Hellenic Diabetological Chronicles 32, 3: 129-130, 2019

Pharmacogenetics of Type-2 Diabetes

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Currently, 7.5 million people in Germany are suffering from diabetes mellitus, more than 95% thereof from type-2 diabetes. The estimated costs for diabetes therapy reach about 16 billion € per year. Since prevalence data and costs will rise in the years to come, there is a clear need of cost-effective use of antidiabetic medication. Pharmacogenetic research aims at contributing to the reduction of therapy costs by allowing patient stratification and precision medicine.

Pharmacogenetics investigates the impact of genetic variation on treatment response and side effects. With respect to treatment response, the identification of gene variants associated with non-response and adverse response is paramount. The genes of interest are usually those related to pharmacokinetics and pharmacodynamics of a drug.

The pharmacogenetically best studied drug is metformin, the first-line drug in type-2 diabetes therapy. As metformin is not metabolized, pharmacogenetic investigation of metformin treatment focused on a manageable repertoire of pharmacokinetic genes. The organic cation transporter gene OCT1 was a major candidate gene because it harbors seven coding variants with reduced transport activity in vitro. Even though smaller studies provided evidence for some of these variants being associated with limited treatment response and metformin intolerance, the MetGen consortium including treatment studies with a cumulative sample size of about 8.000 subjects could not verify pharmacogenetic importance of these variants. Large collections of metformin treatment studies and the technological advances of the last 10 years finally allowed studying the impact of genetic variants on metformin response on a genome-wide scale (pharmacogenomics). These studies identified numerous non-coding variants in and around the ATM and SLC2A2 genes being associated with metformin treatment response. Unexpectedly, carriers of these variants revealed super-response to the drug limiting the usefulness of these findings for precision medicine. Larger study collections and consortia for pharmacogenomic investigation of other antidiabetic drugs are currently not available.

In close collaboration with pharmaceutical industry, we

could recently provide evidence for pharmacogenetic importance of pharmacodynamic gene variants in diabetes treatment using DPP4 and SGLT2 inhibitors. The pharmacodynamic target of SGLT2 inhibitors is the sodium/glucose transporter SGLT2 encoded by the SLC5A2 gene. SGLT2 is expressed in the proximal tubules of the kidney and is responsible for about 90% of renal glucose reabsorption. With rs3116150, we identified a common non-coding genetic variant in the SLC5A2 gene that is associated with elevated plasma glucose levels and increased systolic blood pressure already at baseline. Even though the treatment response was unaffected with respect to plasma glucose lowering, homozygous carriers of this variant revealed a substantial increase in systolic blood pressure (+8.9 mmHg) during 24 weeks of empagliflozin treatment. Thus, an estimated number of 40.000 T2D patients in Germany homozygous for this variant and treated with SGLT2 inhibitors are expected to experience blood pressure increase.

A pharmacodynamic target of DPP4 inhibitors and GLP1R agonists is TCF7L2, a transcription factor of pancreatic β-cells downstream of the GLP1R-cAMP-PKA signaling cascade which induces incretin receptor, prohormone convertase and insulin gene expression. We could demonstrate that the non-coding TCF7L2 variant rs7903146, the most important type-2 diabetes risk variant known to date, is associated with incretin resistance and impaired insulin secretion. Moreover, in a 24-week pharmacogenetic study, homozygous carriers of the variant revealed limited response to linagliptin treatment with respect to HbA1c lowering. Thus, about 400.000 T2D patients in Germany homozygous for this variant and treated with DPP4 inhibitors or GLP1R agonists are expected to experience limited treatment response. With Nor-1, encoded by the NR4A3 gene, we recently described a novel incretin-responsive transcription factor in β-cells which is likewise downstream of the GLP1R-cAMP-PKA axis and stimulates the expression of the insulin gene and a series of genes involved in the insulin secretory pathway. Additionally, we demonstrated that the non-coding variant rs12686676 in the NR4A3 gene locus interacts with TCF7L2 rs7903146 and enhances the insulin-secretion-impairing effect of TCF7L2 rs7903146. A similar synergism between the two SNPs was also observed with respect to incident type-2 diabetes in the EPIC-Potsdam study. Thus, we anticipate that subjects carrying both variants will have a markedly limited treatment response to DPP4 inhibitors and GLP1R agonists.