Balanced translocation (14;20) in a mentally handicapped child with cystinuria

M Sharland, M Jones, M Bain, R Chalmers, J Hammond, M A Patton

Abstract

A mentally handicapped 3 year old child with cystinuria is presented. Routine chromosomal analysis showed an apparently balanced de novo translocation in the child with breakpoints 14q22 and 20p13. Family studies suggested that the child is a type I/type II compound heterozygote for cystinuria. This translocation may indicate a possible locus for the gene for cystinuria.

Cystinuria is a disorder of amino acid transport involving the epithelial cells of the gastrointestinal tract and renal tubule.[1] Cystinuria commonly presents with renal stones which, if untreated, may cause renal damage and failure. The urine contains an excess of cystine, ornithine, arginine, and lysine. Although classical cystinuria is inherited in an autosomal recessive manner, three distinct groups of patients can be identified. These are thought to result from allelic mutations in the cystinuria gene.[2] The location of the cystinuria gene is, at present, unknown. We present a child with cystinuria, mental retardation, and a translocation between chromosomes 14 and 20.

Case report

A female infant was born at term weighing 3350 g. The healthy, unrelated, Caucasian parents (father 24 years and mother 22 years) had one previous normal child. There was no family history of renal disease. Global developmental delay was recognised at 18 months of age. Clinical examination at 3 years showed a child with normal linear growth and head circumference and moderate mental retardation. She had no dysmorphic features or structural abnormalities. Routine investigation showed the karyotype 46,XX,t(14;20) (q22;p13) (fig 1). Urine amino acid analysis on three occasions indicated grossly increased excretion of cystine, ornithine, lysine, and arginine. Her renal function and renal ultrasound were normal. Both parents had normal karyotypes.

Results

A 24 hour urine collection was performed on the child and both parents. The results are shown in the table. Amino acids were measured using cation exchange HPLC, incorporating post column derivatisation with ninhydrin, and detection at 570 nm wavelength. The child was subsequently given an oral loading dose of L-cystine dihydrochloride of 0·25 mmol/kg body weight. The changes in plasma cystine concentration are shown in fig 2.

Discussion

Homozygotes for both type I and type II cystinuria excrete significantly increased quantities of cystine, ornithine, arginine, and lysine in the urine. They also both exhibit total impairment of intestinal absorption of cystine after an oral load. However, they can be discriminated by studying the phenotype of their parents. Type I heterozygotes excrete normal quantities of amino acids in the urine, whereas

South West Thames Regional Genetic Service, St George's Hospital Medical School, Cranmer Terrace, London SW17 0RE.
M Sharland
M A Patton

Department of Child Health, St George's Hospital Medical School, Cranmer Terrace, London SW17 0RE.
M Jones
M Bain
R Chalmers

Department of Paediatrics, Queen Mary's Hospital for Children, Carshalton, Surrey.
J Hammond

Correspondence to Dr Sharland.

Received 3 July 1991.
Revised version accepted 3 December 1991.

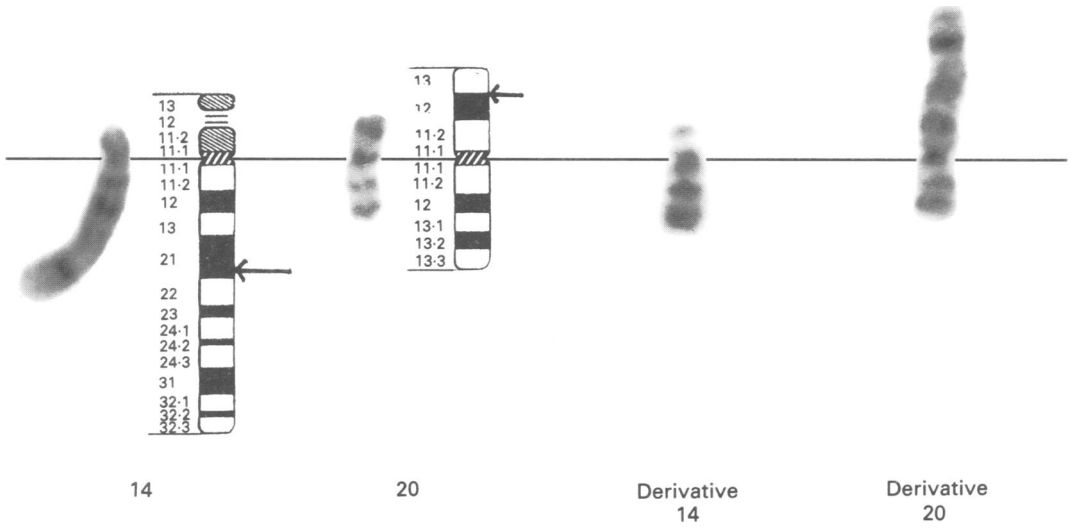

Figure 1 Karyotype of affected child: 46,XX,t(14;20)(q22;p13).

