RESEARCH NOTE

A study of a rare chromosomal disorder: mosaic 46,XX,del(18)(p11.2)/46,XX,i(18q)

DAN PENG*, PAN-PAN LONG, BO WEN and RONG-HUI YU

Genetic Counseling Unit, Department of Centralab, The First People's Hospital of Changde City, Changde 415000, Hunan, People's Republic of China

[Peng D., Long P.-P., Wen B. and Yu R.-H. 2013 A study of a rare chromosomal disorder: mosaic 46,XX,del(18)(p11.2)/46,XX,i(18q). *J. Genet.* **92**, 611–615]

Introduction

Fissions, isochromosomes and whole arm translocations with breakpoints at or very near the centromere arising limited to chromosomes 12, 18 and X are uncommon in human clinical cytogenetics. Although, a few prenatally diagnosed cases of monosomy 18p and trisomy 18q mosaicism were reported before (Badalian *et al.* 1983; Sutton and Ridler 1986; Qumsiyeh *et al.* 1995), morphological characteristics of such syndromes are not yet fully described due to the rarity of incidence and their spontaneous termination or poor postnatal survival. Here we describe an adult patient with a rare and complex chromosomal disorder of monosomy 18p and trisomy 18q mosaicism. After initial diagnosis by method of standard cytogenetic technique, we ultimately confirmed the karyotype of mosaic 46,XX,del(18)(p11.2)/46,XX,i(18q) by fluorescence *in situ* hybridization (FISH). Theoretically, the clinical features of our case would be expected to be a combination of these two types of chromosomal disorders. Relevantly, syndrome of monosomy 18p, with deletion of all or part of the short arm of chromosome 18 (Grosso *et al.* 2005; Turleau 2008), is manifested as short stature, round face with short philtrum, palpebral ptosis, flat nasal bridge, large ears with detached pinnae, and short neck. Mental retardation and speech delay are very frequent, and intellectual deficiency is mild to moderate (Wester *et al.* 2006; Maranda *et al.* 2006; Koshy *et al.* 2011). Isochromosome 18q is a rare cytogenetic abnormality usually viewed as Edwards syndrome for its trisomy 18q and the similar features, the clinical characters of which are variable, and overlap with monosomy 18p (Hook *et al.* 1989; Turan *et al.* 2005; Pal *et al.* 2007). Interestingly, phenotypic characters of our patient were mainly consistent with those previously described in cases of monosomy 18p, while fractionally with trisomy 18q syndromes. A possible mechanism for the origin of such a mosaicism and genotype–phenotype correlations are discussed.

Materials and methods

Case report

Patient, a 22-year-old woman under evaluation for infertility, had experienced secondary amenorrhoea for 6 months. As her mother described, from the menarche age of 13, she had menstruated very irregularly and always with little amount of flow until her menses ceased half a year ago. Hormonal replacement had not been adopted. Her delivery was uneventful, and she was the firstborn of a family with two children. No family history of hereditary disease or mental retardation was noted. Her parents and brother were phenotypically normal. Physical examination showed weight of 48 kg, height of 140 cm, and facial dysmorphisms: round and expressionless face, flat and broad nasal bridge, large and floppy ears, bushy eyebrows, and with a short neck, also in apparent good health (figure 1 in electronic supplementary material at http://www.ias.ac.in/jgenet/). Secondary sexual characteristics were obviously reduced in view of her age. Marked slowness in motion and action was noted. Mild mental retardation and communication disorders were observed. Ultrasound diagnosis showed hypoplastic uterus. Both her right and left ovary were normal with respect to dimension and form. The patient had low levels of gonadotropins and thyroid-stimulating hormones (LH, 0.87 IU/L; FSH, 0.90 IU/L; TSH, 0.23 mIU/L).

Cytogenetic studies

Peripheral blood specimens were collected and cytogenetic analysis was performed on GTG-banded metaphase spreads

*For correspondence. E-mail: dasan0988@126.com.
Dan Peng and Pan-Pan Long contributed equally to this work.

Keywords. chromosome 18; mosaicism; monosomy; trisomy; isochromosome.

