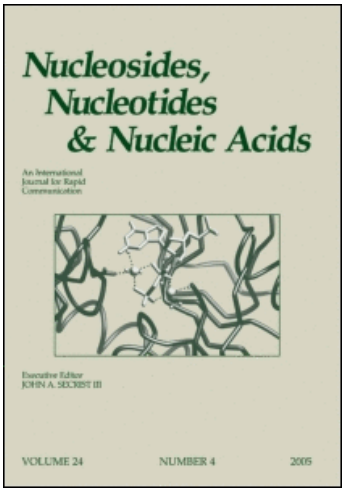

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

The Genetic Basis of the Interaction Between Pyrimidine 5' Nucleotidase I Deficiency and Hemoglobin E

E. Escuredo[a]; A. M. Marinaki[a]; J. A. Duley[a]; S. L. Thein[b]; D. C. Rees[b]
[a] Purine Research Unit, Department of Chemical Pathology, Guy's and St. Thomas Hospitals, London, UK [b] Department of Haematology, King's College Hospital, London, UK

Online publication date: 27 October 2004

To cite this Article Escuredo, E. , Marinaki, A. M. , Duley, J. A. , Thein, S. L. and Rees, D. C.(2004) 'The Genetic Basis of the Interaction Between Pyrimidine 5' Nucleotidase I Deficiency and Hemoglobin E', Nucleosides, Nucleotides and Nucleic Acids, 23: 8, 1261 — 1263
To link to this Article: DOI: 10.1081/NCN-200027532
URL: http://dx.doi.org/10.1081/NCN-200027532

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
Vol. 23, Nos. 8 & 9, pp. 1261–1263, 2004

The Genetic Basis of the Interaction Between Pyrimidine 5′ Nucleotidase I Deficiency and Hemoglobin E

E. Escuredo,[1,*] A. M. Marinaki,[1] J. A. Duley,[1] S. L. Thein,[2] and D. C. Rees[2]

[1]Purine Research Unit, Department of Chemical Pathology, Guy's and St. Thomas Hospitals, London, UK
[2]Department of Haematology, King's College Hospital, London, UK

ABSTRACT

We have previously described a family in which the interaction between pyrimidine 5′ nucleotidase I (P5N-I) deficiency and hemoglobin E resulted in severe haemolytic anaemia. In this study we explored the genetic basis of the severe clinical phenotype and look for evidence of the interaction between these conditions. A P5N-I gene mutation (IVS8 + 1−2delGT) was found in the family, confirming that the severe phenotype results from the interaction between two genetic diseases.

Key Words: Pyrimidine metabolism; Pyrimidine 5′nucleotidase (P5N-I); Uridine monophosphate hydrolase I; Haemolytic anaemia; Hemoglobin E; Beta-thalassaemia.

INTRODUCTION

Hemoglobin E (HbE:β^{26}Glu-Lys) is a common Hb variant in Bangladesh, Southeast Asia and India. It is usually asymptomatic in heterozygous and homozygous states.[1] The importance of this haemoglobin variant lies in its interaction with

*Correspondence: E. Escuredo, Purine Research Unit, Department of Chemical Pathology, Guy's and St. Thomas Hospitals, London, UK.

DOI: 10.1081/NCN-200027532
1525-7770 (Print); 1532-2335 (Online)

β-Thalassaemia. E^{β}-Thalassaemia results in a variable clinical phenotype ranging from asymptomatic to a life threatening condition.[2,3] Pyrimidine 5 nucleotidase-I (P5N-I) deficiency typically presents as mild haemolytic anaemia. The main haematological characteristic is the presence of basophilic stippling in blood films. The disorder is autosomal recessive and it is considered to be the third cause of inherited haemolytic anaemia.[4] We studied the case of a Bangladeshi family where the two conditions were present resulting in severe haemolytic anaemia.[5]

MATERIALS AND METHODS

Details of this family have been published previously[5] and are shown in Table 1. P5N-I and deoxypyrimidine 5 nucleotidase-II (P5N-II) activities were measured using HPLC based method measuring the breakdown either of uridine or deoxy-uridine monophosphate to uridine or deoxyuridine respectively. We previously found that a P5N-I/P5N-II activity ratio <0.7 predicts heterozygosity for P5N-I deficiency, <0.1 in P5N-I deficient.[6,7] DNA was extracted using standard methods. Exons 1 to 10 were amplified, purified and directly sequenced.

