

LETTERS TO THE EDITOR

Thalassaemia in Azerbaijan

A recent study referred to the incidence of molecular mutations and the clinical picture of thalassaemia in Azerbaijan (Kuliev *et al.* *J Med Genet* 1994;31:209-12). Unfortunately the section on α thalassaemia described in this report is incomplete. The incidence and clinical picture of α thalassaemia in this region of the former USSR have been extensively studied and published in Russian language publications between 1983 and 1985. Different forms of α thalassaemia have been identified in Azerbaijan. We studied the clinical picture and laboratory findings of different forms of α thalassaemia (haemoglobin H disease, $\alpha\beta$ thalassaemia, and HbS/ α thalassaemia) in 137 patients¹⁻³ and our data suggest considerable genetic heterogeneity of α thalassaemia in Azerbaijan. However, the clinical picture and laboratory findings were similar to the α thalassaemia found in the Mediterranean area. We also studied the frequency of α thalassaemia in two regions endemic for haemoglobinopathy (Kutkashen and Shaeki) and in the capital Baku by estimations of Hb Bart's in 1000 cord blood samples by electrophoresis and immunochemical methods.^{4,5} In the Kutkashen region, among 200 cord blood samples, Hb Bart's was detected in 28 cases with a percentage ranging from 0.8% to 28%. In the Shaeki region, in 54 out of 600 cord blood samples, Hb Bart's from 0.8% to 25% was detected. In 10 out of 200 cord blood samples from the Gynecology and Obstetrics Department of Baku, Hb Bart's ranged from 0.8% to 9.5%. We found a trimodal distribution of Hb Bart's with values of 0.8% to 5%, 6% to 11%, and 25% to 28%. We consider that these values corresponded to genotypes of α thalassaemia 2, α thalassaemia 1, and α thalassaemia 1/ α thalassaemia 2 respectively.^{6,7} Our studies indicate that α thalassaemia 2 trait is more prevalent than α thalassaemia 1 trait in Azerbaijan (in Kutkashen 11.5% and 2%, in Shaeki 7.8% and 1%, in Baku 4% and 1% respectively).

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Blepharophimosis-mental retardation syndrome and terminal deletion of chromosome 3p

Three unrelated patients were published in *Journal of Medical Genetics* in 1987, 1988, and 1989¹⁻³ with an unknown syndrome whose symptoms included abnormal facies, hypothyroidism, postaxial polydactyly, and severe mental retardation. The author of the 1989 paper³ concluded that these patients were affected by the same syndrome of unknown aetiology.

We recently examined a 5 month old boy referred because of hypotonia and growth retardation (-3 SD). He was microcephalic and severely hypotonic. He exhibited facial dysmorphism with blepharophimosis, ptosis,

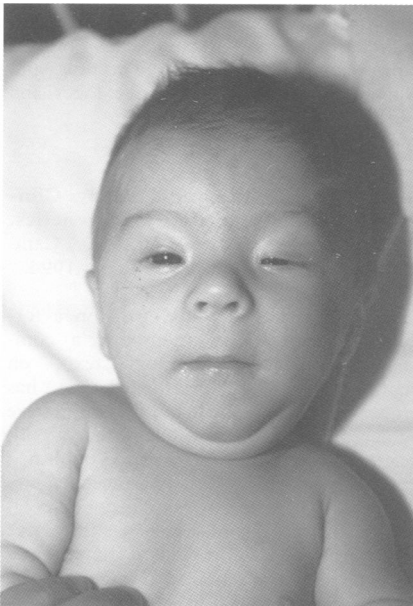


Figure 1 Facial features of the proband at 7 months. Note the blepharoptosis, bulbous nose, long philtrum, and thin upper lip.



Figure 2 High resolution R banded chromosomes 3 of the patient. The right shows del(3)(p25-3pter).

hypertelorism, upward slanting palpebral fissures, short nose with a broad nasal tip, long philtrum, micrognathia, bilateral preauricular pits, and postaxial polydactyly on the left hand (fig 1). Chromosome analysis was performed using R banding and was found to be normal.

However, a patient reported in *Atlas des Maladies Chromosomiques*⁴ with a 3p25-pter deletion showed a striking resemblance to our patient.

The clinical features so closely resembled those of 3pter deletion that we carefully checked this region on the R banded karyotype and found the expected 3p25-3pter deletion, which was then confirmed by high resolution banding (fig 2). Without the clinical indications, this deletion would have remained undetected.

On the basis of this finding, we suggest that similar patients reported by Young and Simpson,¹ Fryns and Moerman,² Cavalcanti,³ and Buntinx and Majeswski⁵ could also have 3pter deletions. The clinical features of these patients and our case are compared in the table. All of them share severe pre- or postnatal growth retardation, hypotonia, and the same facial dysmorphism: microcephaly with blepharophimosis, ptosis, epicanthus, a broad nasal tip, and micrognathia. It is just possible that these deletions may have been missed on standard chromosome analysis if they were as small as the one which we observed.

Sixteen published cases with 3pter deletions had a larger deletion including the whole of band 3p25-pter.⁶ Growth retardation, mental retardation with neonatal hypotonia, blepharophimosis, blepharoptosis, epicanthus, hypertelorism, and thin upper lips are consistent features. Microcephaly is present in 70% of cases, postaxial polydactyly in 50%. Less frequently observed anomalies are congenital heart defect, renal malformation, cryptorchidism, and rocker bottom feet. Hypothyroidism was diagnosed in one patient with 3p deletions as well as hearing loss (table).

We think that 3pter deletions can be diagnosed clinically and should be confirmed by high resolution banding or FISH using markers in this region⁷ when a standard karyotype is normal.

