rocket Science” association studies should be gratefully acknowledged. The identification of the LRRK2 Gly2385Arg variant could potentially facilitate the development of clinical, bioimaging, genetic and biological biomarkers, useful in the monitoring and neuroprotective therapy in asymptomatic individuals.

While there could be more surprises ahead for investigators in this field,9 we learn from this experience that conventional wisdom does not always apply in medical science and sometimes a single innocent observation not in the most robust scientific sense could bring about important clinical discovery.

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REFERENCES