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Pharmacogenetics Fordiabetes Mellitus

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Diabetes mellitus is not just one disease, but a progressive, multifactorial, heterogeneous group of disorders clinically characterized by obesity, insulin resistance and pancreas β-cell dysfunction.Current estimates demonstrate that diabetes affects 23.6 million people in the United States alone, which represents 7.8% of the population, and close to 250 million people worldwide [1]. Twin studies suggest a modulating role for genetic factors in the susceptibility to type 2 diabetes mellitus (T2DM) [2]. Pharmacologically, an extensive range of oral anti-diabetic drugs for type 2 diabetes exist for the treatment of T2DM, including insulin and its analogues, sulfonylureas, biguanides, thiazolidinediones (TZDs), meglitinides, α-glucosidase inhibitors.

Although a variety of pharmacological treatments available, response, doses and tolerability to drugs are highly variable with many patients initially respond to anti-hyperglycemic drugs, yet over time, failing to react to mono-therapy. By far, a large inter-individual variability in drug response has been noticed and a number of factors validated to contribute to those differences in drug response including age, sex, disease, drug and food interactions, comorbidity, as well as genetic factors. Genetic variability in genes coding for drug-metabolizing enzymes, drug receptors and proteins involved in pathway signaling is an vital factor determining inter-individual variability in drug response [3].

Pharmacogenetics (PG) traces back to the late 1800s [4] and is generally regarded as the study or clinical testing of genetic variation that links to different response to drugs. coupled with technological improvements in genomic tools like genome-wide association studies (GWAS). Pharmacogenetics hold the promise of realizing the probability of bringing "personalized medicine" to direct drug and dosing decisions, reduce disease morbidity and mortality, and improve life quality for T2DM patients.

Current state of T2DM pharmacogenomics

Sulfonylureas: Sulfonylureas causes the release of insulin from the β-cells by primarily binding to the high affinity plasma membrane receptor (SUR1) coupled to an ATP-dependent K+ channel (KATP), further closing the K+ channel (coding by KCNJ11) which ultimately lead to a corresponding increase in intracellular calcium levels. Multiple genes are involved in the formation of the sulfonylurea complex including the inwardly rectifying potassium channel (KCNJ11) and the ATP-binding cassette transporter sub-family C member8 (ABCC8). A number of studies have showed that these genes are in close relation to hypoglycemia, diabetes, and sulfonylurea failure. Examples include the carriers of the Lys23 variant of the KCNJ11 Glu23 Lys polymorphism and the susceptibility to secondary failure [5], and rare monogenic mutations in ABCC8 with neonatal diabetes [6]. Sulfonylureas are metabolized primarily by the cytochrome P4502C9 enzyme (CYP2C9), and individuals carrying at least one *2 or *3 allele exhibit reduced CYP2C9 activity. Patients with diabetes mellitus who are carriers of a CYP2C9*3 allele require lower doses of tolbutamide to regulate their serum glucose levels compared to patients with the wild-type genotype [7].

Biguanides (Metformin): Metformin reduces hepatic gluconeogenesis mainly by improving insulin sensitivity and other than being metabolized, Metformin undergoes rapid renal elimination via filtration in the glomerulus and net secretion in the proximal tubules. Two related transporter are organic cation transporter 1 (OCT 1) expressed in hepatocytes which mediates the uptake of the drug and organic cation transporter 1 (OCT 2) abundantly in the kidney which participate in renal epithelium of Metformin. Metformin lowered glycemic excursion by 7.5% with intact OCT1 function. However, in those with polymorphisms in OCT1 that caused decreased up take of metformin, the glycemic excursion was not altered by metformin [8].

Thiazolidinediones: Thiazolidinediones (TZD) are a group of insulin-sensitizing drugs, generallyagonists for thenuclear receptor peroxisome proliferator-activated receptor-γ (PPAR-γ). A nonsynonymous SNP in PPAR-γ (Pro12Ala) was one of the first common genetic variants associated with a predisposition to T2DM. Patients with the Pro12Ala genotype in the PPARgamma2 gene had a better therapeutic response to rosiglitazone than did patients with the Pro12Pro genotype. The genetic variations in the PPARgamma2 gene can affect the response to rosiglitazone treatment in patients with type 2 diabetes mellitus [9]. The increased receptor sensitivity lead to significant hypoglycemic effect and side effects such as edema. The metabolism and kinetics of TZD are associated mainly with CYP2C8 and the plasma pioglitazone concentrations, assessed as area under the curve, were higher in CYP2C8*1/*3 and *3/*3 compared to *1/*1 individuals [10].

