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Precision Medicine Communications

DOI: doi.org/10.55627/pmc.001.001.0071-0075

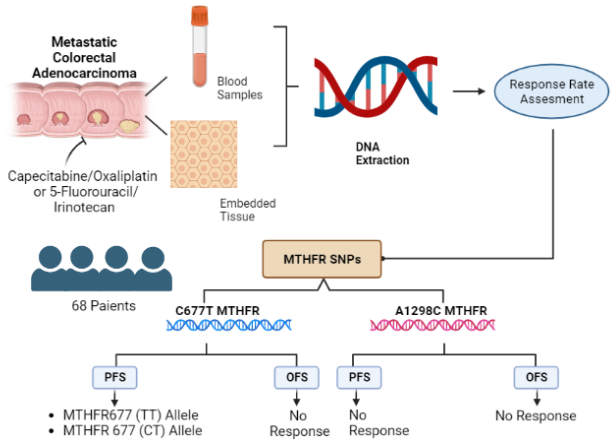
Editor's Choice

Editor's Selection of the Important Research Investigations in the Field of Precision Medicine from Around the World

Editorial Staff

MTHFR Gene Polymorphisms and Response to Chemotherapy in Metastatic Colorectal Cancer (doi.org/10.55627/pmc.001.001.0075)

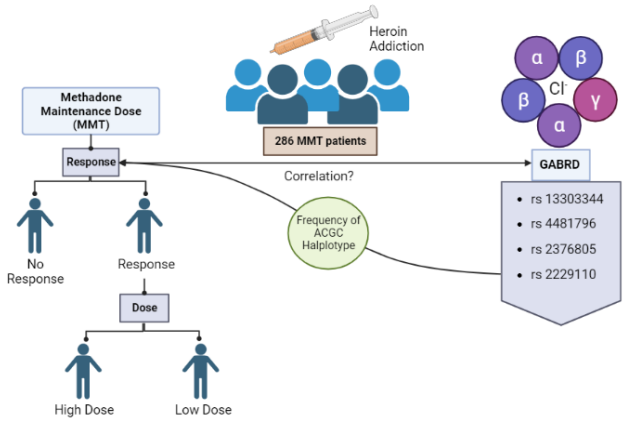
Ramos-Esquivel and colleagues investigated the association between the first-line fluoropyrimidine-based chemotherapy administered to patients diagnosed with metastatic colorectal adenocarcinoma and C677T, A1298C single nucleotide polymorphisms (SNPs) of the enzyme methylenetetrahydrofolate reductase (*MTHFR)*. Between January 2019 and November 2020, 68 individuals admitted to San Juan de Dios Hospital in Jose, Costa Rica, were subjected to a prospective follow-up. Capecitabine/5-fluorouracil was co-administered with oxaliplatin/irinotecan. Their findings reveal that patients that were homozygotes for the wildtype allele demonstrated a poorer overall response rate as compared to those that possessed one or both *MTHFR677T* T alleles. *MTHFR* A1298C genotypes and overall response exhibited no association. Patients with progression-free survival did not contain the *MTHFR* 677 TT and CT genotypes compared to CC individuals. These conclusions continued to hold post-adjustment of confounding factors. A hazard ratio of 1.35; 95% CI, 0.72–2.55; $P = 0.34$ showed no association between progression-free survival and the *MTHFR* A1298C SNP. Moreover, no SNP was associated with overall survival. The authors conclude that *MTHFR C677T* SNP homozygotes and heterozygotes had a better overall response and longer progression-free survival than patients that were homozygous for the wildtype allele. ***Pharmacogenet Genomics***. 2021 Dec 1;31(9):191-199.



