

Patient report

Juan Diego Mejia, Luisa Cervantes, Herminia Puerta, Mislen Bauer and Alejandro Diaz*

Neonatal diagnosis of a patient with hypoparathyroidism, sensorineural deafness and renal dysplasia (HDR) syndrome associated with cerebral infarction

Abstract: Hypoparathyroidism, sensorineural deafness and renal dysplasia syndrome (HDRS) is comprised of a triad of conditions. It is an autosomal dominant condition caused by mutations in the *GATA3* gene, located at 10p15, a critical region in the development of the embryonic parathyroid glands, inner ear, and kidneys. Here we describe the case of a patient with all three components of HDR syndrome diagnosed in the neonatal period who presented with cerebral infarction, hypocalcemia, and renal anomalies. Upon chromosomal microarray he was found to have an interstitial deletion at 10p, which produced a partial deletion in the *GATA3* gene.

Keywords: *GATA3* gene; HDR syndrome; hypoparathyroidism; sensorineural deafness; renal dysplasia.

DOI 10.1515/jpem-2014-0004

Received January 19, 2014; accepted April 1, 2014; previously published online May 23, 2014

Introduction

The triad of hypoparathyroidism, deafness, and renal dysplasia is known as hypoparathyroidism, sensorineural deafness and renal dysplasia syndrome (HDRS) and is also sometimes referred to as the Bakarat syndrome. In 1977, Barakat et al. reported the case of two brothers, ages 5 and 8 years, who had steroid-resistant nephrosis with progressive renal failure, sensorineural deafness, and

hypoparathyroidism (1). In 1992, Bilous et al. reported on two brothers and on two daughters of one of these brothers affected by the condition (2). Based on these reports, an autosomal dominant mode of inheritance was proposed and confirmed by later research. In 1997, Hasegawa used the acronym, HDR, in the report of a girl with this triad (3).

Deletions on specific regions within the short arm of chromosome 10 have been found to produce complex phenotypes, including those described in HDRS. Van Esch et al. performed deletion-mapping studies in two patients with HDRS and defined a critical 200 kb region inside 10p that contains the *GATA3* gene. Search for *GATA3* mutations in three additional probands with HDRS identified one nonsense mutation and two intragenic deletions that predicted a loss of function of the gene, as confirmed by absence of DNA binding by the mutant *GATA3* protein. These results demonstrated that *GATA3* is essential in the embryonic development of the parathyroid glands, auditory system, and kidneys, and showed that *GATA3* haploinsufficiency produces the HDRS phenotype (4). In 1991, Joulin et al. mapped *GATA3* at 10p15 and, to date, several mutations of this gene have been reported, including deletion of the entire gene, intragenic deletions or insertions, nonsense or missense mutations, and splice-site mutations (5).

The clinical characteristics of HDRS are heterogeneous among patients and are dependent on penetrance. Ferraris et al. described the phenotypical findings of 77 patients with HDRS reported in the medical literature and found that 62.3% had the complete triad, 28.6% have hypoparathyroidism and deafness, and 2.6% have deafness and renal disease (6). Familial studies of probands with HDRS have identified *GATA3* mutations in subjects with deafness as the only clinical finding (7).

We describe the case of a boy who was diagnosed in the neonatal period with the triad phenotype of the syndrome who presented with a cerebral infarction. To our knowledge, only two cases with this association have been reported.

*Corresponding author: Alejandro Diaz, MD, Division of Pediatric Endocrinology, Miami Children's Hospital, 3100 SW 62nd Ave, Miami, FL, USA, E-mail: alejandro.diaz@mch.com

Juan Diego Mejia: Division of Pediatric Endocrinology, Miami Children's Hospital, Miami, FL, USA

Luisa Cervantes: Department of Radiology, Miami Children's Hospital, Miami, FL, USA

Herminia Puerta and Mislen Bauer: Division of Genetics, Miami Children's Hospital, Miami, FL, USA