Quantitative 24 hour excretion of dibasic amino acids.

Subject	24 hour urinary excretion (μmol/24 h/kg body weight)*			
	Cystine	Lysine	Ornithine	Arginine
Child	7·3	45·9	7·0	8·1
Mother	9·2	47·5	1·4	1·0
Father	0·9	5·8	0·4	Not detected

* Normal ranges for excretion of amino acids in μmol/24 h/kg body weight are: cystine 0·5–3·7, lysine 1·1–29·6, ornithine 0·1–0·8, arginine 0·1–1·0.[3]

type II heterozygotes have a dibasic hyperaminoaciduria.[4]

It is apparent from the increase in the child's plasma cystine levels after the oral load test, and the gross differences in the 24 hour excretion of dibasic amino acids between the parents, that the child is not a homozygote for either type of cystinuria. The mother is a type II heterozygote owing to raised 24 hour urinary levels of cystine and lysine, comparable to those of the child, but only moderately raised levels of ornithine and arginine. If the child is also a type II heterozygote, then the urinary levels of arginine and ornithine would be expected to be much lower, but in fact the levels lie between the ranges described for type II heterozygotes and cystinuria homozygotes. It is possible that this may be because of increased urinary excretion of arginine and ornithine in infancy, which decrease with age.[5] A separate genotype has been described consisting of compound heterozygotes for both type I and type II cystinuria, where levels of urinary excretion of dibasic amino acids are also intermediary between these two ranges.[3] The oral load test results suggest that this child may be a compound heterozygote for both the type I and type II genotypes. The father in this family has a normal urine amino acid profile. It cannot be differentiated whether he is a type I heterozygote or has no genetic abnormality. The population heterozygote frequency of cystinuria is approximately 1 in 80. It is therefore most likely that the father is not a heterozygote. The type I genotypic abnormality found in the child must then be the result of a gene deletion associated with the translocation.

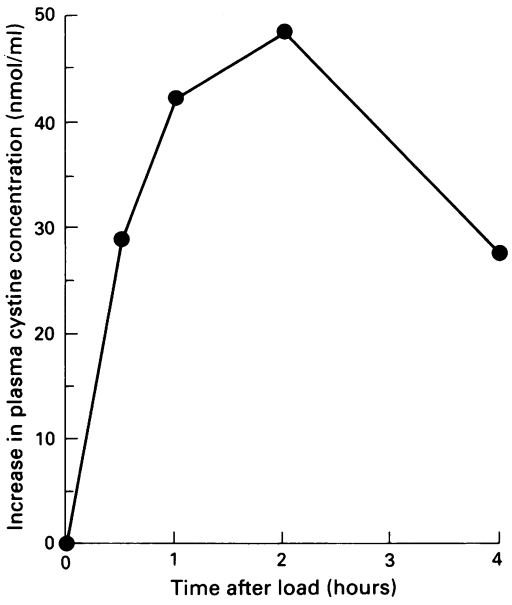

Figure 2 Changes in plasma cystine levels after an oral L-cystine dihydrochloride load of 0·25 mmol per kg body weight in the cystinuric child.

Scriver *et al*[6] suggested that defective brain transport mechanisms in cystinuria patients could produce mental retardation. However, a large clinical study of childhood cystinuria in New South Wales found no evidence of mental retardation.[7] Extensive investigations have indicated no cause for this child's developmental delay. It is recognised that up to 10% of children with apparently balanced translocations have some mental retardation, presumably owing to submicroscopic deletions. It is possible that this child has a significant deletion at either 14q22 or 20p13. This deletion may explain her mental retardation and be responsible for an abnormality in the cystinuria gene. Further molecular studies of cystinuric families using probes from these areas could help to locate the gene for cystinuria.

1 Rosenberg LE, Durant JL, Holland JM. Intestinal absorption and renal extraction of cystine and cysteine in cystinuria. *N Engl J Med* 1965;**273**:1239–45.
2 Rosenberg LE. Cystinuria: genetic heterogeneity and allelism. *Science* 1966;**154**:1341.
3 Morin CL, Thompson MW, Jackson SH, Sass-Kortsak A. Biochemical and genetic studies in cystinuria, observation on double heterozygotes of genotype I/II. *J Clin Invest* 1971;**50**:1961–76.
4 Rosenberg LE, Downing S, Durant JL, Segal S. Cystinuria: biochemical evidence for three genetically distinct diseases. *J Clin Invest* 1966;**45**:365–71.
5 Scriver CR, Clow CL, Reade TM, *et al.* Ontogeny modifies manifestations of the cystinuria genes; implications for counselling. *J Pediatr* 1985;**106**:411–6.
6 Scriver CR, Whelan DT, Clow CL, Dallaire L. Cystinuria: increased prevalence in patients with mental disease. *N Engl J Med* 1970;**283**:783–6.
7 Smith A, Yu JS, Brown DA. Childhood cystinuria in New South Wales. *Arch Dis Child* 1979;**54**:676–81.