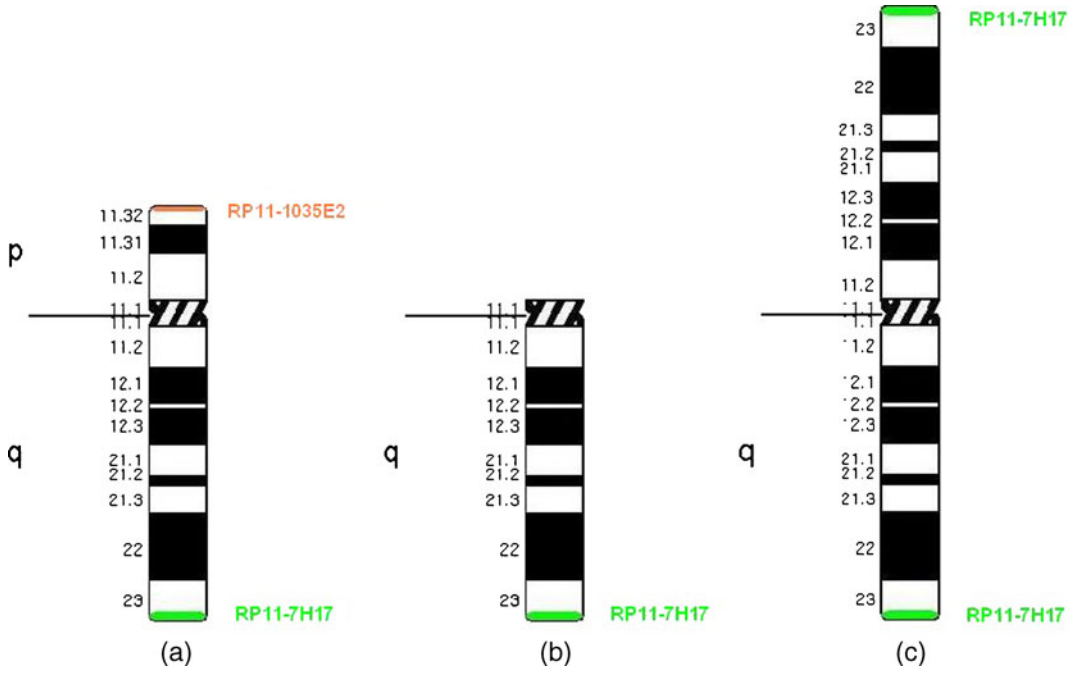

Figure 1. Schema of tested probes for chromosome 18: (a) normal, (b) 18p, and (c) isochromosome 18q.

prepared from phytohaemagglutinin (PHA)-stimulated peripheral blood lymphocytes. The harvesting of the cultures was done after 72 h of incubation and 100 GTG-banded metaphases were karyotyped; chromosomes were analysed according to guide lines provided by the International System for Human Cytogenetic Nomenclature (Lisa *et al.* 2012).

Fluorescence *in situ* hybridisation (FISH) was performed according to the protocol recommended by the probe supplier (Vysis-Abbott, Downers Grove, USA). Two types of DNA FISH probes were used in our study to describe the structure of abnormal chromosomes: RP11-7H17 (green fluorescence) specific for the distal portion of 18q situated at 18q23 and RP11-1035E2 (orange fluorescence) for the distal portion of 18p situated at 18p11.32 (figure 1). Chromosome preparations were observed under an epifluorescence Olympus BX51 microscope (Olympus Optical, Tokyo, Japan) fitted with the appropriate filters and a Mega-Pixel digital CCD camera (Video Test, Saint-Petersburg, Russia).

