LETTER TO THE EDITOR

PRENATAL DIAGNOSIS OF PARTIAL MONOSOMY 1q (1q42.3→qter) ASSOCIATED WITH HYDROCEPHALUS AND CORPUS CALLOSUM AGENESIS

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A 27-year-old primigravid woman underwent amniocentesis because of abnormal sonographic findings of severe hydrocephalus at 21 weeks of gestation. Level II ultrasound revealed a singleton fetus with fetal biometry equivalent to 19 weeks, bilateral ventriculomegaly and corpus callosum agenesis. The cisterna magna was not enlarged and the cerebellum was normal. Cytogenetic analysis of the cultured amniocytes revealed a karyotype of 46,XX,del(1)(q42.3) with partial monosomy 1q (1q42.3→qter) (Fig. 1). The parental karyotypes were normal.

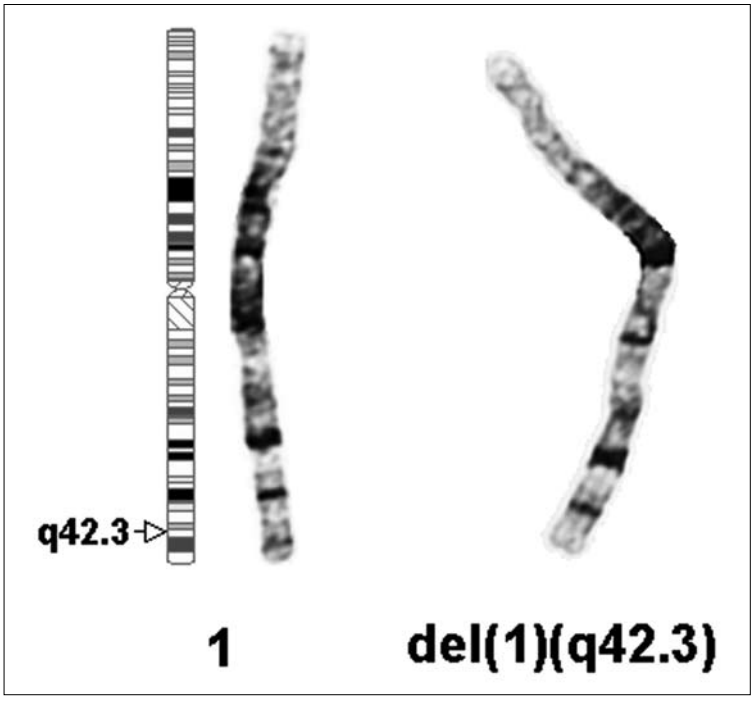

Figure 1: Partial karyotype of the fetus. The arrow indicates the breakpoint.

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The pregnancy was subsequently terminated. A malformed 328-g fetus was delivered with hypertelorism, large low-set ears and micrognathia (Fig. 2). An autopsy was not granted, and there was no postmortem pathological study. Polymorphic DNA marker analysis using fetal and parental DNA confirmed the paternal origin of the deletion. Molecular analysis using array-based comparative genomic hybridization (CGH) with high-density fine-tiling oligonucleotide arrays (NimbleGen, Madison, WI, USA) revealed a 13.4-Mb deletion of 1q42.3→qter with the first deleted clone at 233,730,000 bp and the last clone at 247,163,852 bp according to UCSC Genome Browser on Human March 2006 Assembly (Fig. 3). Mutation analysis of the *FH* gene revealed no mutation.

