# The Impact of ATIC (rs2372536) Polymorphism on Responsiveness to and Toxicity of Methotrexate (MTX) in Rheumatoid Arthritis

**Original Article**

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## ABSTRACT

**Background:** Rheumatoid arthritis (RA) is a chronic autoimmune disease marked by ongoing inflammation of the synovial membranes and chronic aggressive arthritis. Despite significant advances in RA treatment in recent years, the total remission rate remains concerning and once bone or joint tissue has been destroyed, it is so hard to return to its original status.

**Objective :** The current study aimed to examine the impact of 5-aminoimidazole-4-carboxamide ribonucleotide transformylase (ATIC) rs 2372536 C >G polymorphism on the responsiveness and toxicity of methotrexate treatment in Egyptian rheumatoid arthritis patients.

**Methods:** This cross-sectional study was performed on 50 rheumatoid arthritis patients. They were selected within the Rheumatology department at Ain Shams University Hospitals from January 2022 to January 2023. The enrolled patients were categorized into two groups in accordance to their response to methotrexate treatment: responders and non-responders. Determination of ATIC gene (rs 2372536) polymorphism was done by real-time PCR for all participants.

**Results:** After 3 months of methotrexate therapy, the enrolled patients were divided into 25 responders and 25 non-responders. ATIC gene rs 2372536 C >G showed a relationship to failure of response to methotrexate treatment in the recessive model [GG vs. (CC+CG)] ($p$ = 0.018). Also, the G allele was substantially found more in the non-responders ($p$= 0.045). Our study found no significant association between ATIC gene rs 2372536 C >G s polymorphism and the toxicity related to MTX.

**Conclusion:** Our results showed that ATIC gene rs 2372536 C >G polymorphism is linked to failure to react to methotrexate therapy in Egyptian rheumatoid arthritis patients but has no association with vulnerability to toxicity from the treatment.

**Key Words:** ATIC, methotrexate, polymorphism, rheumatoid arthritis.

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## INTRODUCTION

Rheumatoid arthritis is a multi- organ inflammatory disease primarily marked by synovium inflammation and joint destruction. The specific reason is unknown; however, genetic and environmental factors share in its development[1]. Complete curative therapy for RA has not been discovered yet. At present, disease modifying anti- rheumatic drugs (DMARDs) are frequently used to slow the course of symptoms and alleviate discomfort[2]. Methotrexate (MTX) is one of the DMARDs. It is used internationally to treat RA as it is affordable and efficient[3]. Yet, around 40% of patients receiving MTX therapy fail to attain recovery and 30% of patients have problems with tolerability and complications[4]. It is estimated that genetic variables or single-nucleotide polymorphisms (SNPs) stands for 15–30% of the variation in drug responses[5].

MTX penetrates the tissue and is converted to methotrexate polyglutamate by the folylpolyglutamate synthase enzyme[6]. This MTX polyglutamate inhibits Five-Aminoimidazole- 4 - Carboxamide Ribonucleotide Transformylase (ATIC), which normally converts aminoimidazole carboxamide adenosine ribonucleotide (AICAR) into formyl- AICAR. The inhibition of ATIC causes AICAR to accumulate intracellularly, which triggers the production of adenosine. The adenosine released into the extracellular space lowers neutrophil adherence and inactivates the activity of immune cells, resulting in powerful anti-inflammatory acts[7].

The most frequently studied genetic polymorphism as regard the ATIC gene is ATIC 347 C >G (rs 2372536) on exon 5, which leads to a swapping of threonine with serine at position 116 of the gene making it more thermolabile and reducing its activity[8].

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## AIM OF THE WORK

The present study sought to assess the impact 5- Aminoimidazole-4- Carboxamide Ribonucleotide Transformylase (ATIC) gene rs 2372536 polymorphism on methotrexate treatment responsiveness in Egyptian rheumatoid arthritis patients.

## PATIENTS AND METHODS

This cross- sectional study was performed on fifty rheumatoid arthritis patients who were gathered from the Rheumatology unit at Ain Shams University Hospital from January 2022 to January 2023.