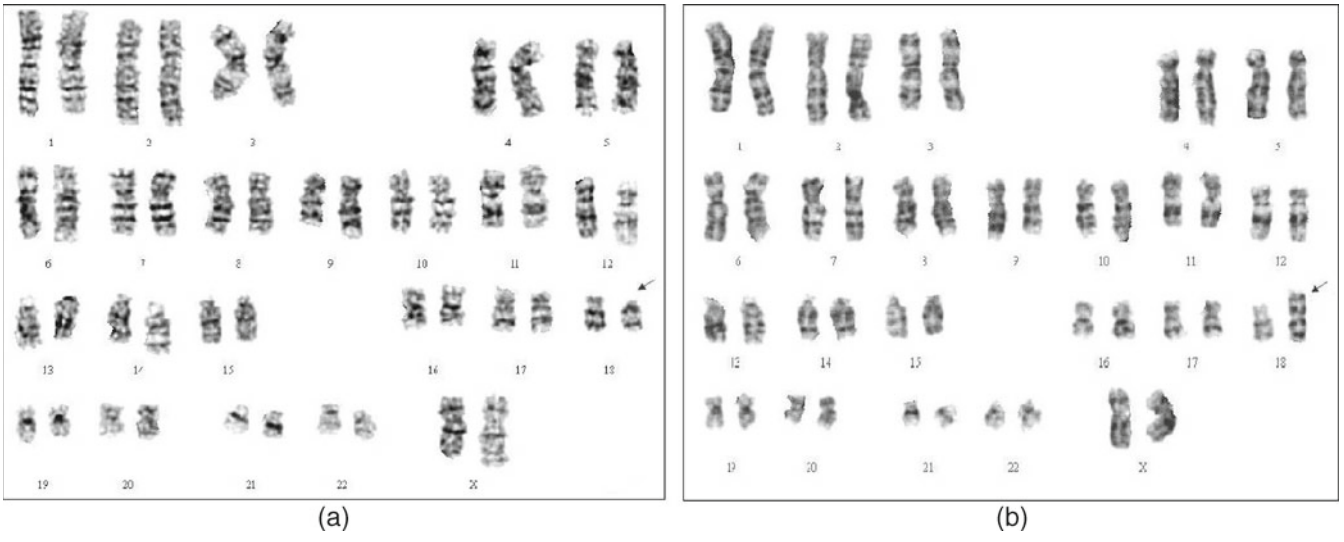

Figure 2. G-banding of two karyotypes: (a) 46,XX,del(18)(p11.2) with 18p, (b) 46,XX,i(18q) with isochromosome 18q.

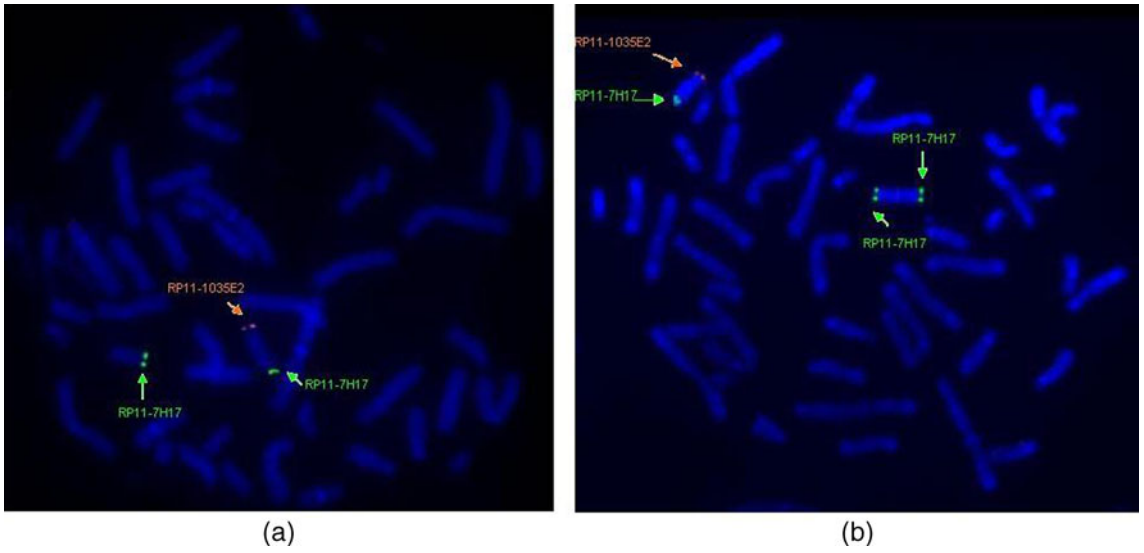

Figure 3. FISH results: (a) no orange fluorescence presented on deleted 18p, which is positive on the normal homologous chromosome 18, (b) double green fluorescent signals presented at both ends of isochromosome 18q.

Results

Karyotype examination showed 57 cells with 46,XX,del(18)(p11.2) and 43 cells with 46,XX,i(18q) in the 100 metaphases analysed (figure 2). The karyotypes of both parents and her brother were normal. *In situ* hybridization with the RP11-1035E2 probe (18p11.32) showed the absence of orange fluorescence both on the deleted 18p

