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RESEARCH NOTE

Prenatal diagnosis of the Dandy–Walker malformation associated with partial trisomy 12p and distal 15q deletion

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Abstract. Dandy–Walker malformation (DWM) is characterized by complete or partial agenesis of the cerebellar vermis, cyatic dilatation of the forth ventricle, and enlarged posterior fossa. However, the mechanism is still not completely understood up to now. In this study, we reported a rare case that a foetus with DWM showed partial trisomy 12p and distal 15q deletion. Karyotype analysis and chromosomal microarray analysis (CMA) were not always concordant with each other, and it is suggested that they should be performed for prenatal genetic diagnosis together. DWM is a rare central nervous system malformation, reported in 1/25–30,000 live births, characterized by complete or partial agenesis of the cerebellar vermis, cyatic dilatation of the forth ventricle, and enlarged posterior fossa (Kumar *et al.* 2001; Klein *et al.* 2003; Agrawal *et al.* 2016). The neurological development of children with DWM may range from normal to severely retarded, and cause variable clinical feature. Although several efforts have been made to explore its pathogenesis, however, it is still not completely understood. During the past decade, some genetic loci, microdeletion or duplication have been reported to be associated with DWM, such as 9p trisomy, partial deletions of the long arm of chromosome 13, genes *ZIC1* and *ZIC4* (von Kaisenberg *et al.* 2000; McCormack *et al.* 2003; Grinberg *et al.* 2004). In the present study, we describe a prenatal diagnosis case that a foetus with DWM on ultrasound scanning accepted genetic testing, and it revealed a microduplication of 12p13.33p11.1 and microdeletion of 15q11.2 in 750K single nucleotide polymorphism (SNP) array, while it showed 46,XX,der(8)(8pter→8q24::12p10→12qter),i(12)(p10) in karyotyping.

Keywords. Dandy–Walker malformation; prenatal diagnosis; trisomy 12p; chromosomal microarray analysis.

Introduction

A 23-year-old pregnant woman, gravida 1 para 0, was referred for genetic counselling at 18 weeks of gestation due to abnormal ultrasound findings. The couple were healthy and had no family history of genetic disorders or chromosomal abnormality. They were nonconsanguineous and the mother had no history of exposing to teratogens, infections, irradiation, or smoking prior to pregnancy and during early pregnancy. The ultrasound examination at 13 weeks of gestation revealed increased nuchal translucency (NT). However, they refused genetic chorionic villus sampling and maternal serum screening in the first and second trimester. Ultrasound scanning at 18 weeks of gestation showed a partial absence of the cerebellar vermis, and enlarged posterior cranial fossa communicating with the fourth ventricle. The couple opted for termination of pregnancy, and part of the foetus tissue and amniotic fluid were sampled for the whole-genome microarray assay and rapid karyotype. But autopsy was not permitted. This study was approved by the ethics committee of Hebei General Hospital, and informed consent was obtained from the couple for participating in the study.

Materials and methods

Amniotic fluid cell culture and karyotype analysis

Amniotic fluid obtained by amniocentesis was inoculated into amniotic fluid culture medium (Irvine Scientific, Santa Ana, USA) at 37°C for 6–7 days after 8 min centrifugation. The amniotic fluid cells were collected for slide preparation when the cells exhibited multiple clones in metakinesis. Giemsa-band karyotyping on metaphase cells was performed according to standard cytogenetic protocol. Chromosomal

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karyotype analysis was performed at ~320-band resolution in accordance with the International System for Human Cytogenomic Nomenclature 2016 (ISCN 2016). Metaphase cells 20–30 were counted and at least five mitotic figures were analysed.

SNP array analysis

Genomic DNA was extracted from foetal tissue according to the manufacturer's protocol using a Genomic DNA Extraction kit (QIAamp DNA Blood Mini kit; Qiagen GmBH, Hilden, Germany). The genomic DNA containing 200,000 gene-centric SNP and 550,000 nonpolymorphic markers was screened using a microarray (Affymetrix CytoScan 750K Array). Array images were analysed using Affymetrix GeneChip Command Console software (v. 4.0) and Chromosome analysis software (v. 2.1).

Results

The cytogenetic analysis of cultured amniocytes obtained from the pregnent women with DWM (figure 1a) revealed a karyotyping of 46,XX,der(8)(8pter→8q24::12p10→12qter),i(12)(p10) in all 30 cells with the limited banding resolution as shown in figure 1b. The karyotype is unbalanced with loss of the segment 8q24qter and gain of 12p10. It showed a i(12p), a single normal copy of 12 and a derivative chromosome 8. The der(8) replaced a normal chromosome, which resulted from a translocation of the chromosome 8 segment distal to 8q24 to the short arm of chromosome 12 at band 12p10. Besides that, an isochromosome of 12p replaced one normal chromosome 12, indicating that there were three copies of 12p. The results of SNP array revealed arr[GRCh38] 12p11.1p13.33(173,786-34,835,641)×3,15q11.2(22,770,421-23,276,605)×1 (figure 1, c&d). Microarray analysis shows a 34.6-Mb duplication in chromosome 12p11.1-p13.33 and a 506.1-kb deletion in chromosome 15q11.2.

