European Journal of Medical Genetics 55 (2012) 476–479

Contents lists available at SciVerse ScienceDirect

European Journal of Medical Genetics

journal homepage: http://www.elsevier.com/locate/ejmg

Short clinical report

Broadening the phenotype associated with mutations in UPF3B: Two further cases with renal dysplasia and variable developmental delay

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ARTICLE INFO

Article history:
Received 20 February 2012
Accepted 31 March 2012
Available online 25 April 2012

Keywords:
UPF3B
Renal dysplasia
Autistic spectrum disorder
Macrocephaly

ABSTRACT

We present two brothers with mutations in *UPF3B*, an X-linked intellectual disability gene. Our family consists of two affected brothers and a carrier mother. Both affected brothers had renal dysplasia. A maternal uncle died from a congenital heart defect at 4 months. The two boys had variable degrees of developmental delay. One had macrocephaly, significant expressive speech delay and constipation. The other brother had normocephaly, obsessional tendencies and was diagnosed with high functioning autism. The phenotypically normal mother had 100% skewed X-inactivation. Our cases expand the phenotype seen with *UPF3B* mutations and highlight the variability within families.

1. Cases

Case 1 was born at 42 weeks weighing 2722 g following a normal pregnancy. The delivery was vacuum assisted. He was diagnosed with lactose intolerance at 6 weeks, this resolved with a change of formula milk. He walked at 13 months, he never crawled. He had a normal neonatal course with normal feeding. His early milestones were normal and concerns were only raised at age 3.5 years regarding his communication. He was diagnosed with pervasive developmental disorder and attention deficit disorders at age 5 years, and was diagnosed with autism at age 10 years. He has been described as having an Aspergers-like personality with some obsessional tendencies. He is described as having dyspraxia and a mild learning disability. He was referred to the genetics clinic at age 11 years. He attends a mainstream school but gets educational support, and is three years behind his classmates. His speech is good but he cannot read. He has no history of hypotonia or constipation, he was fully toilet trained by 3 years. He has asthma, hayfever and is lactose intolerant. He sometimes exhibits hand flapping and high pitch shouting behaviour.

On examination his head circumference was 54.5 cm at 10 yrs 6 months (50th centile). He had a long face with a high nasal bridge, a short philtrum, and a protruding and prominent upper lip. His lower lip was also prominent and he had a gap between his two front teeth. He had deep set eyes (see Fig. 1).

Renal ultrasound scan done because of his brother's history at age 11 years showed an enlarged right kidney measuring 11.3 cm. The left kidney could not be visualised raising the possibility of an absent of dysplastic left kidney with compensatory hypertrophy of the right kidney. An MRI brain scan revealed normal brain parenchyma and a small pineal cyst. Repeat MRI one year later showed no change in size of this cyst. He had normal karyotype, 46,XY and normal Fragile X testing.

Case 2 was born at 37th week by lower segment caesarean section. There was oligohydramnios, and inter-uterine growth retardation was noted from 33 weeks of pregnancy. His birth weight was 2 kg, and he had jaundice in the early neonatal period which resolved. He required phototherapy for two days. He spent the first 4 weeks in hospital with feeding difficulties and had nasogastric feeding initially. He was re-admitted at 11 months with failure to thrive. He was noted to have macrocephaly and hepatosplenomegaly. He had a history of constipation from age 1 year. He remains on a laxative since then, and this is a significant problem for the family. He was macrocephalic, OFHC 50 cm (>97th centile), his head growth decelerated over time being 51 cm at 17

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doi:10.1016/j.ejmg.2012.03.010

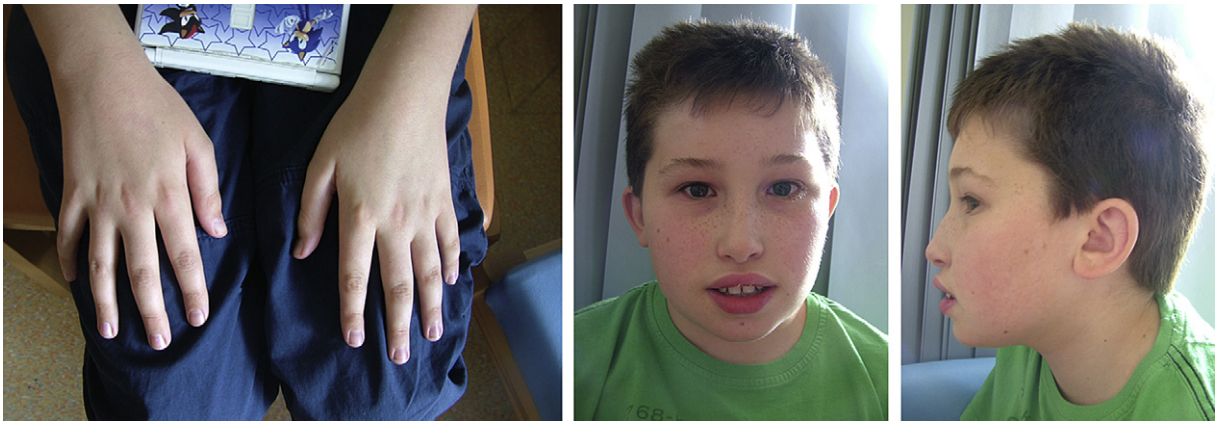

Fig. 1. Photographs of case 1 demonstrating the long face, high nasal bridge, short philtrum & full lips.

months (91st centile) and 55 cm at aged 6 years 5 months (between 75th and 91st).