Genetic Polymorphisms in GABRD and Treatment Response and Dose in Methadone Maintenance Treatment (doi.org/10.55627/pmc.001.001.0073)

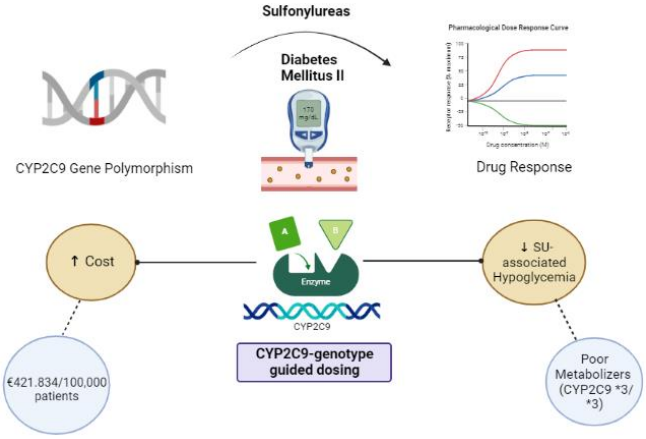
Xie and colleagues studied the association between the genetic polymorphs of the GABA receptor *delta* subunit (*GABARD*) and dose response to methadone in heroin addicts subjected to methadone maintenance therapy (MMT) was studied. They investigated two groups: responders and non-responders, were created from a total of 286 recruited MMT patients where the parameter for classification was retention time

in therapy. According to stabilized methadone dose, 177 patients were divided into subgroups of high dose and low dose. TaqMan SNP assay was used for *GABRD* genotyping, and the following single nucleotide polymorphisms (SNPs) were identified rs2376805, rs13303344, rs2229110, and rs4481796. MMT treatment response and dose showed no significant association with the SNPs, whereas the ACGC haplotype for the 4 SNPs varied slightly between the non-responder and responder groups. They concluded that genetic polymorphs of the *GABARD* do not play a significant role in affecting treatment response to methadone *Per Med*. 2021 Sep;18(5):423-430.



Cost of Pharmacogenetic-Guided Therapy in Type-2 Diabetes Mellitus (doi.org/10.55627/pmc.001.001.0071)

Connections between drug response and genetic variations may serve to optimize patient care. Drug response in type 2 diabetes mellitus (T2D) has been associated with various genetic polymorphisms. One pharmacological drug class commonly used for T2D management is Sulfonylureas. Incidences of severe hypoglycemia have been reported in patients that possess the CYP2C9*3/*3 variant of the enzyme in patients with co-administered glimepiride. Fokoun and colleagues investigated CYP2C9 genotype data to find out if it can assist in managing sulfonylureas treatment regimens in patients about to start glimepiride. They also studied the possible impact on clinical and economic outcomes and the factors that can influence the cost-effectiveness of this approach. By adopting the perspective of the French national health insurance system, analysis was carried out over the course of 1 year using a decision tree. They found that €421 834 was the final cost for preventing a hypoglycemic episode per 100,000 individuals, of which the genotyping costs proved to be the most notable factor in the cost-effective incremental ratio.

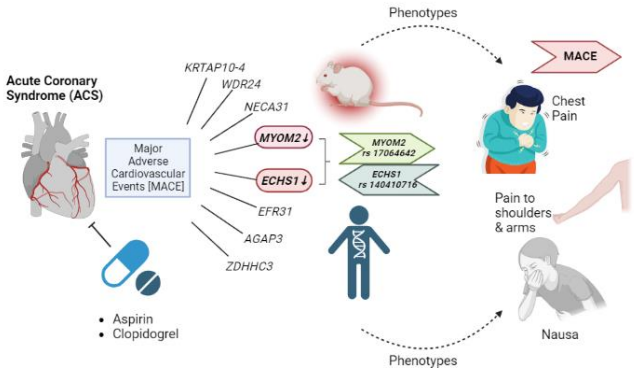


Their study concluded that CYP2C9 genotyping guiding for glimepiride dosing yielded modest improvements in the frequency of hypoglycemic events but at a relatively higher cost. However, further studies are indispensable to determine whether this cost can be reduced further. ***Pharmacogenomics J***. 2021 Oct;21(5):559-565.

