Clin. Lab. 2025;71:1-4

ORIGINAL ARTICLE

Target Gene Polymorphisms and Clinical Response to Methotrexate in Chinese Rheumatoid Arthritis Patients

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SUMMARY

Background: **This study aimed to evaluate the associations between genetic polymorphisms within target genes and clinical response to methotrexate (MTX) in Chinese rheumatoid arthritis (RA) patients.**
Methods: **One hundred and fifteen RA patients treated with MTX for approximately 3 months were enrolled, and clinical response was determined by European League Against Rheumatism (EULAR) response criteria and disease activity score in 28 joint counts - erythrocyte sedimentation rate (DAS28-ESR) low disease activity (LDA). Thirty genetic polymorphisms within *DHFR*, *TYMS*, *ATIC*, *ADA*, and *AMPD1* were genotyped.**
Results: **The major allele of *ATIC* rs2372536 (RR = 0.85, 95% CI = 0.72 - 0.99, p = 0.04), *ATIC* rs4673991 (RR = 0.85, 95% CI = 0.73 - 0.99, p = 0.04), *ATIC* rs4673993 (RR = 0.85, 95% CI = 0.73 - 0.99, p = 0.04), *ADA* rs2057638 (RR = 0.86, 95% CI = 0.76 - 0.99, p = 0.03), and *ADA* rs6017375 (RR = 0.86, 95% CI = 0.76 - 0.99, p = 0.03) were found to be significantly associated with EULAR response under dominant model, while the major allele of *ADA* rs371927 (RR = 1.23, 95% CI = 1.04 - 1.46, p = 0.02) was shown to be significantly associated with EULAR response under recessive model. Moreover, the major allele of *ADA* rs1799880 (RR = 0.60, 95% CI = 0.43 - 0.84, p = 0.003) and rs6031697 (RR = 0.61, 95% CI = 0.47 - 0.78, p < 0.001) were detected to be significantly associated with DAS28-ESR LDA.**
Conclusions: **Genetic polymorphisms within *ATIC* and *ADA* were significantly associated with clinical response to MTX in Chinese patients with RA.**
(Clin. Lab. 2025;71:1-4. DOI: 10.7754/Clin.Lab.2025.241250)

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Manuscript accepted February 11, 2025

Supplementary Data

Table S1. European League Against Rheumatism (EULAR) response criteria based on disease activity score in 28 joints - erythrocyte sedimentation rate (DAS28-ESR).

Current DAS28-ESR	The difference in DAS28-ESR from baseline to the end of follow-up		
	> 1.2	> 0.6 and ≤ 1.2	≤ 0.6
≤ 3.2	good	moderate	poor
> 3.2 and ≤ 5.1	moderate	moderate	poor
> 5.1	moderate	poor	poor

Table S2. Single nucleotide polymorphisms (SNPs) within target genes of methotrexate (MTX) selected to be included in our present study.

Gene	SNP
DHFR	rs1650697, rs408626
TYMS	rs2790, rs2847153, rs2853532, rs2853533, rs699517
ATIC	rs16853834, rs2372536, rs3821353, rs4673991, rs4673993, rs7585489
AMPD1	rs12038990, rs17602729, rs2070986
ADA	rs1799880, rs2057638, rs2299694, rs244076, rs371927, rs379863, rs427483, rs446125, rs447833, rs452159, rs6017375, rs6031682, rs6031697, rs8119756

Table S3. The Hardy-Weinberg equilibrium (HWE) test results for the single nucleotide polymorphisms (SNPs) included in our present study.

Gene	SNP	Genotype	n (%)	p
DHFR	rs408626	C/C	51 (44.35)	0.96
		T/C	51 (44.35)	
		T/T	13 (11.30)	
TYMS	rs2790	A/A	45 (39.13)	0.06
		G/A	46 (40.00)	
		G/G	24 (20.87)	
	rs2847153	G/G	49 (42.61)	0.07
		A/G	45 (39.13)	
		A/A	21 (18.26)	
	rs2853532	C/C	61 (53.04)	< 0.001
		T/C	11 (9.57)	
		T/T	43 (37.39)	
	rs699517	T/T	54 (46.96)	0.64
		C/T	48 (41.74)	
		C/C	13 (11.30)	

Table S3. The Hardy-Weinberg equilibrium (HWE) test results for the single nucleotide polymorphisms (SNPs) included in our present study (continued).

Gene	SNP	Genotype	n (%)	p
ATIC	rs16853834	C/C	67 (58.26)	0.55
		T/C	40 (34.78)	
		T/T	8 (6.96)	
	rs2372536	C/C	57 (50.00)	0.49
		G/C	45 (39.47)	
		G/G	12 (10.53)	
	rs3821353	G/G	32 (27.83)	0.89
		T/G	58 (50.43)	
		T/T	25 (21.74)	
	rs4673991	C/C	59 (51.30)	0.38
		T/C	44 (38.26)	
		T/T	12 (10.43)	
	rs4673993	T/T	59 (51.30)	0.38
		C/T	44 (38.26)	
		C/C	12 (10.43)	
	rs7585489	C/C	32 (27.83)	0.59
		T/C	60 (52.17)	
		T/T	23 (20.00)	
AMPD1	rs12038990	G/G	30 (26.09)	0.20
		T/G	64 (55.65)	
		T/T	21 (18.26)	
	rs17602729	G/G	115 (100.00)	-
	rs2070986	G/G	37 (32.17)	0.22
		A/G	62 (53.91)	
		A/A	16 (13.91)	
ADA	rs1799880	G/G	63 (54.78)	0.78
		C/G	45 (39.13)	
		C/C	7 (6.09)	
	rs2057638	T/T	67 (58.26)	0.86
		G/T	42 (36.52)	
		G/G	6 (5.22)	
	rs2299694	A/A	57 (50.44)	0.62
		G/A	48 (42.48)	
		G/G	8 (7.08)	
	rs244076	T/T	81 (70.43)	0.23
		C/T	33 (28.70)	
		C/C	1 (0.87)	
	rs371927	A/A	51 (44.35)	0.60
		G/A	53 (46.09)	
		G/G	11 (9.57)	
	rs379863	T/T	72 (62.61)	0.05
		C/T	42 (36.52)	
		C/C	1 (0.87)	

Table S3. The Hardy-Weinberg equilibrium (HWE) test results for the single nucleotide polymorphisms (SNPs) included in our present study (continued).

Gene	SNP	Genotype	n (%)	p
ADA	rs427483	C/C	82 (71.30)	0.02
		G/C	26 (22.61)	
		G/G	7 (6.09)	
	rs446125	G/G	62 (53.91)	0.69
		T/G	46 (40.00)	
		T/T	7 (6.09)	
	rs447833	T/T	60 (52.17)	0.96
		C/T	46 (40.00)	
		C/C	9 (7.83)	
	rs452159	G/G	53 (46.09)	0.54
		T/G	48 (41.74)	
		T/T	14 (12.17)	
	rs6017375	G/G	67 (58.26)	0.86
		C/G	42 (36.52)	
		C/C	6 (5.22)	
	rs6031682	G/G	67 (58.26)	0.18
		C/G	38 (33.04)	
		C/C	10 (8.70)	
	rs6031697	T/T	54 (46.96)	0.64
		C/T	48 (41.74)	
		C/C	13 (11.30)	
	rs8119756	A/A	90 (78.26)	0.26
		G/A	22 (19.13)	
		G/G	3 (2.61)	