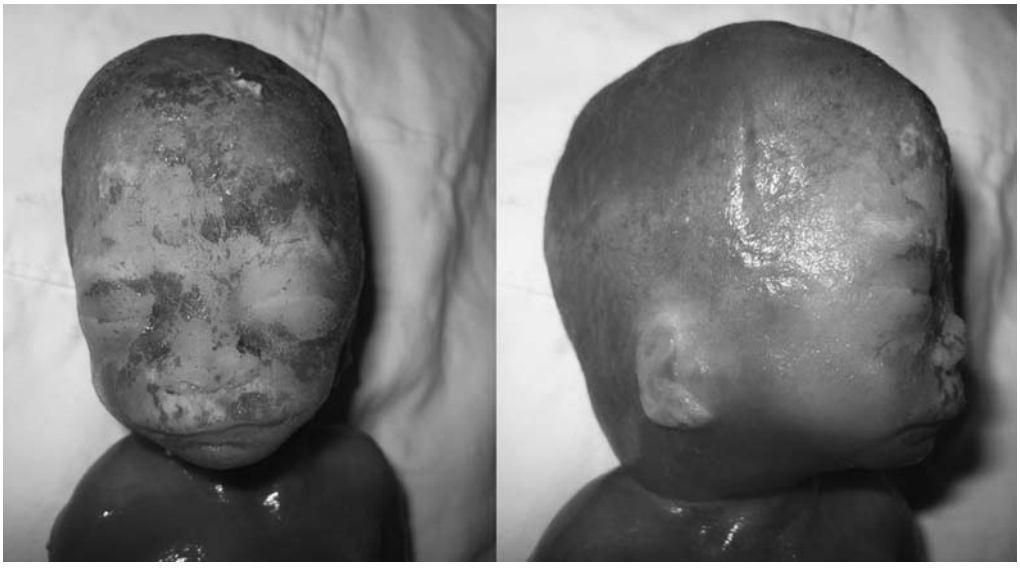

Figure 2: The fetus at birth.

Rotmensch *et al*. (6) first reported prenatal diagnosis of a pure distal deletion of 1q41→qter in a 19-gestational-week fetus with omphalocele, cerebral ventriculomegaly and increased nuchal fold thickness. Dallapiccola *et al*. (2) reported prenatal diagnosis of a distal deletion of 1q42→qter inherited from maternal translocation of t(1;17)(q42;p13) in a 19-gestational-week fetus with intrauterine growth restriction, microcephaly and a ventricular septal defect. The present case had a 13.4-Mb *de novo* deletion of 1q42.3→qter. The deleted region contains the genes of *RGS7*, *FH*, *AKT3*, *ZNF238*, *C1orf100*, *ADSS*, *C1orf101* and *C1orf121* (*PNAS-4*) that may be associated with brain development.
The *FH* gene encodes fumarase which exists in both cytosolic and mi-