The karyotype analysis in peripheral blood lymphocyte culture of parents showed a 46,XX normal karyotype (figure 1e) and a 46,X,Yqh- karyotype (figure 1f). SNP array analysis of the couple was recommended for confirming the origin of markers; however, they refused genetic testing due to high cost.

Discussion

DWM is a neuropathologic disorder with high incidence of motor dysfunction and mental retardation without effective treatment measures, and aetiologic heterogeneity of the disease puzzled researchers and clinicians. Prenatal diagnosis of DWM is mainly based on ultrasound examination and magnetic resonance imaging (MRI); MRI is more accurate than ultrasound in evaluation of foetal cerebellar vermis and posterior fossa abnormalities. However, the pregnant women in the study was not recommended for foetal MRI before invasive prenatal genetic diagnosis, since it was less useful for foetus < 19 weeks of gestation due to the smaller size of the cerebellar and limited spatial resolution of MRI (Bernardo *et al.* 2015) .

Partial trisomy 9p, heterozygous loss of ZIC1 and ZIC4 on chromosome 3q2 was reported to contribute to the brain malformations (Grinberg *et al.* 2004; Temtamy *et al.* 2007). Distal 12p deletion was found in foetus with the DWD, but that result could not confirm the correlation (Chen *et al.* 2002). Pallister–Killian syndrome (PKS) is a rare genetic disorder characterized by mosaic distribution of an extra isochromosome 12p (Izumi *et al.* 2012). Chromosome 12p contains ~350 genes, including developmental genes such as *NANOG* (MIM: 607937), *CHD4* (MIM: 603277), and *SOX5* (MIM: 604975), and cancer-associated genes such as *KRAS* (MIM: 190070) and *ING4* (MIM: 608524). The presence of tetrasomy 12p in PKS could cause multi-system developmental disorder including intellectual disability, anal atresia, craniofacial dysmorphism, congenital heart defects, pigmentary skin anomalies, congenital diaphragmatic hernia, hypotonia and epilepsy; the aberration had been proven to be prezygotic and is of maternal origin in most cases (Izumi and Krantz 2014; Blyth *et al.* 2015). It is reported that foetus with PKS could show DWM in prenatal sonographic examination (Doray *et al.* 2002). Patients with trisomy 12p can have some features that differ significantly from that of PKS, however, some individuals with complete or partial trisomy 12p exhibited phenotypic overlap with PKS, and the duplication of the genes located within 12p13.31 might cause the core phenotype of PKS (Inage *et al.* 2010; Izumi *et al.* 2012). In this study, foetus with DWM showed trisomy 12p in karyotyping and SNP array, but autopsy was not permitted for further research, the correlation between trisomy 12p and PKS or DWM was still unclear. Further research was needed to explore the correlation between PKS and trisomy 12p.

In the 506.1 kb deleted region of 15q which covers eight already known genes including four OMIM genes named *NIPA1* (MIM: 608145), *NIPA2* (MIM: 608146), *TUBGCP5* (MIM: 608147) and *CYFIP1* (MIM: 606322) respectively. *NIPA1* (MIM: 608145) is a definite pathogenetic gene which is believed to represent the critical gene involved in autosomal dominant spastic paraplegia 6. According to ClinGen database, the 15q11.2 band is involved in the deletion syndrome region of (BP1–BP2) (include *NAPA1*) has a haploinsufficiency score of two points. Clinical phenotype includes developmental delay, autism spectrum disorders. However, some studies have reported that carriers with this region haploinsufficiency have a normal clinical phenotype (Doornbos *et al.* 2009). This is a common variant which is not known to cause Dandy–Walker. It has variable penetrance and appears to be a risk factor for mild developmental delay, mild learning difficulties and/or an Autistic spectrum