Case report

The patient initially was referred to us at age 6 weeks for evaluation of hypoparathyroidism. Review of his past medical history showed he was the first living child of a 37-year-old mother and a 36-year-old father. They had a previous miscarriage at 9 weeks of pregnancy. There was no history of consanguinity between the parents. The mother had hypothyroidism and received levothyroxine during the pregnancy. On obstetric ultrasound, the patient was found to have a right renal cyst and a hypoplastic left kidney. A karyotype performed via amniocentesis showed a normal pattern 46, XY. The patient was born at 39 weeks

of gestational age after an uncomplicated C-section. His birth weight was 3140 g (25–50th percentile), birth length was 51 cm (50–75th percentile), and head circumference was 33.5 cm (10–25th percentile). His Apgar scores were 8 and 8 at 1 and 5 min, respectively. At birth he was noticed to have bilateral preauricular tags and right hemiparesis without dysmorphism. Soon after birth he was noted to have apneic spells. CT and MRI of the brain showed a large brain infarct in the territory of the left medial cerebral artery (Figure 1). EEG showed attenuation of the activity on the left hemisphere and electrographic seizures with minimal clinical correlation, and he was started on phenobarbital. Renal ultrasound showed absence of the right

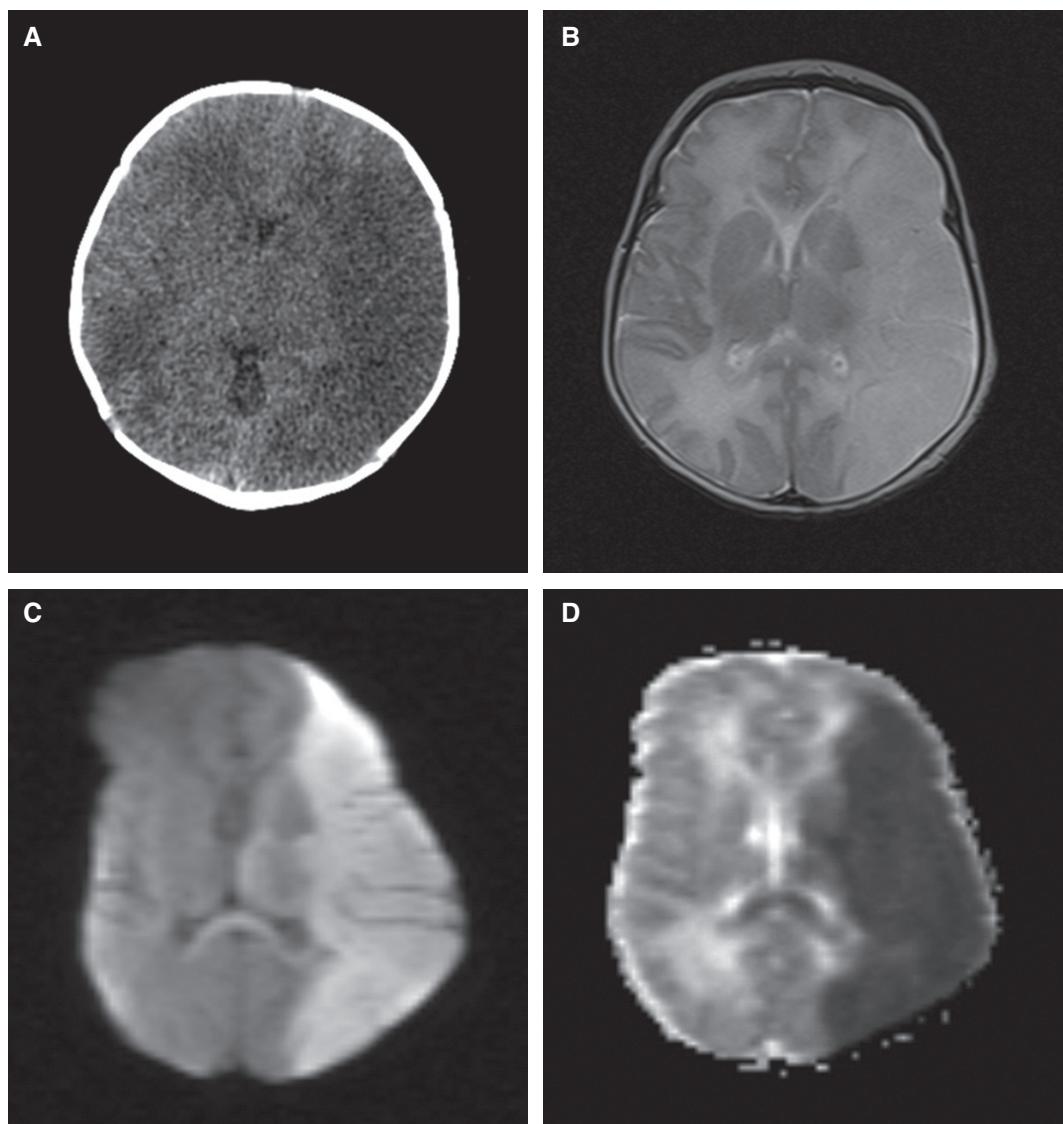