### *Inclusion criteria*

Rheumatoid arthritis patients met the American College of Rheumatology/ European League Against Rheumatism 2010 criteria. All patients received low- dose methotrexate for minimum 3 months.

### *Exclusion Criteria*

i. Patients who have contraindications to MTX therapy,

ii. Patients who were receiving any biological treatment concomitantly during the 3 months before the enrollment in the study,

iii. Pregnancy or lactation,

iv. Refusing to give consent to participate in the study.

The enrolled patients were categorized according to their response to methotrexate treatment into two groups: respondents and non-respondents.

**All patients underwent**

I) Full history taking, II) Clinical evaluation and assessment of disease activity state by reporting DAS28-ESR[9]. III)Radiological evaluation including CT-scan. IV)Laboratory Investigations: Complete Blood Picture which was performed by ADVIA (120 hematology system, Siemens Healthineers, Germany), Rheumatoid factor and Anti-CCP which were analyzed by Cobas E411 (Roche Diagnostic GmbH, Mannheim, Germany), creatinine, AST, ALT, alkaline phosphatase, direct and indirect bilirubin which were assayed by COBAS C6000( Roche Diagnostic GmbH, Mannheim, Germany) and Determination of ATIC gene rs2372536 C>G polymorphism using Real Time-PCR.

### *Sampling*

Under complete aseptic conditions, ten mL of blood was taken out of all subjects. 3 mL of blood were delivered into an EDTA vacutainer and stored at -20°C to be used for DNA extraction and detection of ATIC (rs2372536) gene polymorphism by PCR. The remaining 7 mL of blood was distributed between 1) Citrate tube for assay of ESR. 2) Gel separating tube for assay of creatinine, anti-CCP, rheumatoid factor, ALT, total bilirubin, direct bilirubin, and alkaline phosphatase. 3) EDTA tube for complete blood count (CBC).

### *Assay of ATIC gene (rs2372536) polymorphism by Real-Time PCR*

I)The Gene JET whole blood genomic DNA purification mini equipment was employed for the quick and efficient extraction of high-quality genomic DNA from whole blood. The extraction process begins with the digestion of samples using proteinase K in the provided lysis solution. The resulting lysate is mixed with ethanol and loaded onto the purification column, where the DNA adheres to the silica membrane. Impurities are effectively eliminated by washing the column with a prepared wash buffer. Finally, genomic DNA is eluted using an elution buffer under low ionic strength conditions.

II) Genotyping for ATIC (rs2372536) single nucleotide polymorphism was detected by TaqMan real-time PCR, ready-to-use kit. The probe sequence for (rs2372536) was as follows: AAGACAGTGGCTTCTCCAGGTGTAA(C/G) TGTTGAGGAGGCTGTGGAGCAAATT.

### *Statistical Methods*

Data were gathered and analysed using the Statistical Package for Social Science (IBM SP SS) version 23. The numbers for parametric factors were provided as mean and standard deviation. Numbers for non-parametric factors were provided as median and inter-quartile range (IQR). Qualitative data were displayed as numbers and percentages.

The chi-square test was used to put into comparison the different qualitative parameters. Quantitative parametric data were put in comparison using independent t-test. Mann-Whitney test was used for comparison of quantitative non- parametric data. *P-value* <0.05 as significant, *P-value* <0.01 as highly significant and *P-value* >0.05 as not significant.

## RESULTS

Study included 50 RA arthritis patients who were categorized in two categories based on their response to methotrexate treatment: responders (no:25) and non-responders (no:25). Demographic data and clinical features of the two categories are displayed in (Table 1). It reveals no significant difference between both groups except for the DAS28 score being significantly higher in the non-respondents.

The Comparative statistics between both groups regarding the laboratory parameters are illustrated in (Table 2). It shows no significant difference between both groups except for ESR levels being significantly higher in the non-respondents.

