Absence of a del(22q11) in a patient with the 3C (cricanirebellocardiac) syndrome

We read with interest the letter by Butler and Mowrey concerning the hypothesis that the 3C syndrome could be associated with a deletion of 22q11.2. In 1994, we had the opportunity to see a 10 day old female newborn who we then diagnosed as having the 3C syndrome. The case report was published in 1995.1

We were able to see her again at 3 years 6 months of age and we performed molecular cytogenetic studies. We found no deletion of 22q11.2. The proband had moderate developmental delay, short stature with macrocephaly (height was 85 cm, <5th centile, weight was 10.75 kg, <5th centile, and OFC was 53.5 cm, +97th centile). Surgery for glaucoma, atrial septal defect, pulmonary stenosis, and a ventriculo-peritoneal shunt had been successful. She still had most of the dysmorphic features of the 3C syndrome (fig 1), including a bulging forehead, a prominent occiput, ocular hypertelorism (inner canthal distance 35 mm, >2 SD), outer canthal distance 98 mm, >2 SD), epicantus, and depressed nasal bridge. The chromosome 22 control probe, D22S39, which is located at 22q13.3. FISH was performed on metaphase spreads from peripheral blood lymphocytes according to the manufacturer’s recommendations (Oncor), but no microdeletion was visible.

The 3C syndrome is characterised by central nervous system, cardiac, and craniofacial anomalies. It is presumed to be autosomal recessive (MIM 220210) and 18 cases have been published,14 of which eight of them from seven families of Canadian native Indians.

Reviewing these 18 case reports, although there may be an overlap in the cardiac defects with the DiGeorge/velocardiofacial phenotype,1 the characteristic facies are remarkably different. The patient with a deletion of 22q11.2, who impressed Butler and Mowrey,1 has none of the dysmorphic features of the 3C syndrome. Mental retardation was present in all 3C patients,14 absent in the patient commented on by Butler and Mowrey,1 and is reported as a feature of 40% of velocardiofacial1 and 77% of DiGeorge syndrome patients. Palatal or pharyngeal abnormalities were described in 11% of 3C,14 98% of velocardiofacial,1 and 48% of DiGeorge patients. The only immunodeficiency associated with the 3C syndrome was a humoral one14 and hypocalcaemia has never been reported.

In another case report,15 a deletion in 22q11 was found in a patient with the initial diagnosis of 3C syndrome. The presence of microcephaly described in this patient15 is quite unusual, as macrocephaly was a feature of 11 of the 18 reported cases of 3C syndrome.14,15 He also had a multicystic and dysplastic kidney, and the only report of renal abnormalities in other 3C patients is a prenatal ultrasound diagnosis of bilateral hydronephrosis, which subsided leaving a unilateral dilated collecting system.14 Taking also into account the absence of cardiac anomaly, a feature of 16 of the 18 reported cases of 3C syndrome14 and the facial features of the patient in the published picture,15 it seems to be a less characteristic case.

However, deletions of 22q11.2 have been detected in a heterogeneous variety of patients. Some cases do not have features included in the acronym CATCH 22 (Cardiac, Abnormal facies, Thymic hypoplasia, Cleft palate, Hypocalcaemia), such as laryng-
A mother with VCFS and unilateral dysplastic kidney and her fetus with multicystic dysplastic kidneys: additional evidence to support the association of renal malformations and VCFS

Drevničt et al. recently described in this journal a female fetus with Potter sequence caused by unilateral renal agenesis and contralateral multicystic renal dysplasia, who was retrospectively found to have a deletion in chromosome 22q11 following identification of the deletion in the father. The father presented with typical VCFS features but no urological anomalies. We describe a patient with a clinical diagnosis of VCFS and a unilateral dysplastic kidney but with negative high resolution cytogenetic and FISH studies, who had a female fetus with bilateral multicystic kidneys. This provides additional evidence to support the conclusion of Drevničt et al. that in VCFS the renal malformation can dominate the clinical phenotype.

Our patient is a 24 year old female initially referred because of facial dysmorphology and developmental delay. She had a long nose and a long, thin face, a small chin, prominent incisors, a deep philtrum (fig 1), a high palate which had the appearance of a cleft, velopharyngeal insufficiency, and long, thin fingers and toes. She also had a repaired ASD, developmental and speech delay, depression, chemical dependency, and seizures. A renal ultrasound showed a unilateral multicystic dysplastic kidney. Karyotype analysis and FISH using a digoxigenin labelled probe localised to 22q11.2 (Oncor Inc, Gaithersburg, MD) were negative. Her first pregnancy was uncomplicated and she delivered a healthy male with no dysmorphic features. He had a normal renal ultrasound and at the age of 2 years is developmentally appropriate. During her second pregnancy, ultrasound examination of her female fetus at 19 weeks 4 days identified bilateral multicystic kidneys and anhydramnios. The pregnancy was terminated and necropsy confirmed the presence of multicystic dysplastic kidneys, hypoplastic bladder, and low set ears. No other abnormalities were noted. Karyotype analysis was normal.

Of patients diagnosed clinically with VCFS, only 68% to 81% have a deletion of 22q11.2.1 3 Several recent articles have noted the presence of nephropathological malformations as a component of VCFS syndrome.4 7 Of the 39 patients reported by Drevničt et al. with 22q11 deletions, four had nephropathological malformations. Another patient with unilateral renal agenesis and dysmorphic features suggestive of DiGeorge sequence had a normal G band karyotype.8 Driscoll et al.9 reported a patient with a multicystic kidney and a normal karyotype; however, molecular studies showed the absence of a paternal 22q11 allele. Of 11 patients with DiGeorge syndrome reported by Palacios et al.,10 one had a dysplastic right kidney and left ureterol- drenephrosis and one had a right megaureter; karyotype analysis was not performed on these two patients. We concur with Drevničt et al. that renal malformations associated with VCFS can lead to the Potter sequence and can dominate the clinical phenotype. These authors retrospectively investigated 10 additional cases of Potter sequence and no other patient with a de(22q11) was found. Thus, patients performing FISH for 22q11.2 on all fetuses with Potter sequence, along with a thorough evaluation of both parents for physical features of VCFS, needs to be examined further.

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