Figure 1 (A) CT axial image demonstrates hypodensity in the left frontal and temporal lobes in the vascular distribution of the left middle cerebral artery. (B) T2-weighted axial image demonstrates abnormal signal intensity in the same distribution with loss of the normal low signal intensity of the cortex (“ribbon sign”). (C,D) DWI and ADC maps show restricted diffusion related to vasogenic edema involving also the posterior corpus callosum indicating acute brain infarct.

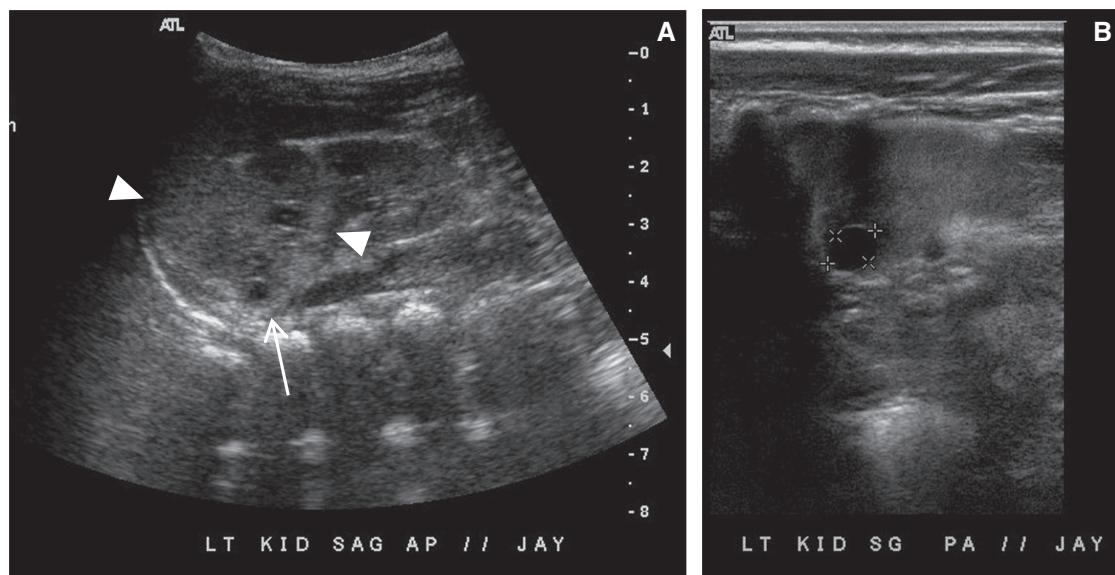


Figure 2 (A) Sagittal image of the left kidney shows abnormal increased echogenicity of the left upper renal pole (arrow heads) with a small cyst (arrow), consistent with renal dysplasia. (B) High resolution image obtained with a linear transducer allows better visualization of the small cyst. The right renal fossa was empty (not shown).

kidney and a small left kidney with dysplasia of the upper pole (Figure 2). Voiding cystourethrogram was normal. During the neonatal period he had mild hypocalcemia (lowest serum calcium of 7.6 mg/dL) (Table 1). He was also found to have right cryptorchidism, a patent foramen ovale that resolved without intervention, and absence of the 12th right rib. The patient was discharged home at 10 days of life with prophylactic anticonvulsive therapy, calcium carbonate, and vitamin D supplementation. Hearing screening the day of discharge was abnormal in the right ear. CT of the temporal bones showed incomplete partition of the cochleae (Figure 3) and abnormal morphology of the right semicircular canal (Figure 4). Chromosome microarray

showed a 5 kb interstitial deletion at 10p14 producing a partial deletion of the *GATA3* gene. His parents' chromosomal microarrays were normal, signifying his mutation was de novo in origin.