**Table 1:** Comparative statistics of demographic data and clinical characteristics between respondents and non-respondents.

| Parameters | | Non-responders (No.=25) | Responders (No.=25) | Test value | *P - value* |
|---|---|---|---|---|---|
| Gender | Females | 16 (64.0%) | 14 (56.0%) | 0.333* | 0.564 |
| | Males | 9 (36.0%) | 11 (44.0%) | | |
| Age (years) | Mean ± SD | 53.76 ± 12.02 | 53.92 ± 11.3 | - 0.048• | 0.962 |
| | Range | 35 - 75 | 30 - 71 | | |
| Treatment Duration (days) | Median (IQR) | 7 (4 - 11) | 7 (4 - 13) | - 0.107‡ | 0.915 |
| | Range | 1 - 17 | 1 - 20 | | |
| Dose of MXT (mg) | Mean ± SD | 19.4 ± 3.63 | 19.6 ± 2.47 | - 0.228• | 0.821 |
| | Range | 15 - 25 | 15 - 25 | | |
| Other diseases | No | 13 (52.0%) | 18 (72.0%) | 2.122* | 0.145 |
| | Yes | 12 (48.0%) | 7 (28.0%) | | |
| DAS28 Score | Mean ± SD | 4.03 ± 0.37 | 3.64 ± 0.38 | 3.642• | 0.001 |
| | Range | 3.4 - 4.8 | 2.8 - 4.5 | | |
| | Low (2.6 – 3.1) | 0 (0.0%) | 2 (8.0%) | 2.083 | 0.149 |
| | Moderate (3.2 – 5.1) | 25 (100.0%) | 23 (92.0%) | | |

**Table 2:** Comparative statistics between respondents and non-respondents regarding laboratory parameters.

| Parameters | | Non-responders No.=25 | Responders No.=25 | Test value | *P - value* |
|---|---|---|---|---|---|
| Creatinine (mg/dl) | Mean ± SD | 0.91 ± 0.53 | 0.86 ± 0.3 | 0.421• | 0.676 |
| | Range | 0.45 - 2.92 | 0.51 - 1.75 | | |
| WBCs ($\times 10^9$/L) | Mean ± SD | 5.32 ± 2.34 | 7.02 ± 3.88 | - 1.878• | 0.066 |
| | Range | 2.6 - 13 | 2.5 - 16 | | |
| Hb (gm/dl) | Mean ± SD | 11.37 ± 1.39 | 10.97 ± 1.34 | 1.023• | 0.311 |
| | Range | 7.5 - 14 | 8 - 13 | | |
| PLT ($\times 10^9$/L) | Mean ± SD | 300.72 ± 113.8 | 270 ± 93.73 | 1.042• | 0.303 |
| | Range | 100 - 500 | 100 - 450 | | |
| CRP (mg/l) | Median (IQR) | 1.4 (0.8 - 3) | 0.9 (0.7 - 1.5) | - 1.574‡ | 0.115 |
| | Range | 0.5 - 21 | 0.1 - 5.5 | | |
| Rheumatoid Factor (titre) | Median (IQR) | 16 (8 - 32) | 16 (8 - 32) | - 0.132‡ | 0.895 |
| | Range | 8 - 64 | 8 - 64 | | |
| Anti - CCP (u/ml) | Median (IQR) | 35 (19 - 200) | 45 (30 - 215) | - 0.777‡ | 0.437 |
| | Range | 1.6 - 1000 | 7 - 500 | | |
| ESR (mm/hr) | Median (IQR) | 45 (20 - 60) | 20 (15 - 35) | - 2.490‡ | 0.013 |
| | Range | 15 - 80 | 10 - 90 | | |
| ALT (u/l) | Median (IQR) | 22 (17 - 37) | 20 (17 - 34) | - 0.418‡ | 0.676 |
| | Range | 10 - 216 | 10 - 160 | | |
| AST (u/l) | Median (IQR) | 21 (18 - 35) | 25 (20 - 39) | - 0.942‡ | 0.346 |
| | Range | 13 - 160 | 10 - 120 | | |
| ALP (u/l) | Median (IQR) | 75 (67 - 100) | 80 (70 - 99) | - 0.204‡ | 0.838 |
| | Range | 39 - 212 | 39 - 205 | | |
| Total Bilirubin (mg/dl) | Mean ± SD | 0.52 ± 0.17 | 0.59 ± 0.27 | - 1.111• | 0.272 |
| | Range | 0.3 - 0.9 | 0.2 - 1.3 | | |
| Direct Bilirubin (mg/dl) | Mean ± SD | 0.19 ± 0.09 | 0.18 ± 0.07 | 0.689• | 0.494 |
| | Range | 0.1 - 0.4 | 0.1 - 0.3 | | |

