Reply to letters regarding clinical features of chromosome 22q11 deletion

One of the difficulties we face when we see anomalies/medical problems in people with a 22q11 deletion is deciding whether or not these are directly attributable to the microdeletion or are found by chance association. With what frequency does a second disorder need to occur before it can be said to be associated with the first?

Dean *et al* commented on the occurrence of craniosynostosis in 22q11 deletion patients. They reported an infant with a 22q11 deletion who had bilateral coronal and sagittal craniosynostosis. Subsequently this child was found to have a de novo P250R FGFR3 mutation. It is more likely that the craniosynostosis in this infant was the result of the FGFR3 mutation rather than the 22q11 deletion. However, the 5/548 (0.91%) reported in our series exceeds the highest population estimate they give. They state that the birth incidence of craniosynostosis varies between 1/3225 (0.03%) and 1/735 (0.13%) live births, with the upper 95% confidence interval being 1/518 (0.19%). However, we will proceed to obtain further clinical information on the five patients with craniosynostosis and undertake FGFR3 mutation analysis as they suggest. This should help to clarify whether craniosynostosis is a feature associated with 22q11 deletion.

In contrast, Di Rocco *et al* comment on the absence of polyarthropathy/juvenile rheumatoid arthritis (JRA) in association with the 22q11 deletion in our series. Their own experience of 3/80 (3.75%) children at the Children's Hospital of Philadelphia having JRA gives an incidence of 50 times that of the general population. There were no reports of JRA/polyarthropathy in our series and it is unlikely that significant arthropathy would have been omitted from questionnaires. If the incidence is 3.75% we would have expected approximately 20 subjects in our series to have JRA. One of the strengths of our paper is the large number of patients reviewed. We hoped this study would clarify the incidence of uncommon features which may be overrepresented in published reports.

Di Rocco *et al* also comment that other autoimmune conditions have been observed in chromosome 22q11 deletion syndrome. In our study, 8/558 (1.4%) patients had autoimmune problems. Four patients had hypothyroidism; two were diagnosed in adult life, one at 5 years, and one at 12 years. This last patient had antithyroid antibodies. Interestingly, the patient's mother also had hypothyroidism, but did not have a 22q11 deletion. One patient had hyperthyroidism secondary to Hashimoto's thyroiditis aged 16 years. Two patients already previously reported had idiopathic thrombocytopenia and one patient had Raynaud's phenomena with positive anticardiolipin autoantibodies. A large proportion of the cases in our series are still children. Autoimmune phenomena may be one of the later complications of the disorder, indicating the importance of following the natural history of the disorder in a series of patients.

Hunter asks for further information about the ascertainment of the patients in the series. For the vast majority, the diagnosis was made by a paediatrician or in a general genetics clinic: 188 (34%) were referred by cardiologists, 39 (7%) through cleft palate clinics, and four by immunologists. It is difficult to disentangle whether the fact that 188 were referred by cardiologists is biased ascertainment or simply reflects the fact that many of these children will present to a cardiologist. However, it is true to say that as our experience of the condition increases, we are making the diagnosis in children with fewer hard signs. The only way of being certain that there is no ascertainment bias would be to screen newborns to identify a cohort of children with deletions.

In conclusion, we feel that the series we have described is the least biased available, while recognising that it may have underestimated adult onset complications. As we become better at recognising the condition, it may become apparent that these cases still represent the more severe end of the spectrum.

Erratum. The reference Dean JCS, Cole GF, Appleton RE, Burn J, Roberts SA, Donnai D. Cranial hemihypertrophy and neurodevelopmental prognosis. *J Med Genet* 1990;27:160-4 should have been De Silva D, Duffty P, Booth P, Auchterlonie I, Morrison N, Dean JCS. Family studies in chromosome 22q11 deletion: further demonstration of phenotypic heterogeneity. *Clin Dysmorphol* 1995;4:294-303.

A RYAN
J A GOODSHIP
D I WILSON
ON BEHALF OF THE EUROPEAN CONSORTIUM
Department of Human Genetics, University of Newcastle upon Tyne, Newcastle upon Tyne, UK

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

We read with interest the letter by Butler and Mowrey[1] 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.[2]

We were able to see her again at 3 years 6 months of age and we performed molecular cytogenetic testing looking for a 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 ventriculoperitoneal 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), epicanthus, and depressed nasal bridge. Immune function was normal both in the first year of life (serum immunoglobulins) and now (absolute number of T lymphocytes, T cell subsets, and serum immunoglobulins).