At the time of the first evaluation he had normal anthropometric measurements and was noted to have delayed development and right hemiparesis. His laboratory results showed an intact PTH of 13 pg/mL (normal range: 15–65 pg/mL) and a serum calcium of 9.2 mg/dL (normal range: 8.6–10.2 mg/dL). His mother was advised to ask her pediatrician to evaluate his calcium levels in case of physiological stress (fever or illness) and/or surgery. His calcium levels were normal upon following evaluations; however, at 6 months, immediately after orchiopexy, he developed severe hypocalcemia requiring hospitalization for treatment with intravenous calcium and calcitriol. During hospitalization, his creatinine and BUN levels were normal, and a kidney ultrasound showed normal growth of his left kidney with no progression of the pelvocaliectasis. The patient was sent home on PM 60/40 formula, calcium carbonate, calcitriol, and vitamin D3 supplementation.

On follow-up visits, calcitriol was discontinued, and he was switched to regular formula due to normalization of calcium and phosphorus levels. His calcium level had ranged from 7.5 to 9 mg/dL, the recommended range for patients with hypoparathyroidism to avoid hypercalcemia. After his first birthday he was diagnosed with infantile spasms. Subsequently, he has had significant regression in his global development.

Table 1 Lab results from 2/8/11 to 2/10/11 during hospitalization after birth of the patient.

| Patient's lab results during neonatal period | | | | |
|--|-------------|-------------|-------------|----------------|
| Date | 2/8/11 | 2/9/11 | 2/10/11 | Normal range |
| BUN | 14 | 11 | 7 | 6–21 mg/dL |
| Creatinine | 1.39 | 1.09 | 0.83 | 0.3–1.00 mg/dL |
| Sodium | 135 | 142 | 140 | 136–145 mmol/L |
| Potassium | 5.4 | 6.3 | 5.6 | 4.0–5.7 mmol/L |
| Chloride | 100 | 106 | 104 | 98–108 mmol/L |
| Glucose | 71 | 66 | 63 | 70–110 mg/dL |
| Calcium | 7.6 | 8.2 | 8.8 | 9–11 mg/dL |
| Prot total | | | 5.9 | 6.4–8.2 g/dL |
| Albumin | | | 2.7 | 3.4–5.0 g/dL |

The results for renal function test and calcium are in bold.

