



PHARMACOGENOMIC DETERMINANTS OF TREATMENT RESPONSE IN OSTEOARTHRITIS: THE ROLE OF ABCB1 (MDR1) GENE POLYMORPHISMS IN PERSONALIZING DISEASE-MODIFYING THERAPY

Ziyotdinova Dilnavo Vokhid kizi

Mamatmuminov Temurbek Bakhtiyorovich

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ABSTRACT

Osteoarthritis is the most prevalent chronic joint disorder worldwide and a leading cause of pain, functional limitation, and disability among adults and elderly populations. Traditionally considered a degenerative disease driven primarily by mechanical wear and tear, osteoarthritis is now recognized as a complex, multifactorial condition involving low-grade inflammation, metabolic dysregulation, genetic susceptibility, and alterations in subchondral bone remodeling. The global burden of osteoarthritis continues to rise due to aging populations, increasing obesity rates, and sedentary lifestyles. Despite advances in symptomatic management, many patients experience persistent pain, progressive structural damage, and substantial deterioration in quality of life.

Introduction

Osteoarthritis is the most prevalent chronic joint disorder worldwide and a leading cause of pain, functional limitation, and disability among adults and elderly populations. Traditionally considered a degenerative disease driven primarily by mechanical wear and tear, osteoarthritis is now recognized as a complex, multifactorial condition involving low-grade inflammation, metabolic dysregulation, genetic susceptibility, and alterations in subchondral bone remodeling. The global burden of osteoarthritis continues to rise due to aging populations, increasing obesity rates, and sedentary lifestyles. Despite advances in symptomatic management, many patients experience persistent pain, progressive structural damage, and substantial deterioration in quality of life.

Pharmacological treatment of osteoarthritis focuses predominantly on symptom control rather than disease modification. Nonsteroidal anti-inflammatory drugs, selective cyclooxygenase-2 inhibitors, intra-articular corticosteroids, and symptomatic slow-acting drugs are commonly used. In more severe cases, off-label application of disease-modifying antirheumatic agents or biologically active compounds has been explored, particularly in inflammatory phenotypes of osteoarthritis. However, therapeutic response varies considerably between individuals. Some patients achieve sustained pain relief and functional improvement, whereas others show minimal benefit or develop adverse drug reactions that limit long-term use.

This variability in treatment response has prompted increasing interest in pharmacogenomics, the study of how genetic variations influence drug metabolism, efficacy, and toxicity. Personalized medicine seeks to tailor therapeutic strategies according to the genetic profile of each patient, thereby maximizing efficacy and minimizing harm. Among the genes implicated in pharmacokinetics and pharmacodynamics, the ATP-binding cassette subfamily B member 1 gene, commonly known as ABCB1 or MDR1, occupies a central role. This gene encodes P-glycoprotein, a transmembrane efflux transporter that regulates the absorption, distribution, and elimination of numerous medications by modulating intracellular drug concentrations.

P-glycoprotein is expressed in various tissues, including the intestinal epithelium, liver, kidneys, blood–brain barrier, and synovial tissue. By actively transporting substrates out of cells, it influences systemic bioavailability and local tissue exposure to pharmacological agents. Polymorphisms within the ABCB1 gene may alter transporter expression or function, thereby affecting therapeutic response. Several single nucleotide polymorphisms have been extensively studied, including C1236T, G2677T/A, and C3435T. These variants have been associated with altered drug plasma levels, differential treatment outcomes, and susceptibility to adverse effects across multiple medical disciplines.

In inflammatory and degenerative joint diseases, the relevance of ABCB1 polymorphisms is particularly intriguing. Although osteoarthritis is distinct from rheumatoid arthritis in pathogenesis, subsets of patients exhibit inflammatory features that respond variably to disease-modifying agents and immunomodulatory therapies. Moreover, analgesics, anti-inflammatory medications, and certain adjunctive treatments used in osteoarthritis are substrates of P-glycoprotein. Genetic variation in ABCB1 may therefore contribute to heterogeneity in clinical outcomes.

Emerging data suggest that pharmacogenomic profiling can identify patient subgroups more likely to benefit from specific medications or require dose adjustments. In osteoarthritis, where long-term therapy is common and polypharmacy is frequent due to comorbid conditions, understanding drug transporter genetics may improve safety and efficacy. Furthermore, older patients—who represent the majority of osteoarthritis cases—often exhibit altered pharmacokinetics due to age-related physiological changes, making genetic considerations even more relevant.

The concept of individualized therapy extends beyond selecting a drug; it encompasses determining optimal dosing, predicting remission or symptom stabilization duration, and anticipating adverse reactions. In the context of chronic musculoskeletal disorders, sustained symptom control is crucial for preserving mobility, independence, and psychosocial well-being. Treatment failure not only prolongs pain but also accelerates structural deterioration and increases healthcare utilization.

Despite growing interest, research on ABCB1 polymorphisms in osteoarthritis remains limited compared to autoimmune rheumatic diseases. Most pharmacogenetic investigations have focused on methotrexate or biologic therapies in inflammatory arthritis. However, as therapeutic strategies for osteoarthritis evolve to include agents targeting inflammatory mediators and cartilage metabolism, transporter genetics may become increasingly relevant.

Additionally, nonsteroidal anti-inflammatory drugs and certain central analgesics are known P-glycoprotein substrates, further supporting the importance of exploring ABCB1 variability.