•: Independent t - test; ‡:Mann - Whitney test

Genotyping and allelic frequency results of ATIC rs 2372536 (C /G) polymorphism of both respondents and non-respondents are presented in (Table 3). It illustrates no substantial difference between respondents and non-respondents regarding genotype frequencies. Also, the dominant genetic model shows no significant difference between the responders and the non-responders. Regarding the recessive model, the GG was significantly higher in non-respondents than the respondents. Also, the G allele frequency was significantly higher in the non-respondents.

**Table 3:** Descriptive and comparative statistics between respondents and non-respondents regarding ATIC genotype results and allelic frequency.

| Parameters | | Non-responders No.=25 | Responders No.=25 | Test value | *P - value* |
|---|---|---|---|---|---|
| Gene | CC | 16 (64.0%) | 19 (76.0%) | 5.657* | 0.059 |
| | CG | 4 (16.0%) | 6 (24.0%) | | |
| | GG | 5 (20.0%) | 0 (0.0%) | | |
| Dominant model | CC | 16 (64.0%) | 19 (76.0%) | 0.857* | 0.355 |
| | CG+GG | 9 (36.0%) | 6 (24.0%) | | |
| Recessive model | CC+CG | 20 (80.0%) | 25 (100.0%) | 5.556 | 0.018 |
| | GG | 5 (20.0%) | 0 (0.0%) | | |
| Alleles | C | 36 (72.0%) | 44 (88.0%) | 4.000 | 0.045 |
| | G | 14 (28.0%) | 6 (12.0%) | | |

*: Chi – square test

The descriptive and comparative statistics between the dominant genetic models (CC Vs CG+GG) in non-responders regarding the occurrence of methotrexate toxicity are described in (Table 4). It revealed no difference between both groups.

**Table 4:** Descriptive and comparative statistics between dominant genetic models in non-responders regarding the occurrence of toxicity.

| Parameters | | ATIC gene groups | | Test value | *P - value* |
|---|---|---|---|---|---|
| | | CC gene | CG +GG genes | | |
| | | No.=16 | No.=9 | | |
| Liver toxicity | No | 15 (93.8%) | 8 (88.9%) | 0.185* | 0.667 |
| | Yes | 1 (6.2%) | 1 (11.1%) | | |
| Kidney toxicity | No | 15 (93.8%) | 7 (77.8%) | 1.392* | 0.238 |
| | Yes | 1 (6.2%) | 2 (22.2%) | | |
| Hematological Toxicity | No | 12 (75.0%) | 9 (100.0%) | 2.679* | 0.102 |
| | Yes | 4 (25.0%) | 0 (0.0%) | | |
| Pulmonary toxicity | No | 15 (93.8%) | 8 (88.9%) | 0.185* | 0.667 |
| | Yes | 1 (6.2%) | 1 (11.1%) | | |

*: Chi–square test

The descriptive and comparative statistics between the dominant genetic models (CC Vs CG+GG) in responders regarding the presence of methotrexate toxicity are illustrated in (Table 5). It revealed no significant difference between the two groups.

