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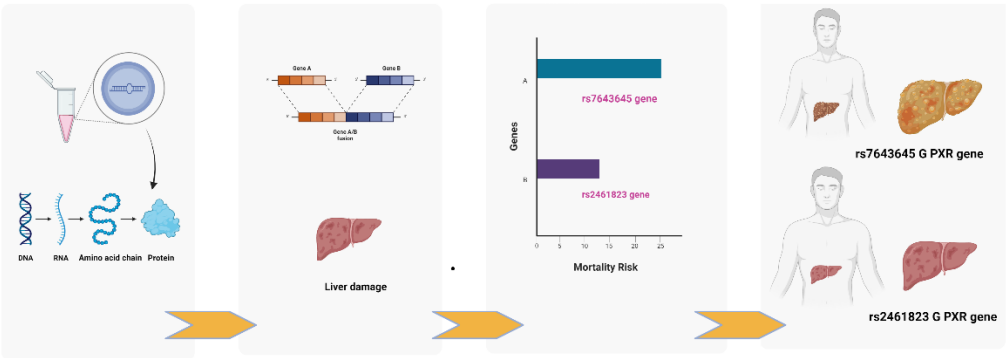
Editor's Choice

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

Editorial Staff

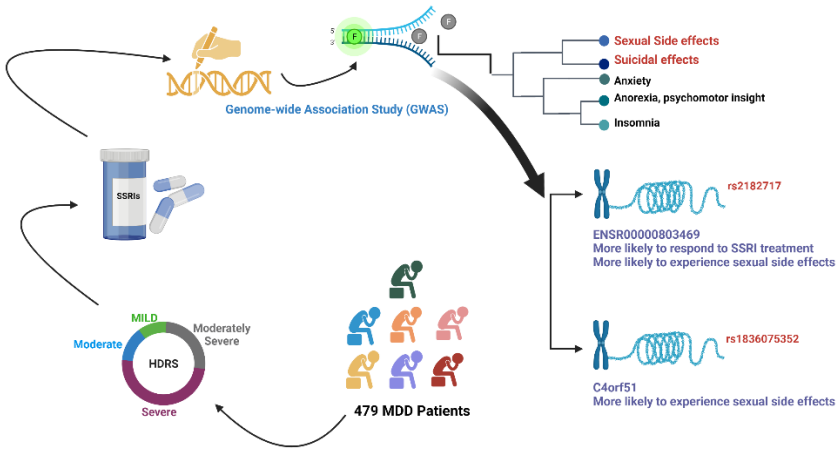
Pregnane X Receptor Gene Variation and Total Mortality in Nonalcoholic Fatty Liver Disease

The pregnane X receptor (PXR) is a nuclear receptor that plays a role in regulating the metabolism and clearance of drugs and xenobiotics in the liver. Variations in the PXR gene, including the rs7643645 variant, have been associated with altered PXR activity and potential implications for various liver-related conditions, including nonalcoholic fatty liver disease (NAFLD). It is known that the more progressive the NAFLD, the higher the hepatic and extra-hepatic mortality and morbidity. Käräjämäki et al investigated the total mortality in Finnish middle-aged ultrasonographically verified NAFLD patients with PXR rs7643645 variants. In up to 30 years of follow-up, PXR rs7643645 GG subjects were at an increased risk of total mortality compared with AA/AG subjects. The statistically significant difference prevailed after multiple adjustments for potentially confounding factors, RR, 2.024 (1.191-3.440), P = 0.009. In the subjects without NAFLD, the mortality risk was not associated with rs7643645 variants, 1.051 (0.708-1.560; P = 0.804). As the rs7643645 G variant disrupts a putative hepatocyte nuclear factor 4α binding site located in the PXR gene promoter and is associated with lower hepatic expression of PXR and its target genes, their result suggests that genetic disruption of xenobiotic metabolism increases mortality in subjects with NAFLD. ***Pharmacogenet Genomics***. 2023 Feb 1;33(2):35-39. doi: 10.1097/FPC.0000000000000489.