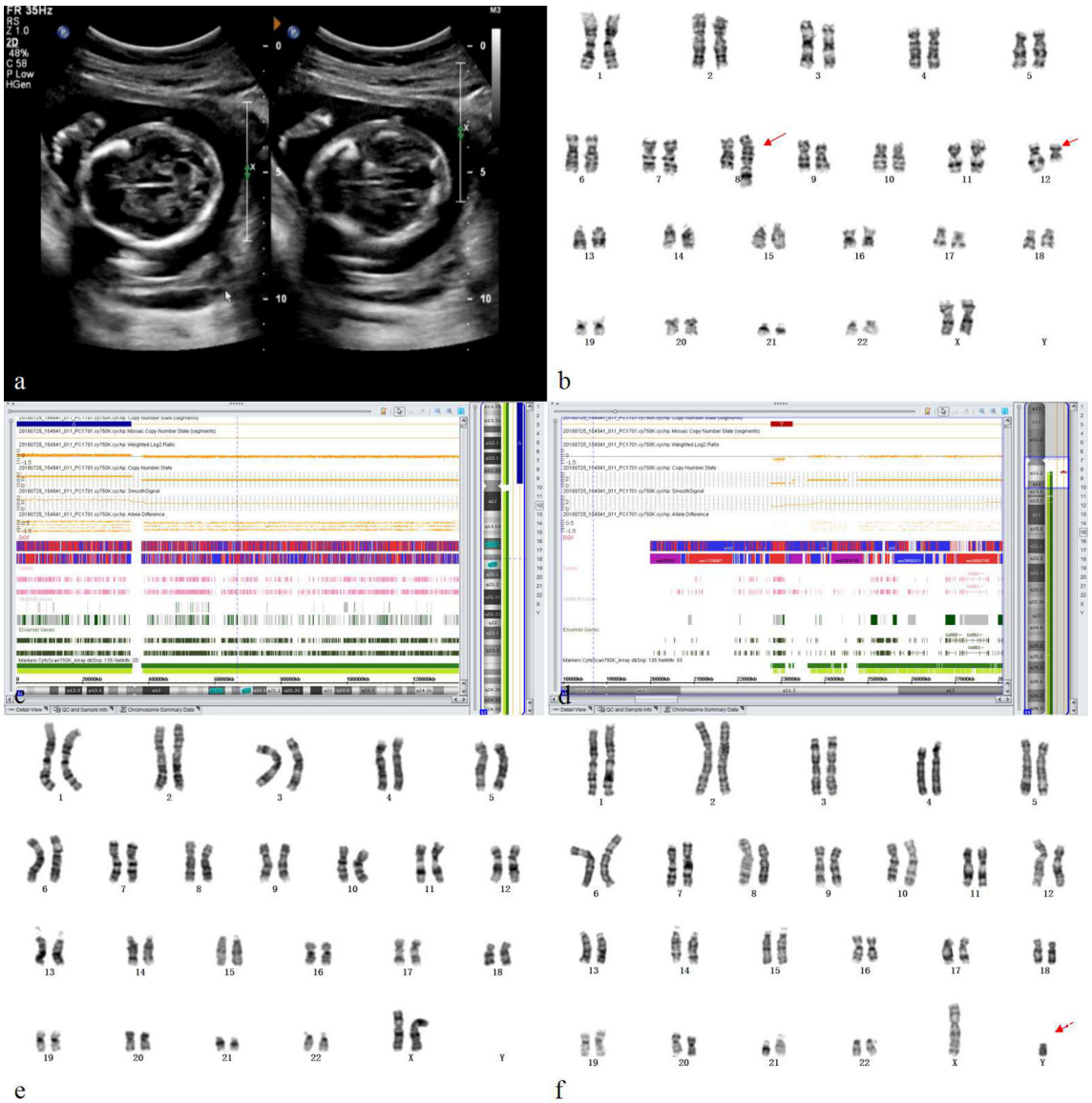

Figure 1. The clinical and genetical data. (a) Dandy–Walker malformation image shown under sonography. It shows a partial absence of the cerebellar vermis, and enlarged posterior cranial fossa communicating with the fourth ventricle. (b) G-band karyotype obtained from amniotic fluid cells showing 46,XX,der(8)(8pter→8q24::12p10→12qter),i(12)(p10). (c) SNP showing the 34.6 Mb duplication of 12p111.1p13.33 region. (d) SNP showing the 506.1 kb deletion of 15q11.2 region. (e) Chromosomal karyotype of mother 46,XX. (f) Chromosomal karyotype of father 46,X,Yqh-.

disorder, and it is frequently inherited from normal parents and grandparents.

Routine chromosome karyotyping is commonly used for detecting foetal chromosomal aberrations in pregnancy with foetal DWM; however, it is not considered to be the gold standard for prenatal testing in many countries now due to the limited resolution. The resolution is about 5–10 Mb for chromosomal abnormalities detection, which may enable microdeletions or duplications smaller than 5 Mb to be missed diagnosis. CMA is taken as a supplement for karyotyping, which can potentially detect copy number variants (CNVs) and minor segments as small as 100 to 200 kb. However, they were not always concordant with each other absolutely just as in this study, because the array banding assignments are those derived from genome browsers, while the traditional cytogenetic banding assignments are those derived from banded chromosomes.

