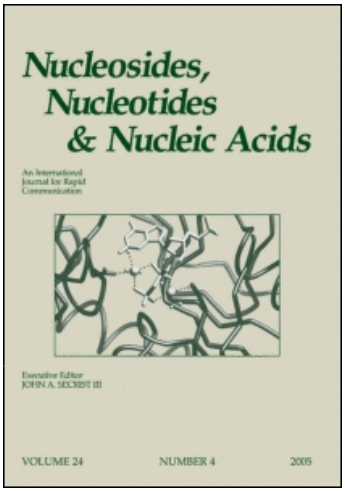


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A. M. Marinaki[a]; S. Sumi[a]; M. Arenas[a]; L. Fairbanks[a]; S. Harihara[b]; K. Shimizu[c]; A. Ueta[d]; J. A. Duley[e]
[a] Purine Research Unit, Department of Chemical Pathology, Guy's and St. Thomas' Hospitals, London, UK [b] Department Biological Sciences, Tokyo University, Japan [c] Department of Biology, Naruto University, Japan [d] Department of Pediatrics, Nagoya City University, Japan [e] Department of Biomedical and Molecular Sciences, University of Queensland, Australia

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# Allele Frequency of Inosine Triphosphate Pyrophosphatase Gene Polymorphisms in a Japanese Population

**A. M. Marinaki,[1,*] S. Sumi,[1] M. Arenas,[1] L. Fairbanks,[1] S. Harihara,[2] K. Shimizu,[3] A. Ueta,[4] and J. A. Duley[1,#]**

[1]Purine Research Unit, Department of Chemical Pathology, Guy's and St. Thomas' Hospitals, London, UK
[2]Department Biological Sciences, Tokyo University, Japan
[3]Department of Biology, Naruto University, Japan
[4]Department of Pediatrics, Nagoya City University, Japan



## ABSTRACT

The enzyme inosine triphosphate pyrophosphatase (ITPase) catalyses the pyrophosphohydrolysis of ITP to IMP. ITPase deficiency is a clinically benign autosomal recessive condition characterised by the abnormal accumulation of ITP in erythrocytes. A deficiency of ITPase may predict adverse reactions to therapy with the thiopurine drug 6-mercaptopurine and its prodrug azathioprine. In this study, we examine the frequencies of *ITPA* polymorphisms in 100 healthy Japanese individuals. The allele frequency of the 94C > A variant in the Japanese sample was 0.135 (Caucasian allele frequency 0.06). The IV2 + 21A > C polymorphism was not found in Japanese (Caucasian allele frequency 0.130). Allele frequencies of the 138G > A, 561G > A and 708G > A polymorphisms were 0.57, 0.18 and 0.06 respectively in the

[#]Current address: Department of Biomedical and Molecular Sciences, University of Queensland, Australia.
[*]Correspondence: A. M. Marinaki, Purine Research Unit, Department of Chemical Pathology, Guy's and St. Thomas' Hospitals, London, UK.



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Japanese population, and with the exception of the 138G > A polymorphism, similar to allele frequencies in Caucasians.

*Key Words:* Azathioprine; 6-Mercaptopurine; ITPA; ITPase; Inosine triphosphate pyrophosphohydrolase; Thiopurine methyltransferase; Japanese.

## INTRODUCTION

The enzyme inosine triphosphate pyrophosphohydrolase (ITPase) catalyses the pyrophosphohydrolysis of inosine triphosphate (ITP) to inosine monophosphate (IMP). ITPase is present in many human tissues as well as in erythrocytes and in addition to ITP, can also utilise other purine compounds as substrates. ITPase deficiency is a clinically benign autosomal recessive condition characterised by the abnormal accumulation of ITP in erythrocytes. A deficiency of ITPase may predict adverse reactions to therapy with the thiopurine drug 6-mercaptopurine and its prodrug azathioprine.

We have reported the structure of the *ITPA* gene and identified five SNPs in 8 families with ITPase deficiency.[1] A missense mutation (94C > A, Pro32 to Thr) and an intron mutation (IV2 + 21A > C) were associated with decreased enzyme activity. Homozygotes for the 94C > A mutation had zero erythrocyte ITPase activity while heterozygotes averaged 22.5% of the control mean. ITPase activity of IV2 + 21A > C homozygotes averaged 60% of the control mean. Compound heterozygotes 94C > A/IV2 + 21A > C were 10% of the control mean. In addition, three silent polymorphisms (138G > A, 561G > A and 708G > A) were found. In this study, we examine the frequencies of *ITPA* polymorphisms in 100 healthy Japanese individuals.



## METHODS

DNA was extracted from blood samples of 100 normal Japanese individuals after informed consent had been obtained. The 5 SNPs in the *ITPA* gene were determined using PCR–RFLP methods as previously described.[1]

***Table 1.*** Frequencies of *ITPA* alleles associated with reduced ITPase activity in healthy individuals of different ethnic groups.

| | 94C > A | IV2 + 21A > C |
|---|---|---|
| *Our study* | | |
| Japanese (n = 200) | 0.135* | 0* |
| Caucasian (n = 200) | 0.060 | 0.130 |
| *Cao et al.*[2] | | |
| Caucasian (n = 250) | 0.07 | Not examined |
| African (n = 120) | 0.05 | Not examined |
| Chinese (n = 120) | 0.15 | Not examined |
| East India (n = 120) | 0.11 | Not examined |

n: Number of alleles.
*Significantly different from Caucasians ($p < 0.05$).

## RESULTS

The allele frequency of the 94C > A mutation in the Japanese sample was 0.135, twice the frequency found in Caucasians (0.06) (Table 1). The IV2 + 21A > C variant was not found in Japanese, although it occurred with a frequency of 0.130 in Caucasians. Allele frequencies of the 138G > A, 561G > A and 708G > A polymorphisms were 0.57, 0.18 and 0.06 respectively in the Japanese population, and with the exception of the 138G > A polymorphism, similar to allele frequencies in Caucasians.

## DISCUSSION

ITPase deficiency fulfils the criteria for a candidate locus important in inter-individual differences in purine drug analogue metabolism; it is a benign condition occurring with polymorphic frequencies in most populations and the enzyme has a broad substrate specificity for both purine and pyrimidine triphosphates. A deficiency of the enzyme would be predicted to lead to the accumulation of the active metabolite of 6-mercaptopurine (and other purine and pyrimidine analogue drugs), namely the triphosphate, and an increased risk of toxicity.



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