For the detection of the 22q11.2 deletion by fluorescent in situ hybridisation (FISH), a digoxigenin labelled locus specific probe, D22S75, which lies in the commonly deleted region, was used, in combination with a 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[3]) and 18 cases have been published,[2 4 5] eight of them from seven families of Canadian native Indians.[5]

Reviewing these 18 case reports, although there may be an overlap in the cardiac defects with the DiGeorge/velocardiofacial phenotype,[6] the characteristic facies are remarkably different. The patient with a deletion of 22q11.2,[7] who impressed Butler and Mowrey, [1] has none of the dysmorphic features of the 3C syndrome. Mental retardation was present in all 3C patients,[2 4 5] absent in the patient[7] commented on by Butler and Mowrey,[1] and is reported as a feature of 40% of velocardiofacial[8] and 77% of DiGeorge syndrome[9] patients. Palatal or pharyngeal abnormalities were described in 11% of 3C,[2 4 5] 98% of velocardiofacial,[8] and 48% of DiGeorge[9] patients. The only immunodeficiency associated with the 3C syndrome was a humoral one[10] and hypocalcaemia has never been reported.

In another case report,[11] a deletion in 22q11 was found in a patient with the initial diagnosis of 3C syndrome. The presence of microcephaly described in this patient[11] is quite unusual, as macrocephaly was a feature of 11 of the 18 reported cases of 3C syndrome.[2 4 5] 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.[12] Taking also into account the absence of cardiac anomaly, a feature of 16 of the 18 reported cases of 3C syndrome,[2 4 5] and the facial features of the patient in the published picture,[11] 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 laryn-

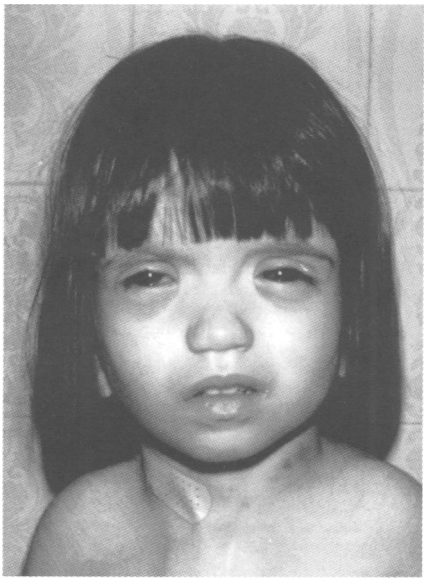

Figure 1 Patient with ocular hypertelorism, epicanthus, and depressed nasal bridge.

geal atresia[13] and renal agenesis and renal dysplasia with von Maeyer-Rokitanski-Küster complex.[14]

As yet, there is no consistent detectable chromosomal or metabolic cause of the 3C syndrome, including the 22q11.2 deletion discussed here. In the 16 families known to have children with the 3C syndrome, four males and 14 females, two had two affected daughters, three are related, and five belong to a small, isolated part of Canada with its own dialect. The most likely aetiology, therefore, is autosomal recessive inheritance, as proposed in the first report of the syndrome. It would be prudent, however, to exclude a deletion in 22q11.2 before a definitive diagnosis of 3C syndrome is made owing to possible overlap of the variable clinical features.

JORGE M SARAIVA
Consulta de Genética, Hospital Pediátrico de Coimbra, Avenida Bissaya Barreto, 3000 Coimbra, Portugal

EUNICE MATOSO
ISABEL MARQUES
Unidade de Citogenética e Diagnóstico Prénatal, Instituto de Biologia Médica, Faculdade de Medicina de Coimbra, Portugal

1 Butler MG, Mowrey P. Should the 3C (cranio-cerebellocardiac) syndrome be included in the spectrum of velocardiofacial syndrome and DiGeorge sequence? *J Med Genet* 1996;**33**:719-20.
2 Saraiva JM, Gama E, Pires MM, Sequeira JF. First report of glaucoma as a feature of the 3C syndrome. *Clin Dysmorphol* 1995;**4**:156-60.
3 McKusick VA. *Mendelian inheritance in man: catalogs of autosomal dominant, autosomal recessive and X-linked phenotypes*. 11th ed. Baltimore: The Johns Hopkins University Press, 1994.
4 Digilio MC, Marino B, Giannotti A, Mingarelli R, Dallapiccola B. Atrioventricular canal and 3C (cranio-cerebello-cardiac) syndrome. *Am J Med Genet* 1995;**58**:97-8.
5 Marles SL, Chodirker BN, Greenberg CR, Chudley AE. Evidence for Ritscher-Schinzel syndrome in Canadian native indians. *Am J Med Genet* 1995;**56**:343-50.
6 Wulfsberg EA, Leana-Cox J, Neri G. What's in a name? Chromosome 22q abnormalities and the DiGeorge, velocardiofacial, and conotruncal anomalies face syndromes. *Am J Med Genet* 1996;**65**:317-19.
7 Lynch DR, McDonald-McGinn DM, Zackai EH, *et al.* Cerebellar atrophy in a patient with velocardiofacial syndrome. *J Med Genet* 1995;**32**:561-3.
8 Goldberg R, Motzkin B, Marion R, Scambler PJ, Shprintzen RJ. Velo-cardio-facial syndrome: a review of 120 patients. *Am J Med Genet* 1993;**45**:313-19.
9 Wilson DI, Burn J, Scambler P, Goodship J. DiGeorge syndrome - part of CATCH 22. *J Med Genet* 1993;**30**:852-6.
10 Lauener R, Seger R, Jörg W, Hallé F, Aeppli R, Schinzel A. Immunodeficiency associated with Dandy-Walker-like malformation, congenital heart defect, and craniofacial abnormalities. *Am J Med Genet* 1989;**33**:280-1.
11 Devriendt K, van Thienen MN, Swillen A, Fryns JP. Cerebellar hypoplasia in a patient with velo-cardio-facial syndrome. *Dev Med Child Neurol* 1996;**38**:949-53.
12 Hoo JJ, Kreiter M, Halverson N, Perszyk A. 3C (cranio-cerebello-cardiac) syndrome - a recently delineated and easily recognizable congenital malformation syndrome. *Am J Med Genet* 1994;**52**:66-9.
13 Fokstuen S, Bottani A, Medeiros PFV, Antonarakis SE, Stoll C, Schinzel A. Laryngeal atresia type III (glotic web) with 22q11.2 microdeletion: report of three patients. *Am J Med Genet* 1997;**70**:130-3.
14 Devriendt K, Moerman P, van Schoubroeck D, Vandenberghe K, Fryns JP. Chromosome 22q11 deletion presenting as the Potter sequence. *J Med Genet* 1997;**34**:423-5.

