Letter to the editor

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Congenital hyperinsulinemic hypoglycaemia in an infant with 9p deletion syndrome

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To the editor,

Constitutional monosomy of part of the short arm of chromosome 9 (chromosome 9p deletion syndrome, OMIM #158170) results in a rare, complex syndromic condition characterized by developmental delay, craniofacial dysmorphism, and multiple congenital anomalies [1-3]. Variability in clinical features may be due to differences in the extent of deletion and haploinsufficiency of specific genes. The genotype-phenotype correlation is unclear due to frequent additional chromosomal rearrangements and inconsistent molecular characterization. Gene disruption within the affected region may reveal recessive traits, contributing to the complex presentation [2]. Congenital hyperinsulinism (CHI) occurs in less than 10% of patients with chromosome 9p deletion syndrome. Its course can be variable, it may require several years of treatment, and the genetic mechanism underlying dysregulated insulin secretion remains unidentified [4-6].

Distal duplication of 14q is rare and is characterized by variable clinical features, including developmental delay, growth retardation, low birth weight, hypotonia, short stature, microcephaly, facial dysmorphism, spasticity, and hyperreflexia; brain, cardiac, digital, and skeletal abnormalities are also likely [7-9].

We present a rare case of CHI in an infant with a karyotype of 46,XX,der(9)t(9p;14q)(p23;q32.2). An 8-month-old female patient was referred to our department for hypoglycemia evaluation. She was the first child born to a 40-year-old mother via cesarean section at 41 weeks of gestation. Her mother had no history of gestational diabetes or other medical conditions, nor did she take any medications during pregnancy. There was no history of diabetes in her father or in three generations of her family. The patient's birth weight, length, and head circumference were 2,990 g (10th–25th percentile), 48 cm (10th–25th percentile), and 35 cm (25th percentile), respectively. After birth, she was admitted to the neonatal intensive care unit because of respiratory failure, hypotonia, cleft palate, and dysmorphic features. Intermittent nasal positive-pressure ventilation was administered immediately after admission because of tachypnea and mild chest retraction. On the first day of life (DOL 1), initial blood glucose level was less than 20 mg/dL. She developed pneumomediastinum with persistent pulmonary hypertension (PPHN). Continuous glucose infusion (glucose infusion rate [GIR], 11 mg/kg/min) dopamine, dobutamine, milrinone, inhaled prostacyclin for PPHN, and intravenous hydrocortisone (5 mg/kg/day) were administered due to PPHN and the possibility of relative adrenal insufficiency. On DOL 2, glucose level reached 29 mg/dL, and a detectable serum insulin level of 93.6 μU/mL, undetectable ketone bodies (0.3 mmol/L), and a normal ammonia level of 51 μmol/L were observed. Echocardiography revealed a mild atrial septum defect, nearly closing the patent ductus arteriosus, and mild septal hypertrophy. Brain magnetic resonance imaging showed a thinning of the corpus callosum, and small T1 hyperintensity in the left frontal deep white matter, suggesting a small hemorrhagic lesion. Karyotyping revealed 46,XX,add(9)(p23). Chromosome microarray analysis (Affymetrix CytoScan 750K Array, Thermo Fisher Scientific, Santa Clara, CA, USA) with human genomic reference sequence GRCh37/hg19 revealed an approximately 10-Mbp deletion at 9p24.3p23, classified as a pathogenic copy number variant (CNV), an 860-kbp duplication at 14q32.2, considered a variant of uncertain significance, and a 9.8-Mbp duplication at 14q32.2q32.33, also classified as a pathogenic CNV (Fig. 1). The patient's karyotype was considered