Genetic implications for Therapy

Recent decades have seen the significant advances of large genetic determinants of T2DM risk. But In many cases, the reported associations merely signal regions of the genome that are overrepresented in disease versus health but do not identify the causal variants [11]. How these genetic determinants help clinicians diagnose, predict, prevent, or treat type 2 diabetes any better remains unsettled.

To successfully apply pharmacogenomic tests, large scale studies with adequate samples sizes should be introduced to further verify the role of genetics on predicting outcome in clinical practice. monogenic forms of the disease have already served as tantalizing proofs of treating diabetes. Patients with hepatocyte nuclear factor-1alpha gene mutations are more sensitive to sulphonylureas than T2DM subjects [12]. Finally, due to the various polymorphisms involved in drug metabolizing enzymes. Examples include Metformin with OCT1 and Anti-Diabetes Drugs with cytochrome P450 enzyme as mentioned

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above. Although a PG test is essentially no different from a routine laboratory test, these tests have potential to serve adequate evidence-based recommendations for individualizing medical care of diabetes mellitus.

References

1. Peek R, Reddy KR (2007) Doctor Griffin Rodgers at helm of the National Institute of Diabetes and Digestive and Kidney Diseases. Gastroenterology 133: 380-381.
2. Poulsen P, Kyvik KO, Vaag A, Beck-Nielsen H (1999) Heritability of type II (non-insulin-dependent) diabetes mellitus and abnormal glucose tolerance--a population-based twin study. Diabetologia 42: 139-145.
3. Swen JJ, Huizinga TW, Gelderblom H, de Vries EG, Assendelft WJ (2007) Translating pharmacogenomics: challenges on the road to the clinic. PLoS Med 4: e209.
4. Meyer UA (2004) Pharmacogenetics - five decades of therapeutic lessons from genetic diversity. Nat Rev Genet 5: 669-676.
5. Sesti G, Laratta E, Cardellini M, Andreozzi F, Del Guerra S, et al. (2006) The E23K variant of KCNJ11 encoding the pancreatic beta-cell adenosine 5'-triphosphate-sensitive potassium channel subunit Kir6.2 is associated with an increased risk of secondary failure to sulfonylurea in patients with type 2 diabetes. J Clin Endocrinol Metab 91: 2334-2339.
6. Babenko AP, Polak M, Cavé H, Busiah K, Czernichow P, et al. (2006) Activating mutations in the ABCC8 gene in neonatal diabetes mellitus. N Engl J Med 355: 456-466.
7. Becker ML, Visser LE, Trienekens PH, Hofman A, van Schaik RH, et al. (2008) Cytochrome P450 2C9 *2 and *3 polymorphisms and the dose and effect of sulfonylurea in type II diabetes mellitus. Clin Pharmacol Ther 83: 288-292.
8. Shu Y, Sheardown SA, Brown C, Owen RP, Zhang S, et al. (2007) Effect of genetic variation in the organic cation transporter 1 (OCT1) on metformin action. J Clin Invest 117: 1422-1431.
9. Kang ES, Park SY, Kim HJ, Kim CS, Ahn CW, et al. (2005) Effects of Pro12Ala polymorphism of peroxisome proliferator-activated receptor gamma2 gene on rosiglitazone response in type 2 diabetes. Clin Pharmacol Ther 78: 202-208.
10. Tornio A, Niemi M, Neuvonen PJ, Backman JT (2008) Trimethoprim and the CYP2C8*3 allele have opposite effects on the pharmacokinetics of pioglitazone. Drug Metab Dispos 36: 73-80.
11. Florez JC (2009) Genetic susceptibility to type 2 diabetes and implications for therapy. J Diabetes Sci Technol 3: 690-696.
12. Pearson ER, Liddell WG, Shepherd M, Corrall RJ, Hattersley AT (2000) Sensitivity to sulphonylureas in patients with hepatocyte nuclear factor-1alpha gene mutations: evidence for pharmacogenetics in diabetes. Diabet Med 17: 543-545.