RESULTS

The II.5 HbE homozygote was found to be homozygous for a two base pair deletion of the highly conserved GT of the intron 8 splice donor site. The mutation is predicted to cause skipping of exon 8 and the deletion of 163 nucleotides, resulting in premature termination of the protein consistent with a complete deficiency of P5N-I activity. The sister II.4 was homozygous and both parents were heterozygous for this mutation (Table 1). The mutation was not found in the brother II.2 who was homozygous for HbE with a P5N-I/P5N-II activity ratio of 0.55, in the carrier range for P5N-I deficiency. DNA was not available from the other brothers II.1 and II.3 for analysis.

Table 1. Haematological data, red cells enzymes and molecular analysis.

	Hb g/dl	Hb type	P5N-I*	P5N-II*	P5N-I/P5N-II	P5N-I genotype	Phenotype
I.1	11.7	AE	4	9	0.44	Heterozygous	Asymptomatic
I.2	13.2	AE	3	7	0.42	Heterozygous	Asymptomatic
II.1	11.2	AA	0.2	10	0.02	NA	Asymptomatic
II.2	13.6	EE	5	9	0.55	Wild type	Asymptomatic
II.3	14.8	AE	6	8	0.75	NA	Asymptomatic
II.4	7.6	AA	0.1	7	0.014	Homozygous	Mild anaemia
II.5	2.8	EE	0.5	10	0.05	Homozygous	Severe anaemia

NA: no DNA available for P5N-I genotype.
*Units: P5N-I 9–20 nmol/mgHb/h, P5N-II 7–28 nmol/mgHb/h.

DISCUSSION

In this study, we have demonstrated that the P5N-I deficiency in this family has a genetic basis. The co-inheritance of complete P5N-I deficiency and the homozygous HbE state results in a haemolytic phenotype more severe than would be expected with either conditions alone. The genetic co-inheritance of P5N-I deficiency thus could be one of the factors that modulates the severity of β-Thalassaemic syndromes. Our results indicate that the inheritance of HbE results in an acquired reduction of P5N-I activity to the carrier range, as seen in II.2. The P5N-1 enzyme is believed to be susceptible to free radical damage.[5] This raises the possibility that coincidental inhibition of P5N-I activity may contribute to the severe haemalytic phenotype associated with some unstable haemoglobin variants.

REFERENCES

1. Rees, D.C.; Styles, L.; Vichinsky, E.P.; Clegg, J.B.; Weathreall, D.J. The hemoglobin E syndroms. Ann. N.Y. Acad. Sci. **1998**, *850*, 334–343.
2. Orkin, Sh.; Kazazian, H.H., Jr.; Antonarakis, S.E.; Ostrer, H.; Goff, S.C.; Sexton, J.P. Abnormal RNA processing due to the exon mutation of betaE-globin gene. Nature **1982**, *300*, 768–769.
3. Weatherall, D.J. Hemoglobin E^{β}-thalassemia: an increasingly common disease with some diagnostic pitfalls. J. Pediatr. **1998**, *132*, 765–767.
4. Paglia, D.E.; Valentine, W.N. Hereditary and acquired defects in the pyrimidine nucleotidase of human erythrocytes. Curr. Top. Hematol. **1980**, *3*, 75–109.
5. Rees, D.C.; Duley, J.; Simmonds, H.A.; Wonke, B.; Thein, S.L.; Clegg, J.B.; Wetherall, D.J. Interaction of hemoglobin E and pyrimidine 5′nucleotidase deficiency. Blood **1996**, *88*, 2761–2767.
6. Marinaki, A.M.; Escuredo, E.; Duley, J.; Simmonds, H.A.; Amici, A.; Naponelli, V.; Magni, G.; Seip, M.; Ben-Bassat, I.; Harley, E.H.; Thein, S.L.; Rees, D.C. Genetic basis of hemolytic anemia caused by pyrimidine 5′nucleotidase deficiency. Blood **2001**, *97*, 3327–3332.
7. Escuredo, E.; Duley, J.; Clegg, J.; Weatherall, D.; Rees, D.C. A new test for β-thalassemia [abstract]. Hematol. J. **2000**, *1*, 36.