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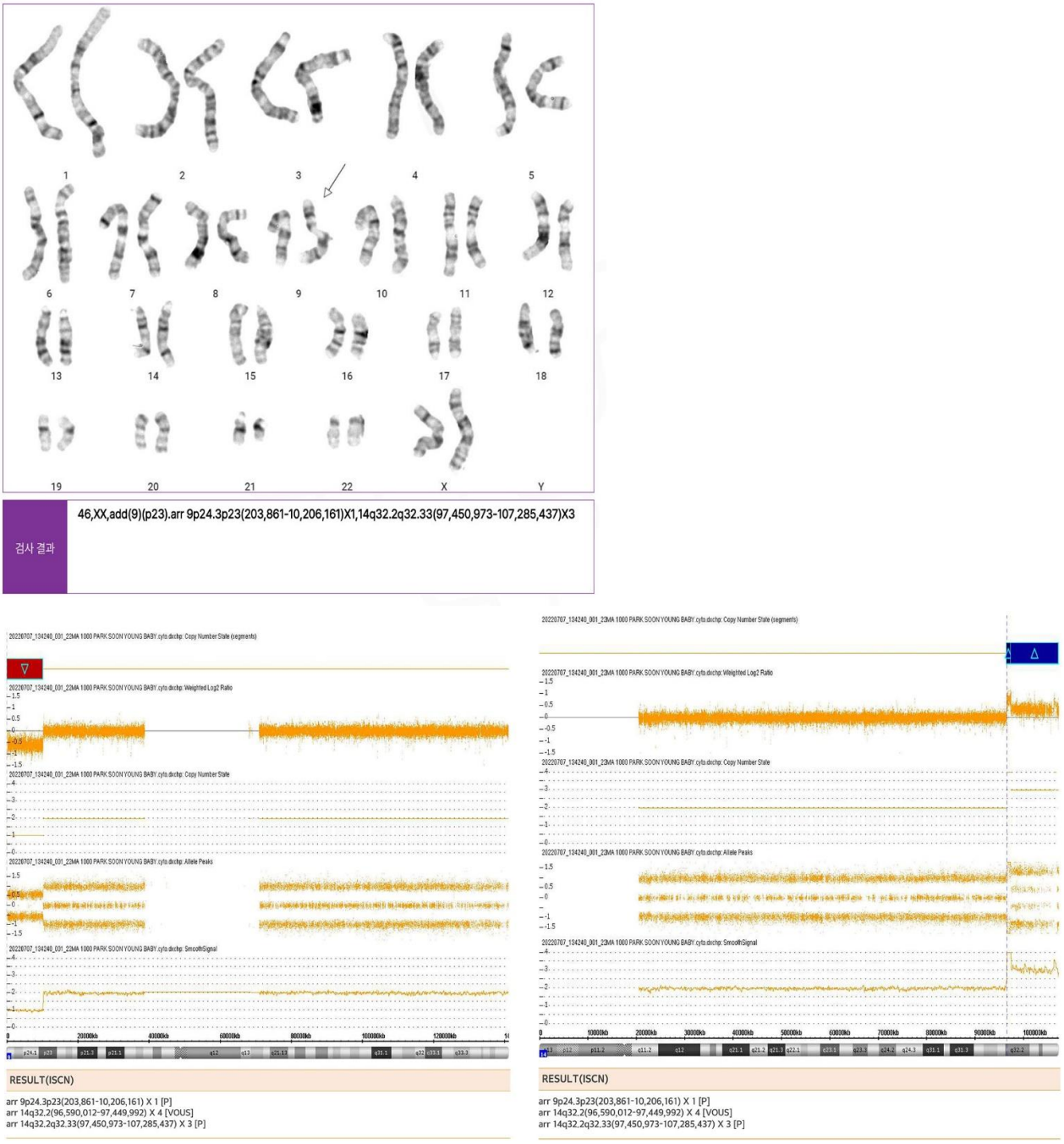

Fig. 1. (A) Karyotyping revealed a 46,XX,der(9)t(9p;14q)(p23;q32.2). (B) Chromosome microarray analysis revealed an approximately 10-Mbp deletion at 9p24.3p23(203,861-10,206,161), an 860-Kbp duplication at 14q32.2(96,590,012-97,449,992), and a 9.8-Mbp duplication at 14q32.2q32.33(97,450,973-107,285,437).

46,XX,der(9)t(9p;14q)(p23;q32.2), which may be attributable to the balanced parental translocation chromosome; however, her parents refused karyotyping. Diagnostic exome sequencing test (DNBSEQ-G400 sequencer; MGI Tech Co., Ltd, Shenzhen, China; 2×100 paired-end reads for 5,870 Mendelian genes) did not reveal any established pathogenic variants for CHI.

Although the feeding volume increased to 150 mL/kg/day (GIR 8 mg/kg/min) on DOL 7, the preprandial glucose level was <60 mg/dL; therefore, she could not be weaned from parenteral glucose infusion until DOC 23. She was discharged on DOL 34, maintaining a glucose level of > 60 mg/dL with regular gavage feeding (>150 mL/kg/day) owing to cleft palate and generalized hypotonia.

At 8 months of age, gavage tube feeding was transitioned to bottle feeding, and the amount of feeding decreased because of febrile illness. She exhibited myoclonic movements with

Table 1. Hypoglycemic symptoms and treatment outcomes in patients with 9p deletion syndrome