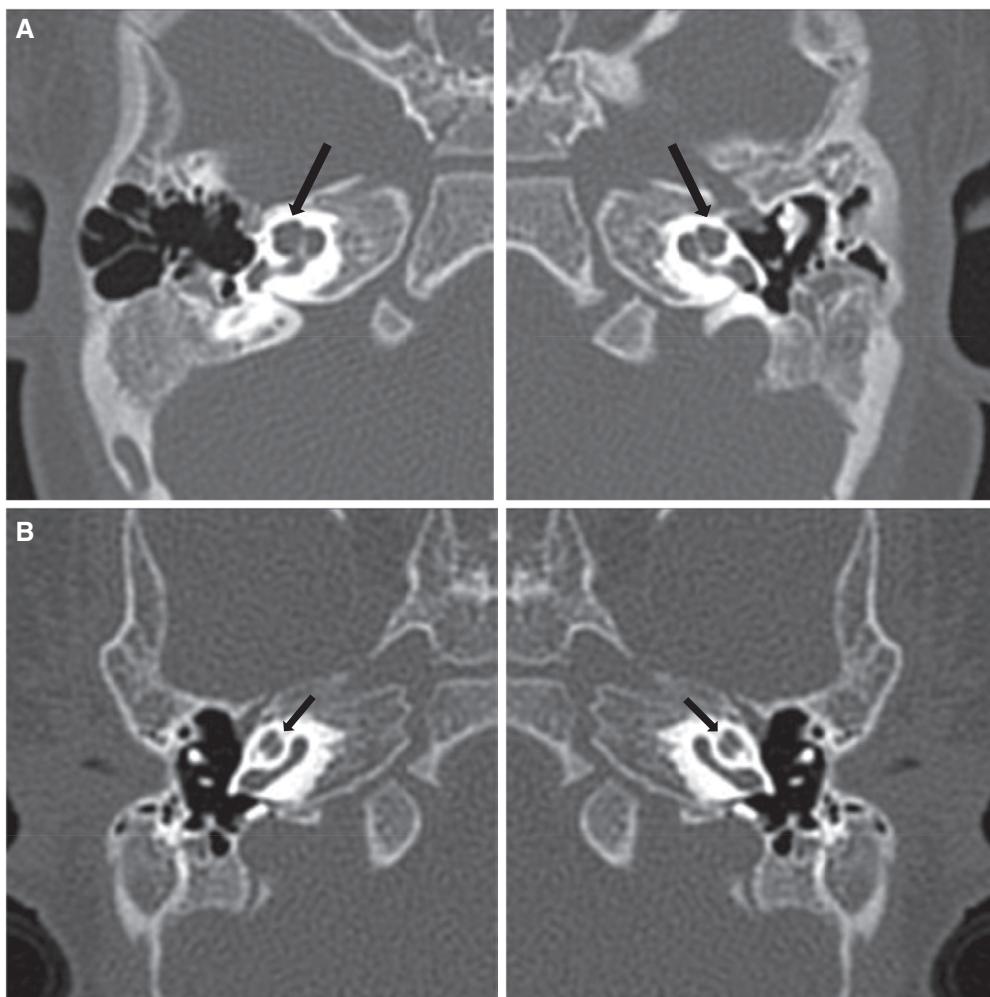


Figure 3 CT of the temporal bones.

(A) Axial images of the right and left temporal bones of the patient demonstrate incomplete partition of the cochlea with fusion of the middle and apical turns (long arrows). (B) CT images of the temporal bones in a normal patient show normal partition of the apical and middle turns of the cochleae for comparison (short arrows).

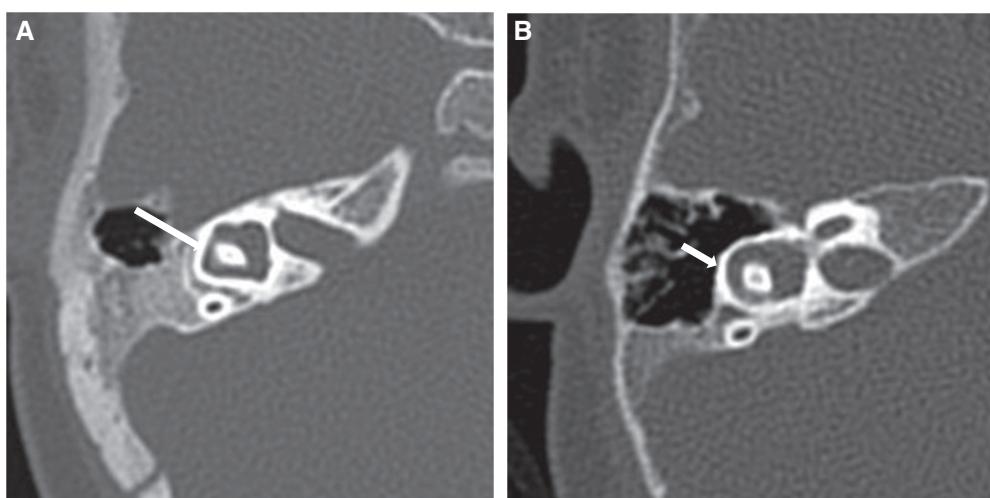


Figure 4 CT of the temporal bone.

(A) Axial image shows deformity with focal narrowing of the lateral semicircular canal (long arrow). (B) Axial image in a normal patient provided for comparison (short arrow).

Discussion

HDRS is an autosomal dominant disorder that has been described in more than 80 patients in the medical literature since the first report by Barakat et al. in 1977 (1). Most patients have been diagnosed after the first month, and following evaluation for hypocalcemic seizures and/or hearing problems (8–10).

The presence of any of the components of this triad should signal a physician to assess for the other two components. Easy access to advanced laboratory tools, such as the chromosome microarray, has allowed physicians to make more timely and precise diagnoses of multiple genetic conditions that previously required more cumbersome and expensive individual genetic tests.

GATA3 is one of six members of the GATA family of transcription factors. *GATA3* encodes a 444 amino acid protein that contains two transactivating domains (TA1 and TA2) and two zinc finger domains (ZnF1 and ZnF2). ZnF2 is highly conserved and essential for binding of its consensus response element, whereas ZnF1 stabilizes this binding and interacts physically with the multiple-type zinc finger friends of GATA (FOG) proteins (11). Any mutation in the *GATA3* that affects the transactivating domains or the zinc finger domains will affect the functionality of the protein, affecting the development of the organs involved in the syndrome.

