Urinary LRRK2 phosphorylation
Penetrating the thicket of Parkinson disease?

While the discovery of the first monogenic cause of Parkinson disease (PD) almost 2 decades ago has revolutionized our understanding of this increasingly prevalent disorder, genotype–phenotype relationships have proven to be much more complex than initially anticipated. An important reason for this observation is reduced penetrance, a conundrum referring to the surprisingly large proportion of carriers of an allegedly pathogenic mutation who do not develop the disease.1

A classic example of a PD gene with markedly reduced penetrance is leucine-rich repeat kinase (LRRK2), mutations in which account for as many as 20%–30% of all PD cases in select populations.2 LRRK2 mutation penetrance is both age and ethnicity dependent3 but remains incomplete in a substantial subset of mutation carriers.4 Further illustrating the scope of this notion, the Exome Aggregation Consortium (ExAC; http://exac.broadinstitute.org) dataset, which is based on whole exomes of 60,706 unrelated, multiethnic individuals not selected for PD, revealed 47 carriers of the most common mutation in LRRK2 (p.G2019S). When extrapolating these numbers to the world population of 7.3 billion people—admittedly an estimate that needs to be interpreted with caution—there may be as many as 5 to 6 million carriers of this mutation worldwide. Identifying LRRK2 mutation carriers has a high imperative, as this condition may have identified the first marker for LRRK2.

With their experimental approach, the authors addressed 2 important questions simultaneously: Can urinary LRRK2 phosphorylation serve as a marker of trait, i.e., is it genotype-specific? Is it also a marker of state, i.e., does it predict affected status of mutation carriers? The answer to both of these questions is yes (figure). Regarding the first question, LRRK2 phosphorylation was 4.8 times higher in patients with PD with a LRRK2 mutation (LRRK2+/PD+) than in healthy controls without mutation (LRRK2−/PD−) and 4.6 times higher in patients with PD without LRRK2 mutation (LRRK2−/PD+), i.e., specific to the LRRK2 genotype and almost independent of the presence or absence of (idiopathic) PD. While this is an important proof of principle and a remarkable finding in its own right, the answer to the second question may be of even greater relevance, as genotypes can be determined easily and highly accurately by genetic testing.

When comparing affected LRRK2 mutation carriers (LRRK2+/PD+) with those (yet) unaffected and thus displaying reduced penetrance of the mutation (LRRK2+/PD−), urinary LRRK2 phosphorylation was 2.2-fold higher in affected than in unaffected mutation carriers, separating both groups with an area under the ROC curve of 0.84.6 With this, the authors may have identified the first marker for LRRK2 mutation carrier as well as disease status, which in fact would be the first of its kind in the field of (genetic)
PD. To our knowledge, the only other study attempting to correlate biological markers with PD penetrance found a selective upregulation of mitochondrial uncoupling protein 2 (UCP2) in patients with p.G2019S LRRK2 (LRRK2+/PD+) when compared to unaffected carriers of the mutation (LRRK2+/PD−). However, UCP2 expression was measured in fibroblasts grown from skin biopsies and the mRNA levels did not distinguish between healthy mutation-positive (LRRK2+/PD+), and mutation-negative (LRRK2−/PD−) individuals.

The findings by Fraser et al. are exciting and promising. However, they remain subject to independent confirmation and have been obtained in a relatively small sample of 18 probands per group. Despite this limitation, it is conceivable that this marker may influence LRRK2 research and therapy development and possibly even allow monitoring of clinical trial outcomes. With the intention to verify the sensitivity of LRRK2 urinary phosphorylation as biomarker in a larger sample, Dr. Andrew West, the corresponding author of the study, is currently recruiting participants for a clinical trial (NCT01860118). Additionally, research efforts of basic scientists should focus on a related question of high translational potential: How and why is LRRK2 phosphorylation relatively decreased in mutation carriers with reduced or delayed penetrance of the mutation and what are the underlying mechanisms of this endogenous disease protection?

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