The severe form of type I hyperprolinaemia results from homozygous inactivation of the PRODH gene

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Since the original reports of hyperprolinaemia by Scriver et al.¹ and Shafer et al.,² two types of this rare metabolic disorder have been biochemically characterised: type I (MIM 239500) results from the defect of the enzyme proline dehydrogenase (oxidase), which ensures the conversion of proline into 1-1-pyrroline-5-carboxylate (P5C), the first step in the conversion from proline to glutamate,³ and type II (MIM 239510) is the result of a defect of the P5C dehydrogenase/aldoxide dehydrogenase 4 enzyme and P5C is excreted in the urine.⁴

The phenotype of type II hyperprolinaemia is characterised by neurological manifestations including seizures and mental retardation.⁵ ⁶ ⁷ Although type I hyperprolinaemia was originally described in a kindred with a familial nephropathy,¹ ² ³ the renal disease was subsequently shown to be coincidental and type I hyperprolinaemia has been considered to be a benign disorder which can be asymptomatic.⁸ Nevertheless, two studies have reported severe neurological manifestations (mental retardation, epilepsy) in two male children with type I hyperprolinaemia.⁹ ¹⁰ While mutations of the ALDH4A1 gene, located on chromosome 1p36, have been identified in families with type II hyperprolinaemia,¹¹ the molecular basis of type I hyperprolinaemia has not been characterised until recently. We have recently identified in schizophrenic patients a heterozygous deletion and mutations of the PRODH gene, located on 22q11, which were associated with moderate hyperprolinaemia. We also found in two unrelated type I hyperprolinaemia children the same homozygous PRODH missense mutation.¹² We now report the identification of a complete homozygous PRODH deletion in a child with type I hyperprolinaemia with severe neurological manifestations.

CASE REPORT
The patient, a male, was the first child of healthy, consanguineous parents of Egyptian origin. At 4 years, he was referred for severe psychomotor delay, permanent hyperactivity, sleep disturbance with bruxism, and status epilepticus. Weight was 13 kg (−3 SD), length 95 cm (−2.5 SD), and head circumference 46 cm (−4 SD). There was no dysmorphism. Cerebral magnetic resonance imaging (MRI), performed at 4 years of age, showed normal myelination and no white matter abnormalities. Metabolic screening showed a very high level of plasma proline level (2246 µmol/l, n=133-227 µmol/l). Proline levels were also raised in urine (631 µmol/mmol creatinine, n<10 µmol/mmol creatinine) and cerebrospinal fluid (21 µmol/l,
DISCUSSION

We examined this patient for a genomic rearrangement of the PRODH gene, as previously described, using quantitative multiplex PCR of short fluorescent fragments (QMPSF), a method based on the simultaneous amplification of multiple short exonic sequences using dye labelled primers under quantitative conditions. The exploration of the PRODH locus is complicated by the presence on 22q11 of a non-functional PRODH-like pseudogene, which shares exons 8-13 with PRODH. Because PRODH specific primers cannot be designed for these exons, detection of heterozygous and also of homozygous rearrangements of the PRODH gene requires quantitative conditions. QMPSF analysis showed a complete homozygous deletion of PRODH in this patient (fig 1A). Additional QMPSFs, exploring the centromeric USP18 and DGCR6 genes and the telomeric LOC200301, DGSA- and DGCR2 genes, surrounding PRODH, showed that the homozygous 22q11 deletion also removed the DGCR6, LOC200301, and DGSA loci (fig 1B). This 22q11 deletion (fig 2), estimated to be approximately 350 kb, is similar to that previously identified, in a severely affected type I hyperprolinemia patient. 

REFERENCES


