Interstitial deletion of 10q23.1 and confirmation of three 10qdel syndromes

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ABSTRACT

A five-year-old girl with global developmental delay and mild dysmorphic features was referred for karyotyping. Cytogenetic analysis identified an interstitial deletion in the approximate position of chromosome band 10q23.1. The patient's DNA was analysed using an Affymetrix SNP6.0 array, and a 7.46Mbp deletion was detected within the region 10q22.3–q23.32. The deletion encompasses the *BMPR1A* gene, but does not extend as far as the phosphatase and tensin homolog (*PTEN*) locus. The location and extent of the deletion is the first of a small group of 10q deletion patients, which has been characterised at the level of resolution afforded by a SNP6.0 chip. Essentially, this case confirms that patients with microdeletions in the 10q23 region can be further divided into three sub-classes, depending on whether the deletion encompasses the *BMPR1A* gene, the *PTEN* gene or both.

Keywords: 10q22-23, *BMPR1A*, SNP array, juvenile polyposis

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INTRODUCTION

There are many reports in the literature of interstitial deletions in the long arm of chromosome 10; however, studies that were supported with molecular analysis are rare.[1-7] In the study reported here, a new patient was analysed by cytogenetic, fluorescence *in situ* hybridisation (FISH) and high-resolution oligonucleotide-based SNP6.0 array technology, which identified the location and extent of a deletion within 10q23.1 that supports the sub-classification of patients with interstitial microdeletions in chromosome 10.

CASE REPORT

A female baby weighing 5.1 kg was born by Caesarean section at 42 weeks after a normal pregnancy. A ventricular septal defect was diagnosed at six months of age, when she presented with poor weight gain and persistent tachypnoea, which was then surgically repaired. The patient's early milestones were not significantly delayed, and she began walking a few months past her first birthday. Although the onset of speech was not delayed, it lacked fluency. She suffered from recurrent middle ear infections and required the insertion of tympanostomy tubes.

Due to persistent developmental delays, the child was assessed by a paediatrician at four years of age. A Griffith Mental Developmental assessment performed at 5.5 years of age demonstrated an overall functioning at the 4– 4.5 year level. Specific scores were: locomotor skills 4–4.5 years; personal-social skills 5 years ± 3 months; hearing

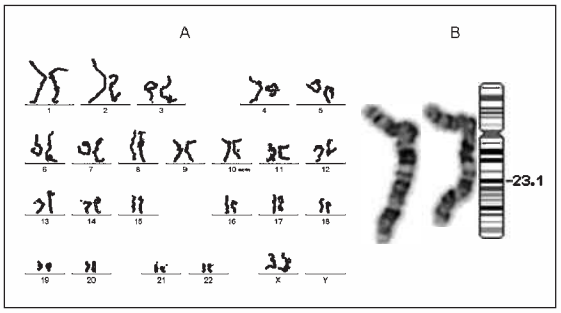

Fig. 1 Karyotype analysis of proband's chromosomes: GTG banded metaphase chromosomes are shown in panel A [46, XX, del(10)(q23.1q23.2)], and a closer view of the patient's normal (left) and deleted chromosomes 10 (centre), together with a chromosome 10 ideogram at 850 band level is shown on the right (panel B).

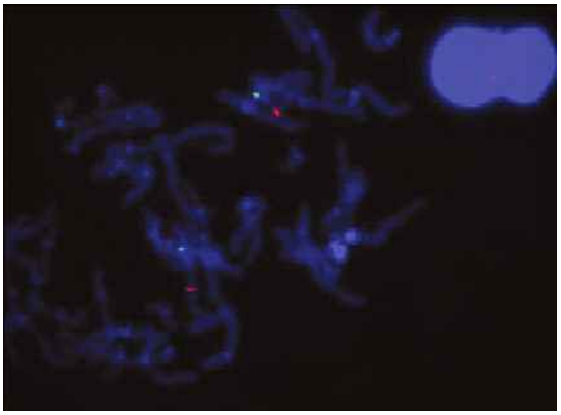

Fig. 2 FISH analysis of proband's chromosomes. FISH analysis using the *PTEN* and chromosome 10 centromeric loci revealed a signal pattern of two green (centromere) and two red (*PTEN*) signals, which is consistent with a normal (negative) result. The data indicates that the deletion does not encompass the *PTEN* locus located at chr10q23.31 (position 89,613,175bp-89,718,512bp).