**Table 5:** Descriptive and comparative statistics between dominant genetic models in responders regarding the presence of toxicity.

| Parameters | | ATIC gene groups | | Test value | *P - value* |
|---|---|---|---|---|---|
| | | CC gene (No.=16) | CG +GG genes (No.=9) | | |
| Liver toxicity | No | 15 (93.8%) | 8 (88.9%) | 0.185* | 0.667 |
| | Yes | 1 (6.2%) | 1 (11.1%) | | |
| Kidney toxicity | No | 15 (93.8%) | 7 (77.8%) | 1.392* | 0.238 |
| | Yes | 1 (6.2%) | 2 (22.2%) | | |
| Hematological Toxicity | No | 12 (75.0%) | 9 (100.0%) | 2.679* | 0.102 |
| | Yes | 4 (25.0%) | 0 (0.0%) | | |
| Pulmonary toxicity | No | 15 (93.8%) | 8 (88.9%) | 0.185* | 0.667 |
| | Yes | 1 (6.2%) | 1 (11.1%) | | |

*: Chi-square test

## DISCUSSION

The pathogenesis of rheumatoid arthritis (RA) remains incompletely understood. It likely arises from the interplay of genetic, environmental, and immunological variables, causing immune system malfunction[10]. Despite the development of several effective treatments in recent years, low-dose methotrexate (MTX) continues to be the cornerstone of RA therapy. It is widely regarded as effective in delaying the progression of symptoms and alleviating pain associated with RA. However, almost 30% of rheumatoid arthritis patients fail to comply to MTX monotherapy. Therefore, there are ongoing attempts to find biomarker(s) that can predict the treatment response[11].

In this study, we observed a significantly higher DAS28-ESR score in non-responders than responders. Our study agrees with ***Gosselt et al.*** (2021) and ***Duong et al.*** (2022) studies which demonstrated that the DAS28 score was among the top predictors of insufficient response to MTX treatment[12,13]. The previous finding can be attributed to that patients who have higher DAS28 scores may have a higher baseline inflammatory burden with a specific cytokine profile and autoantibody production, leading to more persistent symptoms and joint erosion and hence, resistance to MTX treatment[14]. Yet, conflicting results were stated in other study where a low DAS 28 score was accompanied with bad response to MTX[15].

As regards laboratory investigations, our study reported a statistically significant difference between respondents and non-respondents in ESR levels; being higher in non-responders to MTX treatment. This finding was also consistent with ***Doung et al.*** (2022) study which showed that ESR was a leading indicator to the lack of response to DMARD treatment. Doung and his co-workers suggested that higher ESR indicates more aggressive inflammatory process and disease activity in the non-responding patients.

ATIC (rs2372536) [C /G] gene polymorphism was investigated by real-time PCR. Our results revealed a relationship between the G allele and the recessive model GG genotype with poor methotrexate treatment response. Similar findings were reported by ***Sha et al.*** (2022) found a major connection between ATIC GG gene & MTX adequate response in Malaysian RA patients[16]. In addition, ***Lee et al.*** (2016) meta-analysis study which revealed a major connection between the ATIC GG + GC genotype and non-responsiveness to MTX in Caucasian RA patients[17]. Contradictory results were proved by ***Muralidharan et al***. (2016) in their study done on 319 RA patients. It showed that genotype and allele frequencies of ATIC 347 C >G SNP showed no difference between responders & non-responders and concluded that this SNP had no relation to methotrexate treatment response in Indian RA patients[18]. Similarly, the study by ***Lv et al***. (2018) conducted on 162 Chinese rheumatoid arthritis patients showed no significant relation between ATIC gene polymorphism and MTX response[19]. The genetic distribution of ATIC may be variable in the studied populations, leading to different associations with MTX response. Also, variability in patient characteristics, disease severity, and treatment regimens across different studies can impact treatment response. Other genetic or environmental factors can influence MTX response and affect the observed associations.

In the current study, no significant association was detected between toxicity and different ATIC genetic dominant models in both the respondents and the non-respondents. Our findings cope with that of ***Sha et al***. (2022) who didn't find a relation between ATIC gene polymorphism & methotrexate toxicity. On the contrary, ***Lee et al***. (2016) stated that the GG + GC genotype of ATIC 347 C /G polymorphism was significantly associated with nonresponse to methotrexate treatment & a higher risk of methotrexate toxicity in Caucasians and not the Asian population. Genetic variations, including polymorphisms like ATIC 347C/G (rs2372536), can exhibit population-specific differences. The prevalence of specific genotypes and their associating clinical effects may vary between different ethnic or geographical groups. This could explain the discrepant findings of the various studies

This study has some limitations that should be mentioned. First, our data is solely derived from Egyptian patients, and thus, applies only to this ethnic group. Second, the limited sample size necessitates a cautious interpretation of the results. Third, heterogeneity and confounding factors might impact our study. Variations in methotrexate dosage, follow up duration, toxicity type, and folate supplements could contribute to this difference. We couldn’t modify these factors and thus they may have influenced our findings.