In conclusion, SNP array and G-band karyotyping were performed for prenatal genetic diagnosis on foetus with DWM, and it revealed trisomy 12p and partial distal 15q deletion. The identification of the chromosomal aberration will contribute to the prenatal genetic diagnosis and counselling for foetuses with DWM, and it is suggested that both CMA and conventional karyotyping should be provided to pregnant women undergoing invasive prenatal testing due to abnormal ultrasonographic findings and more research was

needed to explore the phenotypic difference between PKS and trisomy 12p.

References

Agrawal S., Dave M., Mahur H., Aswani M., Goyal R., Pansari N. and Kaswan P. 2016 Dandy Walker syndrome: a rare presentation in adult. *J. Assoc. Physicians India* **64**, 112.

Bernardo S., Vinci V., Saldari M., Servadei F., Silvestri E., Giancotti A. *et al*. 2015 Dandy-Walker malformation: is the "tail sign" the key sign? *Prenat. Diagn.* **35**, 1358–1364.

Blyth M., Maloney V., Beal S., Collinson M., Huang S., Crolla J. *et al*. 2015 Pallister-Killian syndrome: a study of 22 British patients. *J. Med. Genet.* **52**, 454–464.

Chen C. P., Chang T. Y., Shih J. C., Lin S. P., Lin C. J., Wang W. *et al*. 2002 Prenatal diagnosis of the Dandy-Walker malformation and ventriculomegaly associated with partial trisomy 9p and distal 12p deletion. *Prenat. Diagn.* **22**, 1063–1066.

Doornbos M., Sikkema-Raddatz B., Ruijvenkamp C. A., Dijkhuizen T., Bijlsma E. K., Gijsbers A. C. *et al*. 2009 Nine patients with a microdeletion 15q11.2 between breakpoints 1 and 2 of the Prader-Willi critical region, possibly associated with behavioural disturbances. *Eur. J. Med. Genet.* **52**, 108–115.

Doray B., Girard-Lemaire F., Gasser B., Baldauf J. J., De Geeter B., Spizzo M. *et al*. 2002 Pallister-Killian syndrome: difficulties of prenatal diagnosis. *Prenat. Diagn.* **22**, 470–477.

Grinberg I., Northrup H., Ardinger H., Prasad C., Dobyns W. B. and Millen K. J. 2004 Heterozygous deletion of the linked genes ZIC1 and ZIC4 is involved in Dandy-Walker malformation. *Nat. Genet.* **36**, 1053–1055.

Inage E., Suzuki M., Minowa K., Akimoto N., Hisata K. and Shoji H. 2010 Phenotypic overlapping of trisomy 12p and Pallister-Killian syndrome. *Eur. J. Med. Genet.* **53**, 159–161.

Izumi K. and Krantz I. D. 2014 Pallister-Killian syndrome. *Am. J. Med. Genet. C Semin. Med. Genet.* **166C**, 406–413.

Izumi K., Conlin L. K., Berrodin D., Fincher C., Wilkens A., Haldeman-Englert C. *et al*. 2012 Duplication 12p and Pallister-Killian syndrome: a case report and review of the literature toward defining a Pallister-Killian syndrome minimal critical region. *Am. J. Med. Genet A.* **158A**, 3033–3045.

Klein O., Pierre-Kahn A., Boddaert N., Parisot D. and Brunelle F. 2003 Dandy-Walker malformation: prenatal diagnosis and prognosis. *Childs Nerv. Syst.* **19**, 484–489.

Kumar R., Jain M. K. and Chhabra D. K. 2001 Dandy-Walker syndrome: different modalities of treatment and outcome in 42 cases. *Childs Nerv. Syst.* **17**, 348–352.

McCormack W. M. Jr., Shen J. J., Curry S. M., Berend S. A., Kashork C., Pinar H., Potocki L. *et al*. 2003 Partial deletions of the long arm of chromosome 13 associated with holoprosencephaly and the Dandy-Walker malformation. *Am. J. Med. Genet. A.* **118A**, 384–389.

Temtamy S. A., Kamel A. K., Ismail S., Helmy N. A., Aglan M. S., El Gammal M. *et al*. 2007 Phenotypic and cytogenetic spectrum of 9p trisomy. *Genet. Couns.* **18**, 29–48.

von Kaisenberg C. S., Caliebe A., Krams M., Hackelöer B. J. and Jonat W. 2000 Absence of 9q22-9qter in trisomy 9 does not prevent a Dandy-Walker phenotype. *Am. J. Med. Genet.* **95**, 425–428.

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