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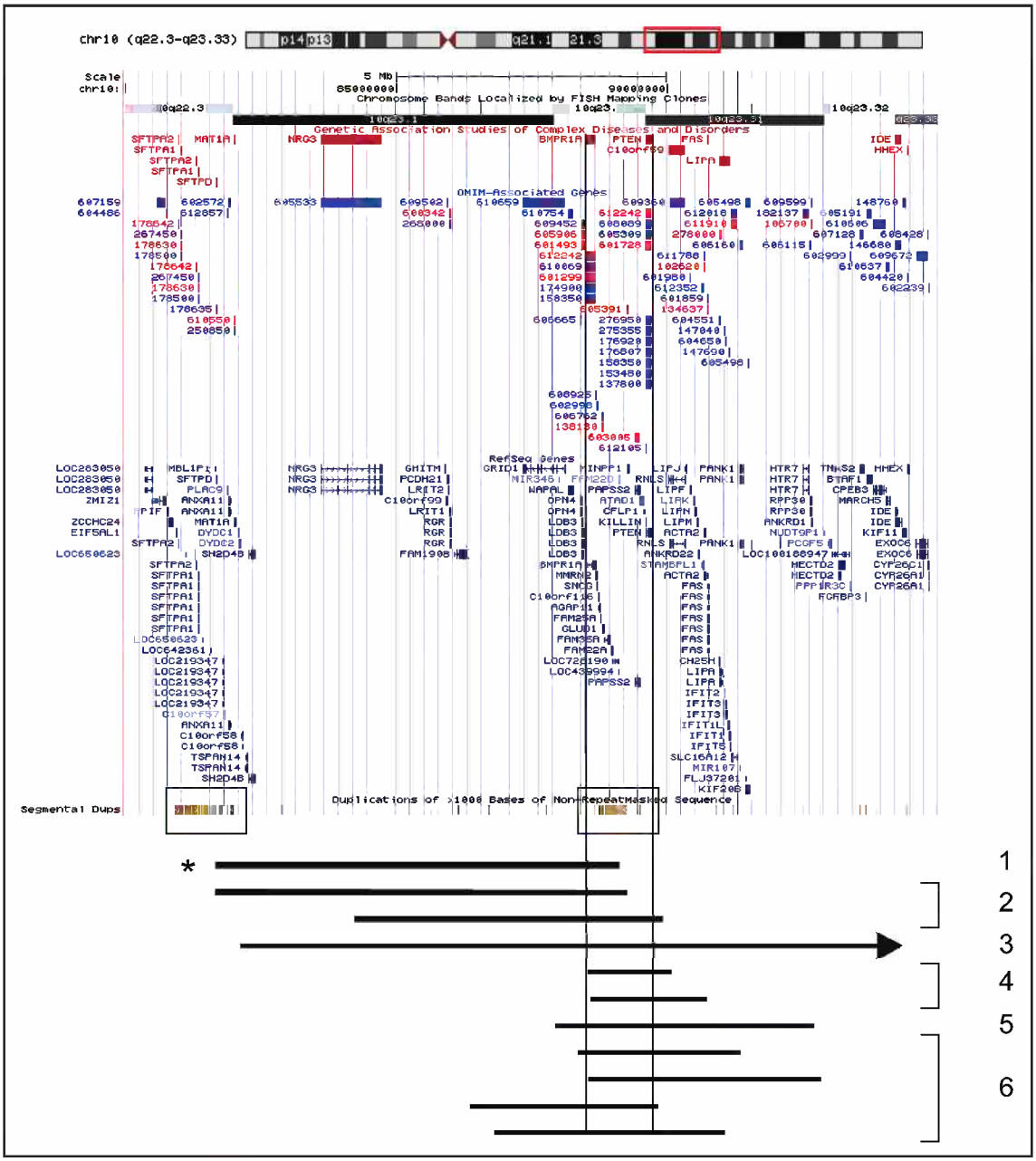

Fig. 3 Location and extent of interstitial deletions in 10q22.3-23.3. The upper panel shows an ideogram of chromosome 10 and the genes that are localised to chr10q22.3q23.32 (available from UCSC genome browser http://genome.ucsc.edu). This figure also shows the regions (boxed) of segmental duplication that comprise the low copy repeat (LCR) domains – LCR3 (proximal) and LCR4 (distal). The location and extent of the interstitial deletions of the patient described here, and of others reported in the literature, are shown in the bottom panel: (1) this study; (2) Balciuniene et al[4] (upper line is UM10qDel-01 and JHU10qDel-01, and lower line is JHU10qDel-02); (3) Salviati et al[3]; (4) Delnatte et al[2]; (5) Tsuchiya et al[1]; (6) Menko et al. [7] The vertical lines delineate the region encompassing the *BMPR1A* and *PTEN* genes.

and language skills 4–4.5 years; performance skills 4–4.5 years; and practical reasoning 4.5–5 years. She exhibited normal growth; at five years of age, her height and weight were at the 97th percentile, her head circumference at the 90th percentile, and the corrected midparental height was at the 50th percentile.

