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Opinion Article

Target Gene Pharmacogenetics and the Associated Disease Pathway

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DESCRIPTION

Numerous instances where the polymorphism of the therapeutic target has been demonstrated and this has been linked to variations in drug response both *in vitro* and *in vivo*. The μ opioid receptor is the primary site of action for the majority of opiate pain relievers. In test systems, the mutant protein was three times more effective than the wild-type protein at interacting with the endogenous opioid b-endorphin. As a result, this Single Nucleotide Polymorphism (SNP) as well as others found in the gene's regulatory region may be connected to phenotypes like stress and pain perception in addition to multifactorial disorders like drug addiction. Inhibitors of the Angiotensin-Converting Enzyme (ACE) are used to lower blood pressure and proteinuria in people with hypertension. When compared to patients with the insertion genotype, patients with a deletion genotype at the ACE gene's intron 16 have been found to have higher levels of circulating ACE activity. In a brief research, it was discovered that individuals homozygous for the deletion allele did not benefit from a 6-month course of enalapril medication, although patients bearing the insertion allele did. Treatments that alter the 5-lipoxygenase pathway are targeted at people in whom leukotrienes contribute to disease vulnerability because asthma is a complex disorder. Patients are therefore assumed to have asthma that is not dependent on leukotrienes if they do not improve after receiving treatment with *ALOX5*-pathway modifiers.

A number of polymorphisms have been identified within the target genes, particularly the 2-adreno-receptor gene, which is one of the most commonly used asthma treatments, 2-Adrenergic Receptor (2-AR) agonists. Several studies have found links between SNPs in these genes and treatment response. According to one study, homozygotes for one allele were up to 5.3 times more likely than homozygotes for the other allele to respond to albuterol. Serotonin (5-hydroxytryptamine; 5-HT) is a neurotransmitter that plays a role in a variety of physiological processes. The serotonin transporter (*5-HTT*) has been identified as a target for diseases impacted by these processes, such as severe depression. A polymorphism in the promoter region of the *5-HTT* gene has been shown to affect the gene's transcriptional activity *in vitro*.

There are 14 subtypes of 5-HT receptors in psychiatric medicine, many of which are polymorphic and other therapeutic agents are directed at these receptors. A single amino acid change at position 124 in the 5HT-1B receptor increases the affinity of sumatriptan (used to treat migraines) for the mutant receptor by more than two fold.

This drug's high affinity for the vasoconstriction-mediating h5-HT1B receptor in the coronary artery may explain why it causes coronary vasospasm in a few number of patients. Clozapine is an antipsychotic medication prescribed to patients suffering from schizophrenia. An analysis of both samples revealed a link between both polymorphisms and clozapine response. Calcitonin, which is used to treat osteoporosis, inhibits bone resorption through receptors on osteoclasts.

The Japanese population has a much lower heterozygote frequency of this polymorphism, which could be linked to a higher incidence of vertebral fractures. Variation in genes, presumably involved in the disease process itself rather than drug absorption or metabolism, has been linked to variation in drug response. Patients with Alzheimer's Disease (AD) are frequently genotyped for the ApoE4 allele, which is linked to disease susceptibility as well as a poor prognosis. Pravastatin, a medication used to lower cholesterol, was the focus of another pharmacogenetic study in the field of cardiovascular medicine.

CONCLUSION

The rarer allele of a polymorphism in the Cholesterol Esterase Transfer Protein (CETP) gene was linked to pravastatin response. The B1 allele was linked to higher CETP concentrations, faster atherosclerosis progression and response to pravastatin, as measured by an increase in mean luminal diameter. Patients with the B2B2 genotype (16% of a study group of 807 men) had no significant increase in mean luminal diameter, despite having significantly lower cholesterol levels. Patients with the B1B2 genotype had an intermediate response to the drug. Although both studies found strong associations between genotype and clinical response, neither found a complete correlation, indicating that genetic associations involving genes in the disease pathway, rather than the drug's target or transporters, are likely to be complex and multifactorial in nature.

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