This article was downloaded by:

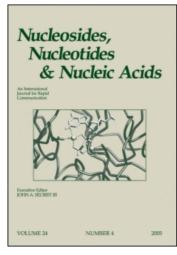
On: 26 January 2011

Access details: Access Details: Free Access

Publisher Taylor & Francis

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-

41 Mortimer Street, London W1T 3JH, UK



## Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information: http://www.informaworld.com/smpp/title~content=t713597286

## Genetic Determinants of the Pre- and Post-Azathioprine Therapy Thiopurine Methyltransferase Activity Phenotype

M. Arenas<sup>a</sup>; J. A. Duley<sup>a</sup>; A. Ansari<sup>b</sup>; E. A. Shobowale-Bakre<sup>a</sup>; L. Fairbanks<sup>a</sup>; S. Y. Soon<sup>b</sup>; J. Sanderson<sup>b</sup>; A. M. Marinaki<sup>a</sup>

<sup>a</sup> Purine Research, Guy's and St. Thomas' Hospital, London, UK <sup>b</sup> Department of Gastroentereology, Guy's and St. Thomas' Hospital, London, UK

Online publication date: 27 October 2004

To cite this Article Arenas, M. , Duley, J. A. , Ansari, A. , Shobowale-Bakre, E. A. , Fairbanks, L. , Soon, S. Y. , Sanderson, J. and Marinaki, A. M.(2004) 'Genetic Determinants of the Pre- and Post-Azathioprine Therapy Thiopurine Methyltransferase Activity Phenotype', Nucleosides, Nucleotides and Nucleic Acids, 23: 8, 1403 - 1405

To link to this Article: DOI: 10.1081/NCN-200027643 URL: http://dx.doi.org/10.1081/NCN-200027643

## PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

## NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS Vol. 23, Nos. 8 & 9, pp. 1403–1405, 2004

# Genetic Determinants of the Pre- and Post-Azathioprine Therapy Thiopurine Methyltransferase Activity Phenotype

M. Arenas,<sup>1,\*</sup> J. A. Duley,<sup>1</sup> A. Ansari,<sup>2</sup> E. A. Shobowale-Bakre,<sup>1</sup> L. Fairbanks,<sup>1</sup> S. Y. Soon,<sup>2</sup> J. Sanderson,<sup>2</sup> and A. M. Marinaki<sup>1</sup>

<sup>1</sup>Purine Research and <sup>2</sup>Department of Gastroentereology, Guy's and St. Thomas' Hospital, London, UK

#### **ABSTRACT**

Thiopurine drug therapy has been reported to lead to a variable increase in red cell TPMT activity that may alter effective dose and therapeutic outcome. The aim of this study was to correlate Variable Number Tandem Repeat (VNTR) in the promoter region of the TPMT gene with induction of red cell TPMT activity in patients treated with azathioprine (AZA). In 58 patients, TPMT activity measured at 3 months was not significantly induced on average above pre-therapy levels. Individual patients showed variation in TPMT activity pre- and post-AZA therapy, however changes in TPMT activity were not predicted by VNTR configuration. In conclusion, TPMT promoter VNTRs are unlikely to play a significant role in changes in TPMT activity in response to AZA therapy.

*Key Words:* VNTR: Variable number tandem repeats; Aza: Azathioprine; 6MP: 6Mercaptopurine and TPMT: Thiopurine methyltransferase.

1403

DOI: 10.1081/NCN-200027643 Copyright © 2004 by Marcel Dekker, Inc. 1525-7770 (Print); 1532-2335 (Online) www.dekker.com

<sup>\*</sup>Correspondence: M. Arenas, Purine Research, Guy's and St. Thomas' Hospital, London SE1 9RT, UK.