A right-sided exotropia was managed successfully by eye patching. Rectal bleeding was never observed by the child's parents, and there was no family history of rectal bleeding or intestinal polyps. When assessed at the genetics clinic, no significant dysmorphic findings were noted. She had mild epicanthic folds and hyperkeratosis of the fifth toenail. The patient's karyotype was found to be 46, XX, del(10)(q23.1q23.2) (Fig. 1). The parental karyotypes were normal, and therefore, she carried a *de novo* deletion. To investigate the presence of the tumour suppressor gene phosphatase and tensin homolog (*PTEN*), the loss of which is involved in several cancers,

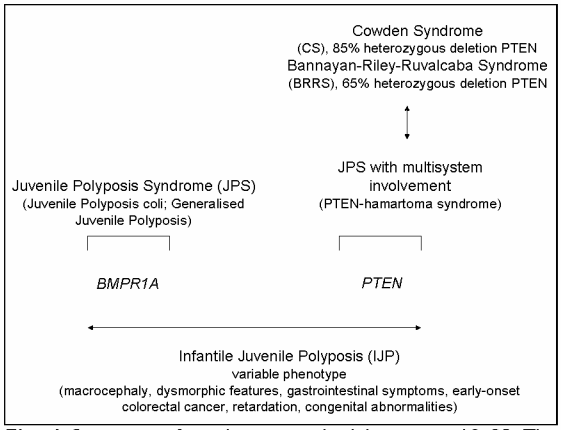

Fig. 4 Summary of syndromes with deletions in 10q23. The syndromes described here have been taken from a variety of sources.[2,7-11]

FISH was undertaken using the locus specific probe (i.e. *PTEN*). Two copies of the *PTEN* region (89,613,175bp-89,718,512bp) were detected (Fig. 2); further testing was thus initiated in order to define the precise breakpoint and to identify genes that were present within the deleted region.

Chromosomal DNA was extracted from blood collected in EDTA using a Qiagen Midi Kit (Qiagen Pty Ltd, Valencia, CA, USA). DNA was processed for hybridisation to an Affymetrix® SNP6.0 chip according to the manufacturer's instructions (Affymetrix Inc, Santa Clara, CA, USA). The subsequently scanned slide was analysed using Genome Console (version 3.1) software. The SNP6.0 array analysis identified a heterozygous 7.46Mbp deletion on chromosome 10q, with breakpoints located at 81,634060bp and 89,068,181bp. Fig. 3 shows the deleted region of chromosome 10 and the genes it contains (Human March 2006 (hg18) assembly; available at: http://genome.ucsc.edu/). This deletion removes several genes that are central to cognitive, behavioural development and cell proliferation, of which the *BMPR1A* gene is the most notable gene involved.

DISCUSSION

In recent years, the interstitial deletion of chromosome 10q22-23 has become a well-documented deletion associated with several syndromes, such as Cowden syndrome, Bannayan-Riley-Ruvalcaba (BRR) syndrome and juvenile polyposis syndrome (JPS).[8] The clinical phenotypes observed in individuals carrying deletions in chromosome 10q23 are variable. Some of these differences may be explained by differences in the extent of the deletions, but there is no strict correlation between the location and extent of a deletion and the clinical phenotype (Fig. 4).

The 10q23 region harbours genes that are important for neurodevelopment and function. *NRG3* is a candidate gene for schizophrenia, and *GRID1* is associated with schizophrenia and schizoaffective disorders.[12] Several genes in the 10q23 region *(NRG3, GRID1, BMPR1A, SNCG, GLUD1)* are of importance to neurobehavioural development and function. Interestingly, mutations in the *BMPR1A* gene are found in 20% of patients with JPS.[13,14] These mutations comprise point mutations as well as exonic and whole gene deletions. Patients with JPS develop gastrointestinal polyps by 20 years of age which, if not treated, will bleed and cause anaemia. Our patient had not undergone an endoscopy as she remained asymptomatic; thus, we could not justify the procedure. In view of this, and of her young age, the possibility of JPS could not be ruled out.

The location and extent of the deletion detected in our patient, as well as the symptoms of mild developmental delay and mild dysmorphism, are very similar to those reported for patients with UM10qDel-01 and JHU10qDel-01.[4] Critically, other patients with deletions in this region were deleted for both the *PTEN* and *BMPR1A* genes.[1,4-15] These patients presented with juvenile polyps and macrocephaly, features which are characteristic of Cowden disease or BRR syndrome. Balciuniene et al proposed that the complex set of low-copy repeats (LCRs) in the 10q23 region increases susceptibility to chromosomal rearrangements.[4] The deletion in the proband has breakpoints that lie in the LCR3 and LCR4 domains (Fig. 3), which suggests that the deletion occurred as a consequence of non-allelic homologous recombination.[16]

In conclusion, this study confirms the sub-classification of patients with microdeletions in the 10q23 region but with mild early-onset symptoms, into those that are deleted for the *BMPR1A* gene alone, as opposed to those with deletions that lie more distal and encompass the *PTEN* gene, and those with deletions that encompass both genes. The data supports the role of segmental duplications in deletion events, as well as the view that array-based analysis of patients with interstitial deletions in 10q23 will allow for improved patient management and counselling.

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