## CONCLUSION

Our study showed that ATIC rs2372536 C>G polymorphism was associated with non response to methotrexate, but it has no association with vulnerability to toxicity from this treatment. Larger-scale studies are recommended to confirm our findings.

## AUTHOR CONTRIBUTION

We declare that all listed authors have made substantial contributions to all of the following three parts of the manuscript:

- Research design, or acquisition, analysis or interpretation of data;
- drafting the paper or revising it critically;
- approving the submitted version.
- We also declare that no-one who qualifies for authorship has been excluded from the list of authors.

## CONFLICT OF INTERESTS

There are no conflicts of interest.

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# العلاقة بين التعدد الشكلي الجيني(rs٢٣٧٢٥٣٦) ATIC ونتائج علاج وسمية الميثوتريكسات في مرضي التهاب المفاصل الروماتويدي

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**الخلفية:** التهاب المفاصل الروماتويدي (RA) هو أحد أمراض المناعة الذاتية الجهازية التي تتميز بالتهاب الغشاء المفصلي المستمر والتهاب المفاصل المزمن. على الرغم من التقدم الكبير في علاج التهاب المفاصل الروماتويدي في السنوات الأخيرة، إلا أن معدل الشفاء الإجمالي لا يزال مثيرًا للقلق، ويكاد يكون من المستحيل عكسه بمجرد حدوث تدمير العظام أو المفاصل.

**الهدف:** هدفت الدراسة الحالية إلى تقييم تأثير تعدد الأشكال ٥-أمينوإيميدازول-٤-كربوكساميد ريبونوكليوتيد ترانسميلاز (ATIC) C>G (rs٢٣٧٢٥٣٦) على الاستجابة وسمية علاج الميثوتريكسيت في مرضى التهاب المفاصل الروماتويدي المصريين.

**لطرق:** أجريت هذه الدراسة المقطعية على ٥٠ مريضاً بالتهاب المفاصل الروماتويدي. تم تجنيدهم من قسم أمراض الروماتيزم بمستشفيات جامعة عين شمس في الفترة من يناير ٢٠٢٢ إلى يناير ٢٠٢٣. وتم تصنيف المرضى المسجلين إلى مجموعتين وفقًا لاستجابتهم لعلاج الميثوتريكسيت: المستجيبون وغير المستجيبين. تم تحديد تعدد أشكال جين ATIC (rs٢٣٧٢٥٣٦) عن طريق تفاعل البلمرة المتسلسل في الوقت الحقيقي لجميع المشاركين.

**النتائج:** بعد ٣ أشهر من العلاج بالميثوتريكسيت، تم تصنيف المرضى المسجلين إلى ٢٥ مستجيبا و ٢٥ غير مستجيبين. أظهر جين C>G ATIC rs٢٣٧٢٥٣٦ وجود علاقة مع فشل الاستجابة لعلاج الميثوتريكسيت في النموذج المتنحي [GG]مقابل (CC+CG) (*P* = ٠,٠١٨). أيضا، كان أليل G أعلى بكثير في غير المستجيبين (*P* = ٠,٠٤٥). لم تجد دراستنا أي ارتباط مهم بين تعدد أشكال الجين C>G s ATIC rs٢٣٧٢٥٣٦ والسمية المرتبطة بـ MTX

**لاستنتاج:** أظهرت نتائجنا أن تعدد أشكال الجين C>G ATIC rs٢٣٧٢٥٣٦ يرتبط بفشل الاستجابة للعلاج بالميثوتريكسيت في مرضى التهاب المفاصل الروماتويدي المصريين ولكن ليس له علاقة بالتعرض للتسمم من العلاج.