Personalized medicine beyond cancer: Impact on other diseases

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With a focus on type 2 diabetes and Parkinson's disease, Dr Priya Hays explores how personalized medicine approaches are impacting the development of therapies for other chronic conditions beyond cancer

Genetic testing and cancer outcomes have been considerably advanced by precision medicine, or personalized medicine, with gene panel testing conducted routinely in patient care and targeted therapy approaches incorporated into oncology. It may be argued that with these significant advances, diseases such as type 2 diabetes, cardiovascular disease, neurological diseases such as Parkinson's disease, and Alzheimer's disease and psychiatric diseases have been unaffected by the gains of personalized medicine. However, this is not entirely accurate as aspects of personalized medicine such as pharmacogenomics, targeted approaches for neurological systems, and single nucleotide polymorphism detection have resulted in safe and effective diagnostics and treatments for cardiovascular disease, diabetes and neurological disorders, and depression and schizophrenia. Outlined here are precision medicine approaches for type 2 diabetes and Parkinson's disease.

Type 2 diabetes

Pharmacogenomic studies revealed genetic markers for variability in response to a number of oral type 2 diabetes medications. Metformin activity was determined to be affected by SNPs in the glucose transporter SCL22AI, which encodes OCT1, and SLC47A1, an organic cation transporter that encodes the multidrug and toxin extrusion MATE-1. Both SNPs are correlated with decreased efficacy of metformin.

The mechanism of action of sulfonylureas is also amenable to pharmacogenomics. They bind to potassium channels in pancreatic beta cells that respond to ATP/ADP concentration, which leads to insulin release. SNP genes KCNJ11 and ABCC8, which encode potassium channel subunits, are associated with decreased sulfonylurea response. The canonical CYP2C9 variant is also implicated in SU metabolism since the loss-of-function variants in the gene have a better glycemic response than the wild-type allele, with hypoglycemic events being minimized.

DPP4 Inhibitors/GLP-1 analogs act by increasing the hormone incretin, a glucagon-like peptide that induces insulin secretion. The incretin pathway is encoded by the CTRB1 and CTRB2 genes, which are revealed in genetic testing.

Sodium-glucose transporters (SGLT) are located in the renal tubules and reabsorb 99% of the filtered glucose during renal filtration. One of the subgroups of these transporters in the renal tubules is type 2. 'SGLT-2 inhibitors reduce hyperglycemia through glucose elimination via urine. A loss-of-function mutation in SLC5A2 gene, which encodes SGLT2, might remove glucose in an insulin-independent mode via glucosuria and decrease uptake of glucose in the tubuli, thus protecting against hyperglycemia via elevated glucose excretion in the kidney.' (1)

Thiazolidinediones (TZDs) are a class of antidiabetic drugs that sensitize cells to insulin and lead to the insulin-dependent production of glucose. They can reduce hemoglobin A1c, a measure of glucose present in the blood over a three-month period, by 0.5-1.4%. Pioglitazone and rosiglitazone are examples of TZDs that may benefit from an individualized genomic workup that would reveal genetic variants that predispose patients to the adverse events of the drugs.

Examples are SNPs for liver metabolizing enzymes CYP2C8 and CYP2C9 that influence the pharmacokinetics of TZDs. Edema is another side effect of this class of drugs and is associated with the rs296766 T allele of AQP2 (aquaporin 2) and the rs12904216 G allele of SLC12A1 (sodium/potassium/chloride transporter). Additionally, decreased fasting blood glucose and HbA1C have been shown in an evaluated P12A variant in PPAR-γ, which is involved in the drug's mechanism of action. Another TZD, rosiglitazone, has been shown to have improved response in carriers of the A allele of rs6467136 in PAX4, a gene also associated with type 2 diabetes.

Parkinson's disease (PD)

There are a number of treatments, both established and being developed, that offer avenues for precision medicine in Parkinson's disease. One of them is deep brain stimulation, or DBS, which has been performed on more than 12,000 patients within the past 30 years and is considered an effective treatment for advanced PD. DBS works by blocking the abnormal neural signals associated with PD that are responsible for the electrical impulses in specific regions of the brain of PD patients, resulting in its characteristic clinical symptoms. The precision medicine component is that certain regions of the brain are targeted, such as the cortico-basal ganglia-thalamo-cortical axis, subthalamic nucleus (STN), and the internal part of the globus pallidus (GPi). These regions, when targeted, are considered to have the most therapeutic value for levodopa-responsive motor symptoms and complications. For instance, one of the major indications for DBS surgery is 'levodopa-induced dyskinesia, a troublesome complication caused by long-term levodopa treatment.' (1)

The Personalized Parkinson Project (PPP) proposes an unbiased biomarker development method for PD patients that is measured longitudinally and quantitatively. Six hundred fifty patients with PD over the age of 18 who are at the early stage of the disease (less than five years) formed a prospective, longitudinal, single-center cohort study that aims to determine the correlations between novel biomarkers, rate of disease response and treatment response. 'The study authors hypothesize that the rate of decline in two key

areas of PD monitoring, motor functioning and cognitive functioning, would associate with potential biomarkers, and these biomarkers would predict disease progression. The participants are followed for two years, with three annual assessments measuring outcomes from motor and neuropsychological tests, structural and functional MRIs, and ECG recordings to predict disease progression after years one and two and determine any potential correlations with these outcomes. Patients also utilize an innovative Verily Study Watch to collect other physiological parameters and environmental data.' [1]

Another genetic biomarker in personalized medicine is the APOE alleles for Alzheimer's disease, and pharmacogenetics plays a crucial role in the administration of warfarin and clopidogrel, medications for cardiovascular disease. The elucidation of the impact of personalized medicine on psychiatric and infectious diseases is ongoing, and personalized medicine will continue to have increasingly impactful roles in diseases beyond cancer.

References

1. Hays P. Advancing Healthcare Through Personalized Medicine, Second Edition. (Cham, Switzerland: Springer Nature). 2021

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