Familial phosphoglycerate kinase deficiency associated with rhabdomyolysis and acute renal failure: abnormality in mRNA splicing?

Sir,

Phosphoglycerate kinase (PGK) is a glycolytic enzyme encoded by a gene located on chromosome X [1]. The clinical appearance of PGK deficiency is often dominated by myopathy usually associated with rhabdomyolysis, myoglobinuria and acute renal failure [2]. Here we describe two new myopathic cases of familial PGK deficiency (father and daughter) where abnormalities in mRNA splicing are suspected.

Cases. Following moderate exercise in a physical education class, a 17-year-old girl presented muscular fatigue, brown-coloured urine, high fever and general malaise. She had a history of repeated effort intolerance exacerbated in physical education classes. Upon admittance, she had: urea 370 mg/dl, creatinine 6.5 mg/dl, potassium 6.9 mEq/l and creatine phosphokinase 25 000 IU/l (normal: -190 IU/l). After 13 days of oliguria and 10 haemodialysis sessions her renal function returned to normal.

Four years previously, her father (36-year-old) presented a similar episode. During a mild respiratory infection combined with alcoholic consumption, he presented diffuse muscular pain. In our unit, the blood tests showed: urea 205 mg/dl, creatinine 8 mg/l, potassium 8 mEq/l and creatine phosphokinase 56 250 IU/l. After 17 days of oliguria and nine haemodialysis sessions his renal function returned to normal.

The presence of rhabdomyolysis complicated with acute renal failure in both father and daughter in the absence of an obvious cause prompted us to suspect a genetic defect. In muscle extracts from both patients, several glycolytic enzymes had normal activities, except for PGK which was decreased. The decrease was more pronounced in the daughter, with only 2% of normal activity (1200–1600 nmol/min/mg protein).

Total RNA was isolated from the muscle biopsies of both patients. Phosphoglycerate kinase cDNA was amplified by RT–PCR from the patients’ mRNA and from that of an unaffected control. The PCR products were subcloned into plasmids and transfected into competent bacterial cells. Screening of the colonies containing the inserts showed that both the father and the daughter had not only normal size PGK mRNA, but also other species of higher and lower molecular weight compared with control. While 100% of the control colonies had normal size PGK cDNA (1300 bases; Figure 1A), only ~23% of the daughter’s and ~14% of the father’s PGK cDNA were of normal length (Figure 1B and C, respectively). These data strongly suggest that both patients have a defect at the PGK mRNA level, probably involving splicing.

Comment. There are 23 reported cases with PGK deficiency at present. In 14 of them the molecular genetic defects have been elucidated [3]. One is a 3 bases deletion, whereas the 11 others are single amino-acid substitutions that impair enzymatic activity by affecting enzyme catalysis or stability. In two of the cases the defects are at the level of mRNA splicing [4,5].

![Fig. 1. PCR screening of several bacterial colonies containing plasmids with PGK cDNA as insert. All the colonies have normal size PGK cDNA (1300 bases) in the case of control (A), while in the case of the patients the PGK cDNA length is heterogeneous. (B) PCR screening for daughter and (C) PCR screening for father.](https://example.com/f1.png)
A notable particularity in our cases is that the defect has been presumably transmitted from father to daughter. The majority of cases with clinical appearance are described in men, but there are several examples of phenotype manifestations in heterozygous females with PGK deficiency [6], including the first case ever described in 1968 [7].

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1. Michelson AM, Markham AF, Orkin SH. Isolation and DNA sequence of a full-length cDNA clone for human X chromosome-encoded phosphoglycerate kinase. Proc Natl Acad Sci USA 1983; 80: 472–476