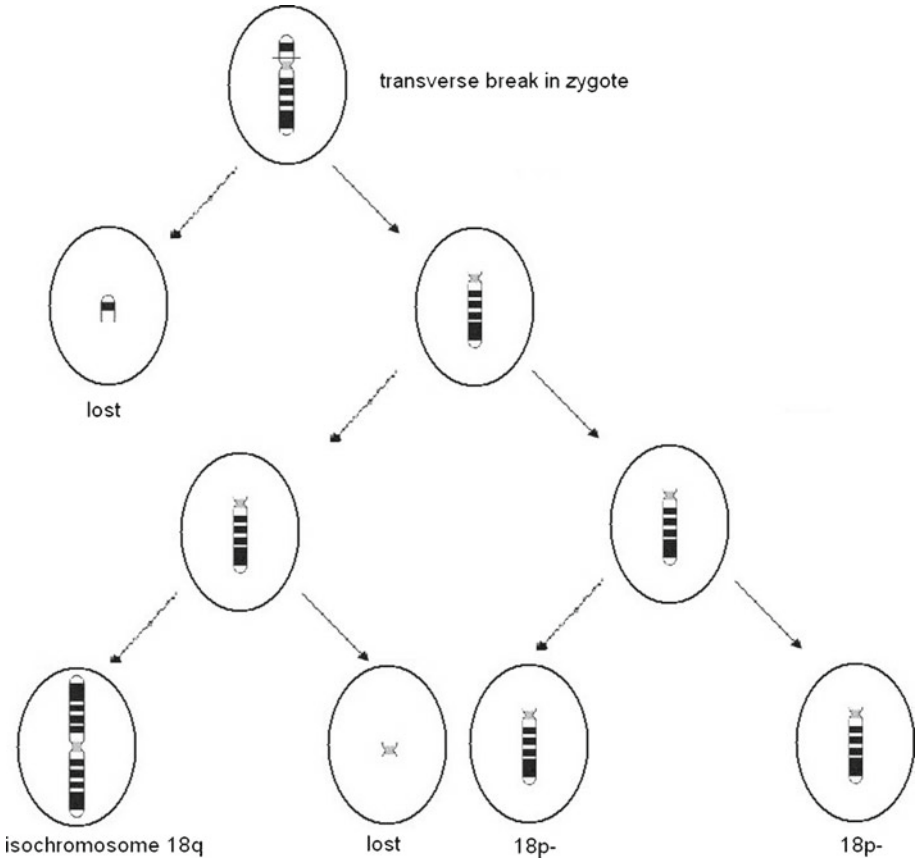

Figure 4. Schema of a possible mechanism for the origin of monosomy 18p and trisomy 18q mosaicism.

and the isochromosome 18q, which presented on the normal homologous chromosome 18 (figure 3). Hybridization with the RP11-7H17 probe (18q23) showed double green fluorescent signals at both ends of isochromosome 18q, which presented single signal on the deleted 18p and normal homologous chromosome 18 (figure 3). By method of FISH we confirmed the breakpoint, and it was manifest that there were distinctive recombinant chromosomes in two different karyotypes: one deleted chromosome consisting of one 18q arm and the proximal portion of 18p from the centromere to region of 18p11. 2; one derivative chromosome made up of two 18q arms.

Discussion

Patient showed a karyotype of mosaic 46,XX,del(18)(p11.2)/46,XX,i(18q), for which we believe the most likely mechanism is a transverse break through the proximal portion of 18p (Forrester and Merz 1999; Calvano *et al.* 2003). Similar to the Robertsonian translocations (Robinson *et al.* 1994; Daynna *et al.* 1996), the whole story of our patient would have started at the break event through the centromere of chromosome 18 in the earliest developmental stage of zygote, spliting the chromosome into a large arm (18q) with functionally complete centromere and a short arm (18p). The formation of the isochromosome 18q could have been a subsequent event: in the process of cell fission, the large arm might fuse to form a single chromosome with a single centromere, and the short arm usually and expectedly might be lost within a few cell divisions (figure 4).

The correlation between the breakpoints and the mental development suggests the critical region of chromosome 18 in this regard is between p11.1 and p11.2, in patients with deletions and mental retardation (Wester *et al.* 2006), and in this case of our patient chanced on the same deletion in the centromeric region between p11.1 and p11.2, and showed intellectual deficiency. In accord with the results of mapping of phenotypic traits, such as round face mapped to the distal 1.6 Mb of chromasome 18 short arm, postnatal growth retardation and seizures to the distal 8 Mb, and short neck to the proximal half of 18p (Brenk *et al.* 2007; Portnoï *et al.* 2007), symptoms manifested in our case confirmed these genotype–phenotype correlations.

As mentioned above, our patient presented with physical abnormalities and mental retardation of the 18p syndrome while with only minimal signs of trisomy 18, hence monosomy of the short arm in all cells seemed to be generally dominant. Probably because there is no one region of chromosome 18 region being sufficient to produce the phenotype of trisomy 18, for the contribution of triplicated loci to the phenotype is known to be neither additive nor invariant (Wilson *et al.* 1990).

Even though there were few prenatally-reported cases of monosomy 18p and trisomy 18q mosaicism before (Badalian *et al.* 1983; Sutton and Ridler 1986; Qumsiyeh *et al.* 1995), here we profile an adult patient phenotypically and genotypically which updates the information of chromosome 18 disorders.