Blepharophimosis-ptosis-epicanthus syndrome with normal intelligence is associated with 3q23 microdeletion.⁸⁻¹⁰ Blepharophimosis and developmental delay were reported together by Biesecker in 1991.⁸ She reported a child with blepharophimosis, simple ears, hypoplastic teeth, developmental delay, and hypotonia. This patient was very similar to a previous report by Fujita *et al*¹¹ and Biesecker suggests that all cases have a distinctive syndrome named Ohdo syndrome. Recently Clayton Smith *et al*,¹² Melnyk,¹³ and Maat-Kievit *et al*¹⁴ have reported six new cases with this syndrome describing additional clinical features. We suggest that some patients are very concordant for 3p-deletions. We recommend that clinicians keep in mind the 3p localisation when examining patients with mental retardation and blepharophimosis.

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- 1 Young ID, Simpson K. Unknown syndrome: abnormal facies, congenital heart defects, hypothyroidism, postaxial polydactyly, and

Comparison of clinical signs between 3p deletions and unknown syndrome: abnormal facies, hypothyroidism, postaxial polydactyly, and severe mental retardation

	Cavalcanti ³	Young and Simpson ¹	Fryns and Moerman ²	Buntinx and Majeswski ⁵	Our case	Nienhaus et al ⁶ 3p deletions
Microcephaly	+	+	-	+	+	11/14
Growth retardation	+	+	+	+	+	16/16
	(<3rd)	(<3rd)	(<3rd)			
Blepharophimosis	+	+	+	+	+	16/16
Blepharoptosis	+	+	+	+	+	16/16
Epicanthus	+	+	+	+	+	10/12
Hypertelorism	+	+	+	?	+	6/14
Long philtrum	+	+/-	+/-	-	+	11/11
Flat nasal bridge	+	?	?	+	+	10/14
Bulbous nasal tip	+	+	+	+	+	10/14
Thin upper lip	+	+	+	+	+	10/16
Micrognathia	+	+	+	+	+	10/12
Malformed or apparently low set ears	+	+	+	+	+	15/15
		Right preauricular pits				
Postaxial polydactyly	+	-	-	+	+	10/14
Clinodactyly	-	-	-	-	-	<50%
Scoliosis	-	-	-	-	-	<50%
Prominent heel	-	-	+	+	-	<50%
Cleft palate	-	-	+	-	-	<50%
Hypothyroidism	+	+	+	-	-	
Hearing loss	-	-	+	-	-	<50%
Heart malformation	-	-	+	-	-	<50%
Cryptorchidism	-	Ventricular defect	+	-	+	<50%

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Genetic Factors in Drug Therapy: Clinical and Molecular Pharmacogenetics. D A Price-Evans. (Pp 657; £120.00.) Cambridge: Cambridge University Press. 1994.

Professor Price-Evans has taken on a formidable challenge in attempting a comprehensive single author text on pharmacogenetics. Nevertheless, he has proved equal to the task and this impressive book represents an exhaustive review of publications up to and including papers published in 1992. Recent research in pharmacogenetics has focused primarily on genetic polymorphisms of drug metabolism and a large part of the book is devoted to the enzymes involved and their genetic determinants. The cytochromes P450 (CYPs) are dealt with first, since they represent the most important group of drug metabolising enzymes. Two major polymorphisms in this gene superfamily have been identified, affecting CYP2D6 (the "debrisoquine/sparteine" polymorphism) and CYP2C19 (the "mephenytoin" polymorphism). The list of drug substrates of CYP2D6 is growing rapidly (presently about 40), many of them in widespread clinical use. These chapters bring home the vast amount of information that has been gained on the molecular genetics, biochemistry, and substrate selectivity of these enzymes. Clinical data on population and ethnic aspects, pharmacokinetic consequences, and disease susceptibility in relation to phenotype and genotype are also considered in depth. However, a more critical evaluation of the clinical significance of the debrisoquine/sparteine polymorphism could perhaps have been expected. Most reports of unwanted drug effects in one or other phenotype are from single case studies, many of which have not been substantiated. There is a similar exhaustive

treatment of other drug metabolising enzymes which show evidence of polymorphism, N-acetyltransferase, S-methyltransferase, and pseudocholinesterase being the ones that have received the most clinical attention.

It is good to see that the difficulties of interpreting pharmacogenetic data are covered, an area that has often been neglected. For example, distinguishing between unimodality and bi- or trimodality in population distributions is a fundamental problem in pharmacogenetic studies of drug metabolism and, in an Appendix, the author summarises the main mathematical techniques proposed for its solution.

The remainder of the book is devoted to a discussion of adverse drug effects having an inherited pharmacodynamic or receptor basis. Well characterised disorders, such as glucose-6-phosphate dehydrogenase deficiency, the porphyrias, and malignant hyperthermia, would be expected to be included but the author has scoured published reports for less well known adverse reactions that may have a genetic basis. For example, in a report of one patient described as "a green man after indomethacin" it was suggested that inhibition by this drug of a rare genetic variant of biliverdin reductase caused his skin, urine, and serum to turn green owing to the accumulation of biliverdin. Unfortunately, this was not followed up with family studies.

From this book it should be abundantly clear to the reader that genetic variability in pharmacokinetics and pharmacodynamics has obvious implications for drug therapy, but with a few exceptions this knowledge has yet to be applied to clinical practice. The debrisoquine/sparteine polymorphism is a good example in that, although the phenomenon was discovered 17 years ago, few controlled prospective studies to evaluate its clinical significance have been performed. The recent emphasis on molecular genetics needs to be augmented by a more determined effort to define phenotypic differences in drug response.

All chapters are clearly written and the text and graphics layouts make the book easy to read. It is also extremely well indexed. There is a danger that, like all works of reference covering an active research area, particularly one in which molecular genetics has made such an impact, this book could become out of

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