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

Devriendt *et al*[1] 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 Devriendt *et al*[1] 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.

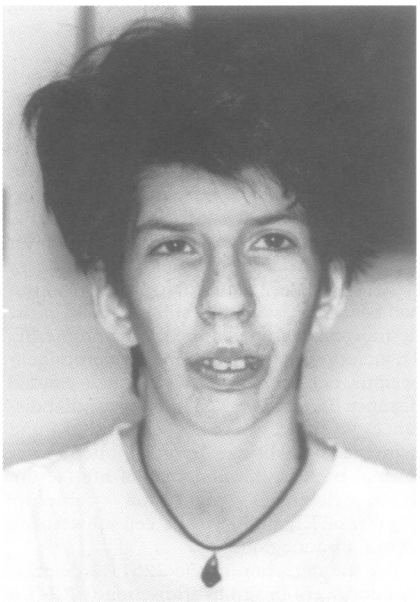

Figure 1 Patient with long nose, long, thin face, small chin, prominent incisors, and deep philtrum.

Of patients diagnosed clinically with VCFS, only 68 to 81% have a deletion of 22q11.2.[2 3] Several recent articles have noted the presence of nephrourological malformations as a component of VCFS syndrome.[4-7] Of the 39 patients reported by Devriendt *et al*[5] with 22q11 deletions, four had nephrourological malformations. Another patient with unilateral renal agenesis and dysmorphic features suggestive of DiGeorge sequence had a normal G banded karytoype.[4] Driscoll *et al*[6] 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*,[7] one had a dysplastic right kidney and left ureterohydronephrosis and one had a right megaureter; karyotype analysis was not performed on these two patients.

We concur with Devriendt *et al*[1] 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 del(22q11) was found. The possibility of 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.

PAULA M CZARNECKI
DANIEL L VAN DYKE
SUBODH VATS
GERALD L FELDMAN
Department of Medical Genetics, Henry Ford Hospital, 2799 W Grand Blvd, CFP-4, Detroit, Michigan 48202, USA

1 Devriendt K, Moerman P, Van Schoubroeck D, *et al.* Chromosome 22q11 deletion presenting as the Potter sequence. *J Med Genet* 1997;**34**:423-5.
2 Driscoll DA, Salvin J, Sellinger B, *et al.* Prevalence of 22q11 microdeletions in DiGeorge and velocardiofacial syndromes: implications for genetic counselling and prenatal diagnosis. *J Med Genet* 1993;**30**:813-17.
3 Lindsay EA, Greenberg F, Schaffer LG, *et al.* Velo-cardio-facial syndrome: frequency and extent of 22q11 deletions. *Am J Med Genet* 1995;**56**:191-7.
4 Baldellou A, Bone J, Tamparillas M, *et al.* Congenital hypoparathyroidism, ocular colobomata, unilateral renal agenesis and dysmorphic features. *Genet Couns* 1991;**2**:245-7.
5 Devriendt K, Swillen A, Fryns JP, *et al.* Renal and urological tract malformations caused by a 22q11 deletion. *J Med Genet* 1996;**33**:349.
6 Driscoll DA, Budarf ML, Emanuel BS. A genetic etiology for DiGeorge syndrome: consistent deletions and microdeletions of 22q11. *Am J Hum Genet* 1992;**50**:924-33.
7 Palacios J, Gamallo C, Garcia M, Rodriquez JI. Decrease in thyrocalcitonin-containing cells and analysis of other congenital anomalies in 11 patients with DiGeorge anomaly. *Am J Med Genet* 1993;**46**:641-6.

New overgrowth syndrome and FGFR3 dosage effect

The 4p16 chromosome band is the object of intense scrutiny because the region is known to be genetically dense,[1] containing many genes responsible for well known disorders such as the HD gene,[2] FGFR3,[3] and the Wolf-Hirschhorn critical region.[4] More recently, the question has been raised whether