1404 Arenas et al.

#### INTRODUCTION

A genetic deficiency of thiopurine methyltransferase (TPMT\*2-\*8) leads to an increase risk of adverse drug reactions to the thiopurine drug azathioprine (AZA). Conversely, high TPMT activity is associated with a poor clinical response. Thiopurine drug therapy has been reported to lead to an unexplained variable increase in red cell TPMT activity that may alter effective dose and therapeutic outcome. TPMT promoter variable number tandem repeats (VNTR) consist of 3 different repeats (Type A, B, and C) and are polymorphic (VNTR\*3-\*9). The aim of this study was to correlate VNTR configuration in the promoter region of the TPMT gene with induction of TPMT activity in patients treated with AZA.

#### MATERIALS AND METHODS

TPMT activity in 58 patients with inflammatory bowel disease was determined prior to the initiation of AZA therapy and at 1, 3, 6, 9, and 12 months during AZA therapy. All patients were genotyped for TPMT promoter VNTRs, TPMT\*2, \*3A and \*3C. Patients heterozygous for an open reading frame mutation were excluded from the analysis.

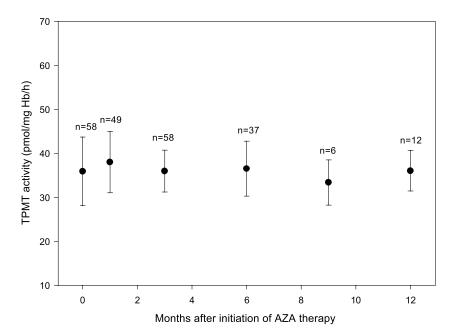


Figure 1. Red cell TPMT activity during the course of 12 months azathioprine therapy. Values are mean  $\pm$  SD. n = number of patients in sample.

#### RESULTS

Although the mean difference ( $\pm$  SD) between pre-therapy TPMT activity and activity after 3 months AZA treatment was small (1.1 U  $\pm$  7.0 U), changes in TPMT activity after 3 months therapy varied greatly in some individuals (range - 29.1 to 13.7 U). There were no significant differences between pre-AZA TPMT activity and activity levels after 1, 3, 6, 9 and 12 months AZA therapy (Fig. 1, Kruskal-Wallis One Way ANOVA on ranks).

Two new VNTR alleles, VNTR\*6c (4A, 1B, 1C) and \*7c (4A, 2B, 1C) were found. No correlation was found between the magnitude of the change in TPMT activity after 3 months AZA therapy and the number of type A, B or total number of VNTR repeats. TPMT activity at 3 months was decreased in 22/58 patients compared to pre- AZA levels. No difference in the distribution of Type A, B or total number of repeats was found when 20 patients with the greatest decrease in TPMT activity after 3 months therapy were compared to 20 patients with the highest enzyme induction.

#### **DISCUSSION**

We have previously shown that VNTRs do not significantly modulate basal TPMT enzyme activity. [3] In the present study, although individual patients showed considerable variation in TPMT activity between pre- and post-AZA therapy groups, neither a reduction in TPMT activity nor an increase in activity were predicted by VNTR configuration. TPMT promoter VNTR are thus unlikely to play a significant role in changes in TPMT activity when patients are treated with AZA. Therefore, other genetic factors within the promoter may play a role in the variation observed in TPMT activity following AZA therapy.

#### REFERENCES

- 1. Lennard, L. TPMT in the treatment of Crohn's disease with azathioprine. Gut **2002**, *51*, 143–146.
- 2. Ansari, A.; Hassan, C.; Duley, J.; Marinaki, A.; Shobowale-Bakre, E.M.; Seed, P.; Meenan, J.; Yim, A.; Sanderson, J. Thiopurine methyltransferase activity and the use of azathioprine in inflammatory bowel disease. Aliment. Pharmacol. Ther. **2002**, *16*, 1743–1750.
- 3. Marinaki, A.M.; Arenas, M.; Khan, Z.H.; Lewis, C.M.; Shobowale-Bakre el, M.; Escuredo, E.; Fairbanks, L.D.; Mayberry, J.F.; Wicks, A.C.; Ansari, A.; Sanderson, J.; Duley, J.A. Genetic determinants of the thiopurine methyltransferase intermediate activity phenotype in British Asians and Caucasians. Pharmacogenetics **2003**, *13*, 97–105.