Side Effects and Genetic Variation During Depression in Taiwanese Han Population

Genetic variation can play a role in individual differences in the response to medications used for the treatment of depression, as well as in the occurrence of side effects. While there have been studies investigating genetic factors associated with antidepressant response and side effects, it is important to note that the field of pharmacogenetics is complex and influenced by multiple genetic and environmental factors. In the case of the Taiwanese Han population and depression, limited specific studies examining the relationship between genetic variation and antidepressant response or side effects have been conducted. Huang and colleagues analyzed the syndromal factor structures of the Hamilton Depression Rating Scale in 479 patients with MDD by using exploratory factor analysis. All patients were followed up biweekly for 8 weeks. In total, 33 independent SNPs for treatment responses were tested in a mixed model, 12 of which demonstrated a p value <0.05. The most significant SNP was rs2182717 in the ENSR00000803469 gene located on chromosome 6 for the core syndromal factor (β = -0.638, p = 1.8×10^{-4}) in terms of symptom improvement over time. Patients with a GG or GA genotype with the rs2182717 SNP also exhibited a treatment response (β = 0.089, p = 2.0×10^{-6}) at week 4. Moreover, rs1836075352 was associated with sexual side effects (p = 3.2×10^{-8}). Pathway and network analyses using the identified SNPs revealed potential biological functions involved in treatment response, such as neurodevelopment-related functions and immune processes. In conclusion, they identified loci that may affect the clinical response to treatment with antidepressants in the context of empirically defined depressive syndromal factors and side effects among the Taiwanese Han population, thus providing novel biological targets for further investigation. ***Pharmacogenomics J.*** 2023 May;23(2-3):50-59. doi: 10.1038/s41397-023-00298-8.

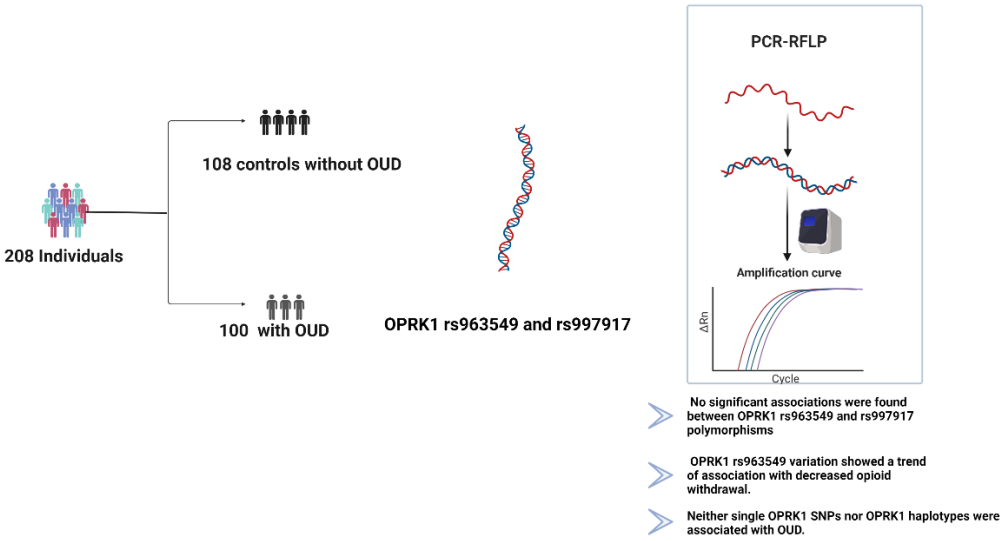


Genetic Variation in *OPRK1* Gene and Opioid Use Disorder

The OPRK gene encodes the kappa opioid receptor, which is involved in modulating the effects of opioids in the brain. Polymorphisms in the OPRK1 gene have been investigated for their potential association with opioid use disorder (OUD) and related phenotypes. OUD refers to a problematic pattern of opioid use characterized by a loss of control over use, craving, and negative consequences. To evaluate the association between *OPRK1* rs963549 and rs997917 and opioid use disorder (OUD) and related

phenotypes, Özkan-Kotiloğlu et al conducted a study.

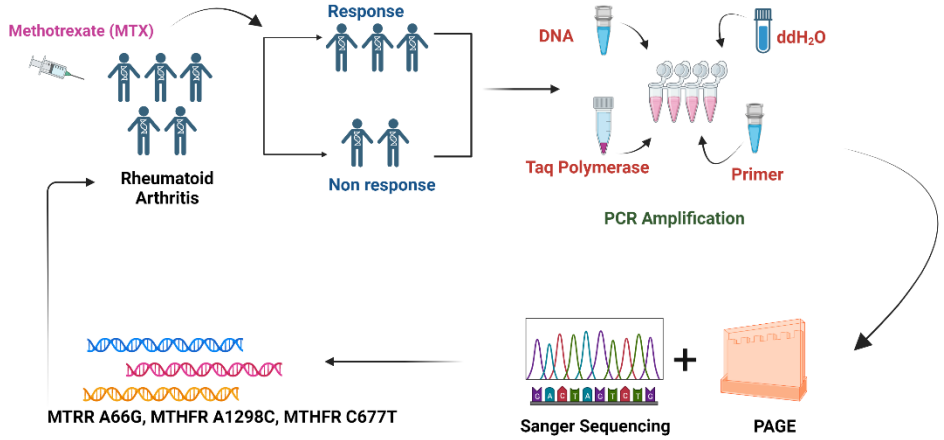
A sample of 208 individuals with (n = 100) and without (n = 108) OUD were enrolled. *OPRK1* rs963549 and rs997917 were analyzed by PCR-RFLP. Craving, opioid withdrawal and the intensity of depressive and anxiety symptoms were measured by the appropriate scales. *OPRK1* rs963549 variation showed a trend of association with decreased opioid withdrawal. No significant associations were found between *OPRK1* rs963549 and rs997917 polymorphisms and craving, depression or anxiety symptoms. Neither single *OPRK1* SNPs nor *OPRK1* haplotypes were associated with OUD. Their results could be useful for treatment failures of individuals who experience greater opioid withdrawal due to their *OPRK1* rs963549 genotypes. ***Pharmacogenomics.*** 2023 May 11. doi: 10.2217/pgs-2023-0037. Online ahead of print.



