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PHARMACOGENETIC APPROACHES IN THE TREATMENT OF OBESITY AND LIPID ABNORMALITIES

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One of the major challenges in the treatment of metabolic disorders and obesity is finding the right treatment for the right patient. Looking at pharmacological and non-pharmacological approaches for many different disorders we must recognize that, for a given indication and a given class of drugs, responder rates are in the range of 50–60%, while the remaining patients can be classified as ‘nonresponders’ or may even present with adverse drug affects that are hardly predictable with standard medical techniques. Therefore, to reduce side-effects and to better individualize therapy, strategies are being developed that may help to better stratify patients regarding therapy efficacy and safety using biomarker and genetic tests. Providing genetic markers that can predict responsiveness and optimal dosage in order to individualize treatment is the major goal of the emerging field of pharmacogenetics. Pharmacogenetic research focuses on variations in the human genome that impact upon drug metabolism, drug targets or signal transduction/metabolic pathways. These variation, termed single nucleotide polymorphism (SNPs), affect the function of metabolic enzymes in the Phase I pathway (for example, CYP2D6; CYP2C) but also Phase II metabolism (NAT2, DPYD, TPMT etc.), but also drug transport (for example, MDR1 transporter). Thus, one pathway by which SNPs affect drug responses can be explained by their significant effect upon pharmacokinetics. It is, therefore, clear to see that many investigators focus upon SNPs that may predict pharmacokinetics in order to use this information for dose adjustment. However, other SNPs impact upon pharmacodynamics. A common C825T polymorphism in the gene GNB3, which encodes the β 3 subunit of heterotrimeric G proteins, has been associated with weight loss depending on physical activity, response to sibutramine in obese subjects, improvement of insulin sensitivity, and mood changes during total fasting. Genetic polymorphisms in the gene GNAS, which encodes the ‘stimulatory’ G protein Gas subunit (mediating the receptor-induced increase in cAMP)

can be shown to predict weight loss under sibutramine, but also identify patients who can lose weight under lifestyle changes alone. Moreover, these SNPs predict blood pressure and heart rate increases under sibutramine therapy. A variety of SNPs have been shown to predict pharmacokinetics and lipid changes under therapy with lipid lowering drugs, especially statins. The talk will give an introduction and overview of pharmacogenetics in the management of obesity and treatment of lipid abnormalities and discuss the hurdles that these new techniques will have to pass before routinely applied in clinical practices.

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