References

Badalian L. O., Mutovin G. R., Malygina N. A. and Petrukhin A. S. 1983 Rare case of mosaicism for chromosome 18, karyotype: 46, XX, del(18) (p11)/46, XX, i(18q). *Genetika* **19**, 1912–1915.

Brenk C. H., Prott E. C., Trost D., Hoischen A., Walldorf C., Radlwimmer B. *et al.* 2007 Towards mapping phenotypical traits in 18p-syndrome by array-based comparative genomic hybridisation and fluorescent in situ hybridisation. *Eur. J. Hum. Genet.* **15**, 35–44.

Calvano S., Croce A. I. and Zelante L. 2003 Clonal evolution of an unbalanced structural rearrangement after telomeric fusion. 4th European Cytogenetics Conference Bologna, Italy.

Daynna J. W., Andrew P. M., Daniel L. V. D., Stuart S. and Huntington F. W. 1996 Molecular definition of breakpoints associated with human Xq isochromosomes: implications for mechanisms of formation. *Am. J. Hum. Genet.* **58**, 154–160.

Forrester M. B. and Merz R. D. 1999 Trisomies 13 and 18: prenatal diagnosis and epidemiologic studies in Hawaii, 1986–1997. *Genet. Test.* **3**, 335–340.

Grosso S., Pucci L., Di B. R. M., Gobbi G., Bartalini G., Anichini C. *et al.* 2005 Chromosome 18 aberrations and epilepsy: a review. *Am. J. Med. Genet. A* **134A**, 88–94.

Hook E. B., Topol B. B. and Cross P. K. 1989 The natural history of cytogenetically abnormal fetuses detected at midtrimester amniocentesis which are not terminated electively: new data and estimates of the excess and relative risk of late fetal death associated with 47, +21 and some other abnormal karyotypes. *Am. J. Hum. Genet.* **45**, 855–861.

Koshy B., Mandal K., Srivastava V. M., Loius P. T. and Danda S. 2011 Familial 18p deletion syndrome and 18p partial trisomy inherited from a mother with balanced translocation. *Clin. Dysmorphol.* **20**, 148–151.

Lisa G. S., Jean M. G. J. and Michael S. 2012 *ISCN 2013: an international system for human cytogenetic nomenclature*. Karger Publishers, Basel, Switzerland.

Maranda B., Lemieux N. and Lemyre E. 2006 Familial deletion 18p syndrome: case report. *BMC Med Genet.* **7**, 60.

Pal S., Siti M. I., Ankathil R. and Zilfalil B. A. 2007 Two cases of isochromosome 18q syndrome. *Singapore Med. J.* **48**, e146–e150.

Portnoï M. F., Gruchy N., Marlin S., Finkel L., Denoyelle F., Dubourg C. *et al.* 2007 Midline defects in deletion 18p syndrome: clinical and molecular characterization of three patients. *Clin. Dysmorphol.* **16**, 247–252.

Qumsiyeh M. B., Tomasi A. and Taslimi M. 1995 Prenatal detection of short arm deletion and isochromosome 18 formation investigated by molecular techniques. *J. Med. Genet.* **32**, 991–993.

Robinson W. P., Bernasconi F., Basaran S., Yüksel-Apak M., Neri G., Serville F. *et al.* 1994 A somatic origin of homologous Robertsonian translocations and isochromosomes. *Am. J. Hum. Genet.* **54**, 290–302.

Sutton S. D. and Ridler M. A. 1986 Prenatal detection of monosomy 18p and trisomy 18q mosaicism with unexpected fetal phenotype. *J. Med. Genet.* **23**, 258–259.

Turan S., Saka N., Guney I. and Bereket A. 2005 A patient with hypopituitarism and isochromosome 18q mosaicism. *Horm. Res.* **64**, 261–265.

Turleau C. 2008 Monosomy 18p. *Orphanet J. Rare Dis.* **3**, 4.

Wester U., Bondeson M. L., Edeby C. and Anneren G. 2006 Clinical and molecular characterization of individuals with 18p deletion: a genotype-phenotype correlation. *Am. J. Med. Genet. A* **140**, 1164–1171.

Wilson G. N., Heller K. B., Elterman R. D. and Schneider N. R. 1990 Partial trisomy18 with minimal anomalies: lack of correspondence between phenotypic manifestations and triplicated loci along chromosome 18. *Am. J. Med. Genet.* **36**, 506–510.

Received 11 July 2013, in final revised form 28 July 2013; accepted 6 August 2013
Published on the Web: 4 December 2013