His weight was 10 kg at 17 months (<25th centile). He was hypotonic. He had a palpable liver edge of 3 cm and his splenic tip was palpable. A renal ultrasound scan revealed a left multicystic dysplastic kidney with a normal hypertrophied right kidney, and a normal bladder. On examination at the age 3 years 5 months his Wt was 14.1 kg (75th centile), height 92.4 cm (75th centile) and OFHC 52.5 cm (>91st). He had motor delay; he sat unsupported at 16 months and walked at 18 months. He didn't crawl. He had marked expressive language delay with approximately 8 words at age 7 years. He had good comprehension of language. He is not yet toilet trained at the age of 8 years. He attends a mainstream school but has a full time special needs assistant. He has occasional temper tantrums & his parents describe his behaviour as being challenging, he has obsessive traits, he hand claps and shouts when excited.

Ophthalmology examination was normal. Echocardiography was normal. MRI brain was normal apart from showing prominent sub-arachnoid spaces. He had very similar facial dysmorphic features to his brother with a long face, a high nasal bridge with a long narrow nose, deep set eyes, a short philtrum and a protruding and prominent upper lip (see Fig. 2). He had mild frontal bossing and a dished out facial appearance. His lower lip was also prominent and he had a gap between his two front teeth.

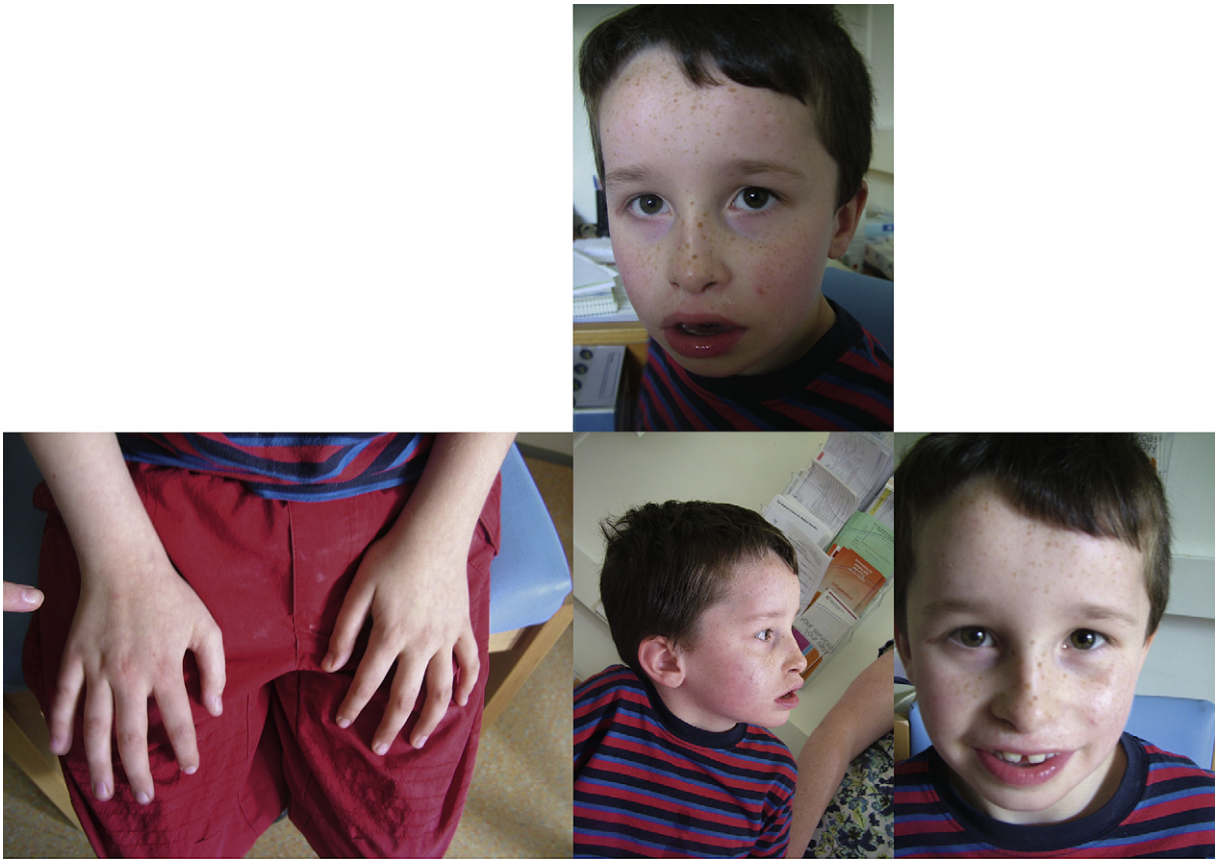

Fig. 2. Showing similar features to his brother with a long face, a high nasal bridge with a long narrow nose, deep set eyes, a short philtrum and a protruding and prominent upper lip.