Journal of Pharmacogenomics & Pharmacoproteomics

Puranik and Niewold, J Pharmacogenomics Pharmacoproteomics 2016, 7:3
DOI: 10.4172/2153-0645.1000e155

Editorial OMICS International

Pharmacogenomics of Methotrexate in Diverse Populations

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Received date: Sep 26, 2016; **Accepted date:** Sep 27, 2016; **Published date:** Oct 08, 2016

Editorial

Methotrexate (MTX) is a commonly used disease modifying antirheumatic drug (DMARD) for the treatment of RA because of its affordability, long-term efficacy and acceptable toxicity profile. MTX is also frequently used in the treatment of other forms of inflammatory arthritis. Although MTX is considered to be a well-tolerated DMARD, there is a significant inter-patient variability in the toxicity and efficacy of MTX treatment. MTX treatment response is often multi-factorial, resulting from complex interplay of various factors such as age, sex, ethnicity, disease duration, disease severity and activity, presence of C-reactive protein and RF factor. It is also clear that genetic factors [1] also make an important contribution to treatment variability.

Folate metabolism is the key therapeutic target of MTX, and numerous studies support the idea that genetic variations in genes encoding Folate-MTX transporters and metabolizing enzymes may impact MTX therapeutic outcome by affecting efficiency of these enzymes [1-3]. While genetic variation in the folate metabolic pathway is clearly important across multiple world populations in MTX response and toxicity, there are considerable differences in pathway polymorphisms between world populations [4-7]. Studies of MTX pharmacogenetics completed thus far have generally not been characterized by broad inclusion of representative world populations, and in some cases lack validation studies [2,8]. In recent work, we have reported significant differences in the allele frequency of SNPs in the folate metabolic pathway in Indian (Asian) subjects as compared to other populations [7]. Many of the comprehensive MTX pharmacogenetics studies till today have mostly been conducted on Western and East Asian population and there is sparse data available in Indian (Asian) RA population [7,9-13]. To address this gap in the literature in our recent study we assessed the influence of genetic variation in 9 potentially important folate-MTX metabolic pathway genes with MTX response (efficacy and toxicity) and pharmacokinetics endpoints in Indian RA patients [14]. We found that of the 12 SNPs analyzed, SNPs in GGH promoter; SHMT1; TS 5' UTR variable tandem repeats and TS 3' UTR deletion was linked with MTX related adverse events (AE) either organ specific or overall AE whereas SNPs in MTHFR and RFC1/SLC19A1 were associated with MTX efficacy. TS5'UTR and SHMT1 polymorphisms were associated with higher plasma levels of MTX while significant correlation was found between the RFC1 nonsynonymous SNP rs1051266 and plasma homocysteine levels in these RA patients [14]. For each patient a toxicogenetic index was calculated using homozygous risk genotypes that showed statistically significant association with adverse events. The toxicogenetic index ranged from 0 to 4. We observed that as the toxicogenetic index increases the percentage of the patients with AE increases. Patients with the highest TI were 2.63 times more likely to present with an AE compared with those with the lowest index of 0. Based on our results we proposed that toxicogenetic index can be used as predictive marker to identify patients who develop adverse events to MTX however further prospective studies are needed to validate its utility as pharmacogenetic predictor. Furthermore, in our study we did not find any significant associations or replicate previous associations of SNPs within the genes MS, MDR1, MTRR and ATIC with MTX efficacy or toxicity [1-3,15]. This study shows Indian (Asian) population is different from other world population and hence it is risky to generalize the results of genetic associations impacting MTX treatment response in subjects of European and African origin to the Indian population. This provides an example that population-specific allele frequency and pharmacogenomic data is required to identify potential risk groups for toxicity and to optimize drug doses for treatment efficacy.

In this study we demonstrated some new associations with MTX-related toxicity in Indian RA patients, including the GGH promoter SNP rs3758149, TS 5' UTR variable tandem repeats, and a TS 3' UTR deletion. These SNPs have previously been associated with MTX dose and MTX efficacy in other ancestral backgrounds [1,3]. The association of the SHMT1 1420C allele with MTX related AE reported in our study is in agreement with the previously reported observations in other ancestral backgrounds [16]. Recently, the RFC1 80G/A SNP have been associated with MTX efficacy in a meta–analysis of several independent observational studies [17]. We observed a similar association in our Indian RA cohort [14]. MTHFR C677T and A1298C are the most widely studied SNPs in relation to MTX toxicity or efficacy. Many studies have explored associations of these SNPs with MTX efficacy and toxicity in different ethnic backgrounds, though the results reported to date are somewhat conflicting [1-3,9,15,18]. Similar to some previous studies [18,19], there was no evidence of association between these SNPs with MTX related toxicity in our Indian RA cohort, while Dutch and Japanese RA patient cohorts showed association of MTHFR A1298C with greater clinical improvement with MTX [20,21].

From the above reports, it is evident that significant diversity exists in MTX pharmacogenomics between populations. Differences in the frequency of gene variants between ancestral backgrounds may result in a differential incidence of MTX related efficacy or toxicity. Given the high prevalence of ethnic differences in allele frequencies in folate pathway genes, it is possible that folate pathway variation may have been impacted by recent human evolution in different world populations. And it is also likely that the common polymorphisms may individually exhibit subtle alterations in enzymatic activity may act in synergistic ways when present with other polymorphisms in the same pathway. Therefore generating pharmacogenomic/toxicogenetic

indexes using combination of SNPs could provide more predictive power for treatment response or toxicity than individual markers considered separately. Other reasons for the heterogeneity between the available MTX pharmacogenomic studies could include differences in patient demographics, differences in outcome measures applied, mixed treatment response definitions, insufficient statistical power, and pharmacological/clinical confounders [2,18]. Nevertheless, variants in few candidate genes have shown reliable associations as potential predictors of MTX efficacy and toxicity. These polymorphisms should be further evaluated in large diverse populations and assessed in prospective pharmacogenetic studies [1,3,19]. Even though use of biologics for RA is rapidly-growing choice of treatment in developed countries, MTX still remains one of the most commonly used treatments for RA, justifying continuing pharmacogenetic studies in multiple world populations.

Funding Sources

Ghodke-Puranik Y–none, Niewold TB–Research grants from the NIH (AR060861, AR057781, AR065964, AI071651), Rheumatology Research Foundation, Cure JM Foundation, the Mayo Clinic Foundation, and the Lupus Foundation of Minnesota.

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