Novel Genetic Variants Associated with Cardiovascular Events in Clopidogrel and Aspirin Users (doi.org/10.55627/pmc.001.001.0074)

Despite reports showing the effects of genetic variations on major adverse cardiovascular events in individuals suffering from acute coronary syndrome (ACS) and in patients undergoing percutaneous coronary intervention (PCI), the data studied until now covers only a minute fraction of the genetic variations of the human genome. Using two-stage large-scale sequencing data, consisting of high-depth exome sequencing of 168 patients in the discovery cohort and 1793 patients of the replication cohort subjected to high-depth targeted sequencing, Lie and colleagues discovered novel variants that show associations

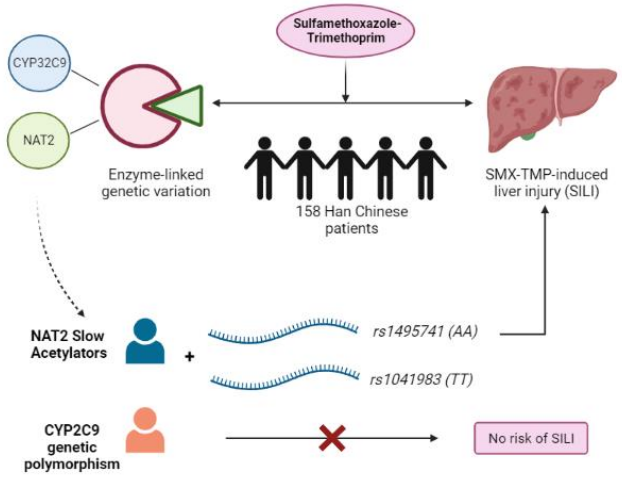
with major cardiovascular events in a 1.5-year-long follow-up.



MYOM2 (rs17064642), *ECHS1* (rs140410716), *AGAP3* (rs75750968), *WDR24* (rs11640115), *EFR3A* (rs4736529), *NECAB1* (rs74569896), *ZDHHC3* (rs3749187), and *KRTAP10-4* (rs201441480) were the eight novel genotypes that we found to bear associations with significant cardiovascular adverse effects in patients with ACS. *MYOM2* and *ECHS1*, interestingly, were downregulated both in human and animal models with adverse effect-related phenotypes. With AUC ranges between 0.92 and 0.94 for three machine-learning methods, Liu and colleagues were able to develop a superior classifier for predicting these adverse events over a period of 18 months. Their findings focus on predicting adverse cardiovascular outcomes and can aid clinicians in optimizing pharmacological intervention while treating patients suffering from ACS. ***Pharmacogenomics J***. 2021 Dec;21(6):664-672.

Hepatic Adverse Effects and Genetic Polymorphisms of NAT2 and CYP2C9 (doi.org/10.55627/pmc.001.001.0072)

Cotrimoxazole, also known as sulfamethoxazole-trimethoprim (SMX-TMP), is a well-established antibiotic combination in clinical medicine. Post metabolism by N-acetyltransferase (NAT) and Cytochrome P450 2C9 (CYP2C9), SMX is bio-transformed into non-toxic and/or toxic intermediates. The pharmacogenetic associations between the variants of these genes and liver injury caused by SMX-TMP are still a mystery. Huang and colleagues studied Han Chinese diabetes patients living in Taiwan. They investigated their susceptibility to SMX-TMP-induced Liver injury (SILI) and polymorphisms in the genes of both NAT and CYP2C9 enzymes. There were 145 controls and 158 SILI patients recruited for this investigation. CYP2C9 rs1799853, rs1057910, and rs4918758, NAT2 rs1495741, rs1041983, rs1801280, and other major genetic variants of these enzymes were assayed. NAT2 rs1495741 variant AA genotype and rs1041983 variant TT were present at a higher frequency in the SILI group than in the control group. Slow acetylators were greater in the SILI than the control (43.7 vs. 25.5%; P = 0.001). CYP2C9 variants, interestingly, did not show any significant difference between the control and SILI cohorts.



Individuals that were NAT2 slow acetylators were at a greater risk of SILI post adjustment of confounding factors, particularly those that had mixed type and hepatocellular SILI. Their study concluded that CYP2C9 genetic polymorphisms are not associated with SILI susceptibility, whereas NAT2 slow acetylators are at an increased risk of SILI in the Han Chinese population. ***Pharmacogenet Genomics***. 2021 Dec 1;31(9):200-20.

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