The present study aims to evaluate the association between common ABCB1 gene polymorphisms and clinical response to pharmacological therapy in patients with osteoarthritis. By analyzing the distribution of C1236T, G2677T, and C3435T variants and correlating genotypes with disease activity, pain reduction, and remission duration, this research seeks to contribute to the development of precision-based treatment algorithms. Understanding how genetic differences influence therapeutic outcomes may facilitate more rational prescribing practices, reduce adverse effects, and improve long-term patient satisfaction.

In addition, this study explores whether specific genotypes predict sustained symptomatic improvement or necessitate alternative therapeutic strategies. Identifying genetic markers associated with suboptimal response could guide early treatment modification, preventing prolonged ineffective therapy. Ultimately, integrating pharmacogenomic insights into routine rheumatologic care has the potential to transform management paradigms for osteoarthritis and other chronic joint disorders.

Materials and Methods

A total of 92 patients diagnosed with primary knee or hip osteoarthritis according to established clinical and radiographic criteria were enrolled in this prospective observational study. The age of participants ranged from 40 to 70 years, with a mean age of 56.8 ± 9.4 years. The cohort included 58 women and 34 men. The average disease duration was 5.2 ± 3.7 years. A control group of 30 healthy individuals without musculoskeletal disorders was included for comparative genotypic analysis.

Inclusion criteria comprised confirmed osteoarthritis with moderate to severe pain requiring pharmacological therapy and willingness to provide informed consent. Patients with inflammatory rheumatic diseases, malignancy, severe hepatic or renal dysfunction, or recent joint surgery were excluded.

Clinical evaluation included assessment of pain intensity using the Visual Analog Scale and functional status measured by the Western Ontario and McMaster Universities Osteoarthritis Index. Radiographic staging was performed using the Kellgren–Lawrence grading system. Blood samples were collected for genotyping of ABCB1 polymorphisms C1236T, G2677T, and C3435T using real-time polymerase chain reaction with allele-specific probes.

All patients received standardized pharmacological treatment consisting of nonsteroidal anti-inflammatory drugs as first-line therapy. In cases of insufficient response, adjunctive agents including symptomatic slow-acting drugs or low-dose immunomodulatory therapy were administered according to clinical indication. Patients were followed for twelve months, and treatment response was categorized as sustained improvement, partial response, or non-response based on predefined criteria.

Statistical analysis involved genotype frequency comparison between patients and controls, as well as correlation analyses between genotypes and clinical outcomes. Multivariate regression was performed to adjust for age, sex, disease duration, and body mass index.

Results

Genotyping revealed that the C1236T polymorphism was the most prevalent variant in both patient and control groups. The distribution of genotypes was consistent with Hardy-Weinberg equilibrium. Among osteoarthritis patients, individuals carrying the TT genotype of C3435T demonstrated a significantly greater reduction in pain scores and improved functional indices compared to CC homozygotes. Heterozygous CT carriers exhibited intermediate responses.

Patients with the CC genotype at position 3435 were more likely to experience persistent pain despite therapy and required escalation to combination treatment. Furthermore, the TT genotype was associated with longer duration of symptomatic remission and reduced need for additional analgesics. A significant correlation was observed between C3435T polymorphism and improvement in functional capacity over the twelve-month follow-up period.

No statistically significant association was identified between G2677T polymorphism and radiographic progression; however, carriers of variant alleles reported fewer gastrointestinal adverse effects during nonsteroidal anti-inflammatory drug therapy. Multivariate analysis confirmed C3435T genotype as an independent predictor of therapeutic response after adjustment for confounding variables.

Discussion

The findings of this study suggest that ABCB1 polymorphisms, particularly C3435T, influence clinical response to pharmacological therapy in osteoarthritis. The TT genotype appears to be associated with enhanced treatment efficacy and prolonged symptomatic control. This observation may be explained by altered P-glycoprotein expression leading to increased intracellular drug concentration within synovial tissues, thereby enhancing therapeutic effect.

Conversely, CC homozygotes may exhibit higher efflux activity, reducing local drug availability and attenuating response. These patients may benefit from alternative agents not primarily transported by P-glycoprotein or from adjusted dosing strategies. The absence of strong associations with radiographic progression indicates that transporter polymorphisms may primarily influence symptomatic rather than structural outcomes.

The study underscores the potential value of incorporating pharmacogenomic testing into osteoarthritis management. Although routine genetic screening is not yet standard practice, declining costs and improved accessibility of molecular diagnostics make implementation increasingly feasible. Personalized therapy guided by ABCB1 genotype could reduce trial-and-error prescribing and enhance patient-centered care.

Limitations include moderate sample size and single-center design. Larger multicenter studies are warranted to validate these findings and explore interactions with other pharmacokinetic and pharmacodynamic genes.

Conclusion

ABCB1 gene polymorphisms, particularly C3435T, play a significant role in modulating therapeutic response in osteoarthritis patients receiving pharmacological treatment. Carriers of the TT genotype demonstrate superior symptomatic improvement and longer remission duration, whereas CC homozygotes may require alternative or intensified therapy. These

results support the integration of pharmacogenomic principles into individualized treatment strategies for osteoarthritis. Future research should expand on these findings to establish standardized genetic-guided algorithms that optimize efficacy, minimize adverse effects, and improve long-term clinical outcomes.

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