Genetic Polymorphism & Methotrexate Therapy Outcomes in Rheumatoid Arthritis

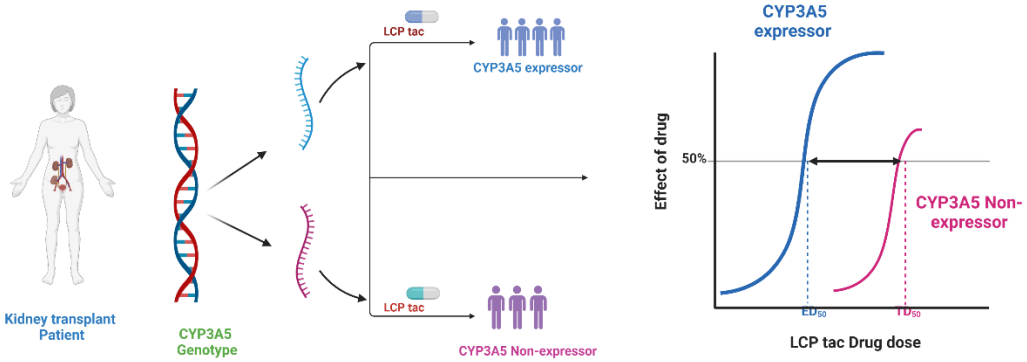
Methotrexate (MTX) is commonly used as a disease-modifying antirheumatic drug (DMARD) for the treatment of rheumatoid arthritis (RA). Genetic polymorphisms in key enzymes involved in MTX metabolism, such as methyl tetrahydrofolate reductase (MTHFR) and methionine synthase reductase (MTRR) have been studied for their potential impact on MTX therapy outcomes in early RA patients. Zhang et al investigated a population of 32 patients in East China with early RA fulfilling the diagnostic standards of the American College of Rheumatology (ACR) were enrolled, all of them received MTX monotherapy. Genotyping of patients MTHFR C677T and A1298C, MTRR A66G using tetra-primer ARMS-PCR method and sanger sequencing to verify its accuracy. The distribution of three polymorphic genotypes that were studied is in accordance with the Hardy-Weinberg genetic equilibrium. The patient pathology variables smoke (OR = 0.088, P = 0.037), drink alcohol (OR = 0.039, P = 0.016) and males (OR = 0.088, P = 0.037) were significantly associated with non-response to MTX. Genotype, allele distribution and genetic statistical models were not found to be related to MTX treatment response and disease activity in both the response groups and non-response groups. Their findings suggest that the MTHFR C677T, MTHFR A1298C and MTRR A66G polymorphisms may not predict MTX clinical treatment response and disease activity in patients with early RA. The study revealed that smoke,

alcohol, and males were possible influential factors for MTX non-response. ***Pharmgenomics Pers Med***. 2023 May 2;16:407-423. doi: 10.2147/PGPM.S404949. eCollection 2023.



Impact of CYP3A5 Genotype on De-novo LCP Tacrolimus Dosing in Kidney Transplantation

The CYP3A5 gene encodes an enzyme called cytochrome P450 3A5, which is involved in the metabolism of many drugs, including tacrolimus. Tacrolimus is an immunosuppressive medication commonly used in kidney transplantation to prevent organ rejection. The CYP3A5 genotype can influence the metabolism and clearance of tacrolimus, leading to variations in the drug levels and response.



LCP tac (an extended release form of tacrolimus) has a recommended starting dose of 0.14 mg/kg/day in kidney transplant. Rao et al assessed the influence of CYP3A5 genotypes on perioperative LCP tac dosing and monitoring in adult kidney recipients receiving de-novo LCP tac. CYP3A5 genotype was measured and 90-day pharmacokinetic and clinical were assessed.

Patients were classified as CYP3A5 expressors (*1 homozygous or heterozygous) or nonexpressors (LOF *3/*6/*7 allele). They concluded that CYP3A5*1 expressors require higher doses of LCP tac to achieve therapeutic concentrations and are at higher risk of subtherapeutic trough concentrations, persisting for 30-day posttransplant. LCP tac dose changes in CYP3A5 expressors are more likely to be under-adjusted by providers. ***Pharmacogenet Genomics.*** 2023 Apr 1;33(3):59-65. doi: 10.1097/FPC.0000000000000494.

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