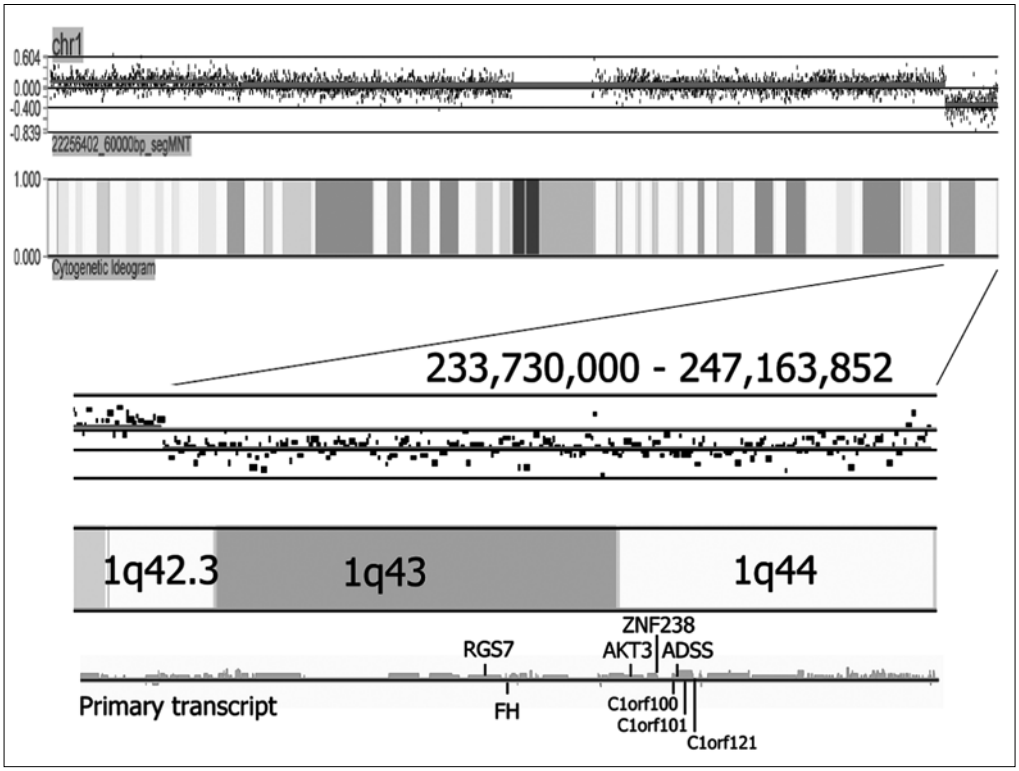

Figure 3: Array-based comparative genomic hybridization (CGH) with the NimbleGen kit (NimbleGen, Madison, WI, USA) showing a 13.4-Mb deletion of 1q42.3→qter.

tochondrial forms and is an enzymatic component of Krebs cycle. *FH* mutations have been associated with fumarase deficiency. A deficiency of fumarase may cause encephalopathy and ventriculomegaly. Remes *et al*. (5) described two siblings with fumarase deficiency, enlarged cerebral ventricles and polyhydramnios *in utero*. Zeman *et al*. (9) observed increase of succinylaminoimidazole carboxamide riboside and succinyladenosine concentrations in the cerebrospinal fluid in a child with fumarase deficiency and communicating hydrocephalus, and suggested that the abnormal levels of succinylpurines may play a role in encephalopathy. Loeffen *et al*. (3) reported a fumarase-deficient patient with *FH* mutations and a phenotype of congenital cerebral ventricular dilation and periventricular cysts.

The *RGS7* gene encodes regulator of G-protein signal 7 which functions as GTPase accelerating protein and is primarily expressed in brain. van Bever *et al*. (7) described a patient with mental retardation, multiple abnormalities including corpus callosum hypoplasia, and a 7.7-Mb distal 1q deletion with the breakpoint region mapped to a 26-kb region within the *RGS7* gene. The *AKT3* gene encodes protein kinase

B-gamma that is involved in glucose uptake, apoptosis and cellular proliferation. The *ZNF238* gene encodes zinc finger protein which mediates transcriptional repression and is involved in chromatin assembly. Boland *et al*. (1) suggested that haploinsufficiency of the *AKT3* and/or *ZNF238* genes is a cause of human microcephaly and corpus callosum agenesis. Orellana *et al*. (4) suggested that the role for *AKT3* and/or *ZNF238* genes in the corpus callosum development should not be excluded.

van Bon *et al*. (8) defined a critical region for corpus callosum abnormalities of 360 kb in 1q44 harboring the genes of *C1orf100*, *ADSS*, *C1orf101* and *C1orf121*. The *ADSS* gene encodes adenylosuccinate synthetase which catalyzes the biosynthesis of adenosine monophosphate from inosine monophosphate. The *C1orf100*, *C1orf101* and *C1orf121* genes are chromosome 1 open reading frame genes, and have a low degree of evolutionary conservation and a lack of homology to known functional domains.

In summary, we have presented clinical findings and molecular cytogenetic analysis of partial monosomy 1q (1q42.3→qter) in a fetus. We speculate that haploinsufficiency of the *FH* gene is most likely responsible for the phenotype of hydrocephalus, and haploinsufficiency of the *RGS7*, *AKT3, ADSS* and *ZNF238* genes is most likely responsible for the phenotype of corpus callosum agenesis in this fetus.

