● PERSPECTIVE

Pharmacogenomics in Parkinson's disease: which perspective for developing a personalized medicine?

Every disease treatment is ideally finalized to prevent symptom occurrence, to stop or slow down the progression of disease, to alleviate complications already present and consequently to improve the quality of life for each patient. Unfortunately, in Parkinson's disease (PD) a treatment able to completely cure the disease is not so far available. Indeed, until now, the current therapies only allow to control the disease symptoms, without ensuring a long term efficacy and without reducing the risk to develop adverse drug reactions. The actual gold standard therapy consists in levodopa treatment, often used in combination with dopamine receptor agonists, catechol-O-methyltransferase (COMT) inhibitors or monoamine oxidase inhibitors. While the treatment with levodopa ameliorates the motor function of the patients, not all patients reach the therapeutic effect and many develop motor complications after using the drug for a prolonged time. On the other side, the dopamine receptor agonist drugs can cause psychosis, visual hallucinations, excessive daytime sleepiness, compulsive behavior and impulse control disorders, while the COMT inhibitors can induce hepatotoxicity. Variability in drug response is a multifactorial character that depends on clinical, environmental and genetic factors. In the last decades, the increasing knowledge in the human genome inter-individual variability led genetics and pharmacogenomics to assume a central role for the study and development of personalized and stratified medicine, with the claimed aim to decrease the number of adverse drug reactions and to increase the efficacy of drug therapy. Although in some fields, such as oncology and psychiatry, pharmacogenomics studies have already allowed the identification and validation of genomic biomarkers able to stratify groups of patients and to guarantee a personalized and precision medicine, in PD this is unfortunately still far to reach.

Pharmacogenomics studies in PD: Levodopa is the principal drug used in PD treatment, and the majority of pharmacogenomics studies have investigated the role of polymorphisms involved in response to its treatment. The investigated genes were mostly chosen on the base of their role in the levodopa metabolism, transport and excretion, such as for example the COMT, the monoamine oxidase B (MAOB), the dopa decarboxylase enzyme (DDC), the dopamine receptors (DRD1, DRD2, DRD3, DRD4 and DRD5), the dopamine transporter (DAT), the organic cation transporters (OCTs) and others (Schumacher-Schuh et al., 2014; Cacabelos, 2017; Politi et al., 2018). Among these, the most confirmed associations have been found with COMT and DRD2 genes. In particular, COMT polymorphisms have been described associated both with levodopa dosing (Cheshire et al., 2014) and with adverse reactions (such as dyskinesia and daytime sleepiness) (de Lau et al., 2012), while DRD2 and DRD3 polymorphisms were associated only with adverse reactions, such as dyskinesia, motor fluctuation, hallucinations, sleep attack (Rissling et al., 2004; Rieck et al., 2012). Unfortunately, the majority of these studies have been performed in small population samples and often these findings have not been adequately confirmed.

Among other anti-PD drugs only few studies reported some interesting associations that are worth to be further explored. Regarding tolcapone/entacapone, a large European study (409 PD samples) reported an association between UGT1A6 A528G SNP (single nucleotide polymorphism) and the risk of liver toxicity as drug adverse reaction ($P < 0.0001$) (Acuña et al., 2002). Instead, regarding the rasagiline, a recent large Canadian study (692 PD patients) reported an association between DRD2 rs2283265 and drug efficacy ($P < 0.05$) (Masellis et al., 2016).

Issues and future perspectives: The main problem regarding the studies here described is the lack of adequate replications that could be due to the small number of subjects investigated in each performed study and to the heterogeneity of the disease. Indeed, when small numbers of subjects are analyzed, the statistical power of a study is low and many genetic contributors could escape the identification, whereas some false positives could be misinterpreted. The associations above described need to be replicated in larger homogenous cohorts and in different populations. Indeed, the differences among populations in terms of presence and frequency of potentially involved genetic variants should be adequately considered. A diverse genetic background could explain why some adverse reactions are more frequent in certain populations rather than in others, or why in different populations there are different rates of good/low responders to specific treatments. Pharmacogenomics studies should therefore consider the different ethnicities present in each investigated cohort. In fact, in some countries the population admixtures do not help to identify genetic variants involved with drug response because the effect of a specific variant could be diluted or hidden. The clinical heterogeneity of this disease is another important point to consider. Indeed, in PD both the neurodegeneration pattern and the involvement of motor and

non-motor symptoms characterize a wide spectrum of clinical differences among patients (Kruger et al., 2017). This heterogeneity should be taken into account to choose the correct therapeutic approach that could ensure a better quality of life for the patient. Therefore, the characterization of a precise phenotype is crucial for patients stratification and treatment, but also for the optimization of pharmacogenomics studies.

It is important to highlight again that drug response is a multifactorial character that is affected by genetic factors but also by environmental factors, co-medications, comorbidities, differences in populations genetic background and many clinical characteristics. Moreover, the picture is furtherly complicated because each genetic factor gives a small contribution to the variability in drug response, and this contribution could be difficult to evaluate when population samples are small and further stratified for risk factors, clinical phenotypes, disease onset and duration, and therapy compliance.

The application of new genomic approaches will be necessary to identify new pathways/genes involved in the pathogenesis of PD and to identify novel drug targets. For example, several Genome Wide Association Study (GWAS) have been recently conducted on PD and have been useful to identify new disease risk loci; however, to date, no GWAS has been performed to analyze the variability in relation to drug response in PD. On the other side, the improvement of new technologies and the decreasing costs of next-generation sequencing, combined with a greater understanding of the clinical significance of the identified variants, could permit in near future to better stratify patients for disease onset and prognosis, and therefore to promote more personalized treatments.

Moreover, it is to consider that the identification and the confirmation of a genetic variant associated with drug response is only the first step of a long process that could bring to its implementation in clinical practice. Indeed, the clinical utility of a pharmacogenomics biomarker, that means its utility weighing both the risks and benefits resulting from genetic test use (Burke, 2009), is to be carefully considered and expects several steps of validation and qualification (Novelli et al., 2010).

In conclusion, future studies in larger cohorts and in different populations will be crucial to confirm the associations identified so far, while the application of new technologies and the possibility to better stratify patients will be necessary to identify new genetic biomarkers useful to implement a personalized therapeutic approach in PD patients and to improve their quality of life.

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