No.	Karyotype	9p deletion	G-age (wk)	B-wt (g)	Age of onset	Age of remission	Diazoxide dose (mg/kg/day)	Reference number
1	46,XX,-9+dert(3;9)(p25;p23)mat	N/A	40	4,210	1 Day	11 Wk	No treatment	3
2	N/A	204193-15359025	37	2,965	1 Day	10 Day	10	5
3	46,XY,del(9)(p22.1)	0-19,200,000	38	4,478	3 Days	26 Day	Dose not available	6
4	Not performed	1-14,000,000	38	3,440	2 Day	43 Wk	10.5	6
5	46,XX,del(9)(p22.2)	0-17,600,000	40	3,200	20 Wk	7 Mo	No treatment	6
6	46,XY,der(9)t(9;13)(p24;q22.3	0-9,806,011	37	2,960	1 Day	4 Yr	5	6
7	46,XX,del(9)(p23),ishdel(9)(pter-)	0-9,330,617	38	3,520	1 Day	1.4 Yr	7	6
8	46,XX,der(9)t(8;9)(q24.1;p24)	0-7,800,000	40	3,670	1 Day	1.3 Yr	Dose not available	6
9	Not performed	0-7,200,000	39	3,510	1 Day	6 Wk	10	6
10	Not performed	0-7,600,000	37	3,000	8 Wk	Ongoing at 8 yr	2	6
11	46,XX,del(9)(p24.1)	0-7,600,000	34	1,700	1 Day	Ongoing at 2.8 yr	6	6
12	46,XY,der(9)t(9;13)(p 23;q33.3)	0-12,450,000	38	3,650	1 Day	Ongoing	10	6
13	46,XY,der(9)t(9;13) (p23;q33.3)	0-12,450,000	41	4,160	1 Day	Ongoing	10	6
14	46,XY,del(9)(p23)	0-10,955,813	42	5,050	1 Day	1 wk (No follow-up)	No treatment	6
15	46,XX,der(9)t(9p;14q)(p23;q32.2)	203,861-10,206,161	41	2,990	1 Day	Ongoing at 2 yr	2	Our case

N/A, not available; G-age, gestational age; B-wt, body weight.

fixed pupils and was therefore admitted. Her weight, length, and head circumference were 8.3 kg (50th–75th percentile), 64.7 cm (5th–10th percentile), and 42.5 cm (25th percentile), respectively. Dysmorphic features including prominent high forehead, midface hypoplasia, hypertelorism, wide flat nasal bridge with bulbous nasal tip, long philtrum, thin tented upper lip, broad mouth, micrognathia, and cleft palate, along with a short neck, generalized hypotonia, and significant global developmental delay were observed. Abdominal ultrasonography and electroencephalography yielded normal results. When preprandial glucose was 42 mg/dL, serum insulin was 5.9 μU/mL, C-peptide level was 1.6 ng/mL, serum ketone bodies were 0.2 mmol/L, serum cortisol was 24.8 μg/dL, and growth hormone levels were 9.01 ng/mL. Diazoxide at a dose up to 10 mg/kg/day, improved early morning preprandial blood glucose levels (70–110 mg/dL). Since then, seizures have not recurred.

In most CHI-associated syndromic conditions, the precise mechanism underlying the dysregulation of glucose sensing and/or insulin secretion remains unclear and is not directly related to the genes that have been identified in isolated CHI. Additionally, the association with CHI in many cases is inconsistent, and metabolic disturbances are transient [4,10].

CHI has been previously reported among patients with 9p deletion syndrome (Table 1). McClure et al. [3] reported a full-term female newborn with 46,XX,-9,+dert(3;9)(p25;p23) mat, weighing 4,210 g at birth with a good Apgar score, who developed hypoglycemia shortly after birth.

Bayat et al. [5] reported a male newborn with a 15-Mb terminal deletion of chromosome 9p (9p24.3p22.3), born at 37 weeks weighing 2,965 g with good Apgar scores, who developed severe hypoglycemia two hours after birth, requiring diazoxide therapy. Banerjee et al. [6] studied 12 cases of chromosome 9p deletion syndrome. Most experienced hypoglycemia within 3 days of birth, requiring diazoxide treatment. Five infants received treatment for over a year, and one continued treatment for 8 years. They identified 9p deletions as an important cause of hyperinsulinemic hypoglycemia, mapping the minimal deleted region to 7.2 Mb (Chr9:0-7,200,000[hg19], 9p24.3-9p24.1), which includes *SMARCA2* and *RFX3*. *In silico* analysis highlighted these genes as potential candidates for hypoglycemia, with *SMARCA2* highly expressed in the pancreas and *RFX3* involved in insulin regulation pathways. However, no experimental evidence was provided. Our patient had a 10-Mbp deletion in the 9p24.3p23 region, encompassing 37 protein-coding genes, including *SMARCA2* and *RFX3* genes. This deletion suggests a similar mechanism for hypoglycemia as proposed by Banerjee et al. [6] In conclusion, although CHI rarely occurs in newborns with chromosome 9p deletion, they should be closely monitored for hypoglycemia.

This study was approved by the Institutional Review Board (IRB) of Daegu Catholic University Medical Center, Daegu, Korea (IRB No. CR-24-052). We obtained informed consent from the patient's parents.

Notes

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