ACKNOWLEDGEMENTS

This work was supported by research grants NSC-96-2314-B-195-008-MY3 and NSC-97-2314-B-195-006-MY3 from the National Science Council, and MMH-E-99004 from Mackay Memorial Hospital, Taipei, Taiwan.

REFERENCES

1. *BOLAND E., CLAYTON-SMITH J., WOO V.G., MCKEE S., MANSON F.D., MEDNE L., ZACKAI E., SWANSON E.A., FITZPATRICK D., MILLEN K.J., SHERR E.H., DOBYNS W.B., BLACK G.C.:* Mapping of deletion and translocation breakpoints in 1q44 implicates the serine/threonine kinase AKT3 in postnatal microcephaly and agenesis of the corpus callosum. *Am. J. Hum. Genet.*, 2007, *81*, 292-303.
2. *DALLAPICCOLA B., FERRANTI G., PACHÌ A.:* Prenatal diagnosis of terminal deletion 1 (q42). *Prenat. Diagn.*, 1992, *12*, 853.
3. *LOEFFEN J., SMEETS R., VOIT T., HOFFMANN G., SMEITINK J.:* Fumarase deficiency presenting with periventricular cysts. *J. Inherit. Metab. Dis.*, 2005, *28*, 799-800.

4. *ORELLANA C., ROSELLÓ M., MONFORT S., OLTRA S., QUIROGA R., FERRER I., MARTÍEZ F.:* Corpus callosum abnormalities and the controversy about the candidate genes located in 1q44. *Cytogenet. Genome Res.*, 2009, *127*, 5-8.

5. *REMES A.M., RANTALA H., HILTUNEN J.K., LEISTI J., RUOKONEN A.:* Fumarase deficiency: two siblings with enlarged cerebral ventricles and polyhydramnios *in utero*. *Pediatrics*, 1992, *89*, 730-734.

6. *ROTMENSCH S., LIBERATI M., LUO J.S., TALLINI G., MAHONEY M.J., HOBBINS J.C.:* Prenatal diagnosis of a fetus with terminal deletion of chromosome 1 (q41). *Prenat. Diagn.*, 1991, *11*, 867-873.

7. *VAN BEVER Y., ROOMS L., LARIDON A., REYNIERS E., VAN LUIJK R., SCHEERS S., WAUTERS J., KOOY R.F.:* Clinical report of a pure subtelomeric 1qter deletion in a boy with mental retardation and multiple anomalies adds further evidence for a specific phenotype. *Am. J. Med. Genet.*, 2005, *135A*, 91-95.

8. *VAN BON B.W.M., KOOLEN D.A., BORGATTI R., MAGEE A., GARCIA-MINAUR S., ROOMS L., REARDON W., ZOLLINO M., BONAGLIA M.C., DE GREGORI M., NOVARA F., GRASSO R., CICCONE R., VAN DUYVENVOORDE H.A., AALBERS A.M., GUERRINI R., FAZZI E., NILLESEN W.M., MCCULLOUGH S., KANT S.G., MARCELIS C.L., PFUNDT R., DE LEEUW N., SMEETS D., SISTERMANS E.A., WIT J.M., HAMEL B.C., BRUNNER H.G., KOOY F., ZUFFARDI O., DE VRIES B.B.:* Clinical and molecular characteristics of 1qter microdeletion syndrome: delineating a critical region for corpus callosum agenesis/ hypogenesis. *J. Med. Genet.*, 2008, *45*, 346-354.

9. *ZEMAN J., KRIJT J., STRATILOVÁ L., HANSI'KOVÁ H., WENCHICH L., KMOCH S., CHRASTINA P., HOUSTEK J.:* Abnormalities in succinylpurines in fumarase deficiency: possible role in pathogenesis of CNS impairment. *J. Inherit. Metab. Dis.*, 2000, *23*, 371-374.

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