Our patient presented with right hemiplegia since birth. A CT and an MRI of the brain performed a few days after birth showed abnormality in the territory of the left middle cerebral artery. Fujimoto et al. reported the case of a Japanese boy with HDRS and recurrent cerebral infarctions bilaterally at the level of the basal ganglia. This boy presented with episodes of left hemiplegia beginning at 7 months of age, and months later, he presented with right hemiplegia. CTs of his brain obtained at the time of initial evaluation revealed areas of low-density in the corresponding contralateral basal ganglia. Cerebral angiography showed no abnormalities. This patient lacked risk factors for cerebral infarctions, and Fujimoto et al. described a possible relation between HDRS and cerebral infarction as a new feature associated with the syndrome (12). Shaw et al. reported on four patients with HDRS, one of whom was found to have a small area of low-density parenchyma in the left hemisphere upon evaluation for seizures, suggesting cerebral infarctions (13).

This report demonstrates the importance of chromosomal microarrays in facilitating the identification of rare conditions. In this specific case, the identification of a deletion in the area of *GATA3* allowed us to evaluate the systems affected by mutations in this gene and to make

an early diagnosis. Thus, we were able to develop an early management plan and prevent complications. Although no causal relationship between HDRS and CNS infarction has been established, to our knowledge our patient is the third case in which this association has been described. Further research is necessary to determine the nature of this relationship.

Acknowledgments: We thank Elizabeth G. Lipman Diaz for the help she provided reviewing and editing the original manuscript.

References

1. Barakat AY, D'Albora JB, Martin MM, Jose PA. Familial nephrosis, nerve deafness, and hypoparathyroidism. *J Pediatr* 1977;91:61–4.
2. Bilous RW, Murty G, Parkinson DB, Thakker RV, Coulthard MG, et al. Autosomal dominant familial hypoparathyroidism, sensorineural deafness, and renal dysplasia. *New Engl J Med* 1992;327:1069–74.
3. Hasegawa T, Hasegawa Y, Aso T, Koto S, Nagai T, et al. HDR syndrome (hypoparathyroidism, sensorineural deafness, renal dysplasia) associated with del(10)(p13). *Am J Med Genet* 1997;73:416–8.
4. Van Esch H, Groenen P, Nesbit MA, Schuffenhauer S, Lichtner P, et al. GATA3 haplo-insufficiency causes human HDR syndrome. *Nature* 2000;406:419–22.
5. Joulin V, Bories D, Eleouet JF, Labastie MC, Chretien S, et al. A T-cell specific TCR delta DNA binding protein is a member of the human GATA family. *EMBO J* 1991;10:1809–16.
6. Ferraris S, Del Monaco AG, Garelli E, Carando A, De Vito B, et al. HDR syndrome: a novel “de novo” mutation in *GATA3* gene. *Am J Med Genet A* 2009;15:770–5.
7. Fukami M, Muroya K, Miyake T, Iso M, Kato F, et al. GATA3 abnormalities in six patients with HDR syndrome. *Endocrinol J* 2011;58:117–21.
8. Nesbit MA, Bowl MR, Harding B, Ali A, Ayala A, et al. Characterization of *GATA3* mutations in the hypoparathyroidism, deafness, and renal dysplasia (HDR) syndrome. *J Biol Chem* 2004;279:22624–34.
9. van der Wees J, van Looij MA, de Ruiter MM, Elias H, van der Burg H, et al. Hearing loss following *Gata3* haploinsufficiency is caused by cochlear disorder. *Neurobiol Dis* 2004;16:169–78.
10. Lim, K-C, Lakshmanan G, Crawford SE, Gu Y, Grosveld F, et al. *Gata3* loss leads to embryonic lethality due to noradrenaline deficiency of the sympathetic nervous system. *Nature Genet* 2001;25:209–12.
11. Nakamura A, Fujiwara F, Hasegawa Y, Ishizy K, Mabe A, et al. Molecular analysis of the *GATA3* gene in five Japanese patients with HDR syndrome. *Endocrinol J* 2011;58:123–30.
12. Fujimoto S, Yokochi K, Morikawa H, Nakano M, Shibata H, et al. Recurrent cerebral infarctions and del (10) (p14p15.1) de novo in HDR (hypoparathyroidism, sensorineural deafness, renal dysplasia) syndrome. *Am J Med Genet* 1999;86:427–9.
13. Shaw NJ, Haigh D, Lealman GT, Karbani G, Brocklebank JT, et al. Autosomal recessive hypoparathyroidism with renal insufficiency and developmental delay. *Arch Dis Child* 1991;66:1191–4.