arthrogryposis as well as otopalatodigital syndrome types I and II (MIM 311300 and 304120), Larsen syndrome (MIM 150250), frontometaphyseal dysplasia (MIM 305620), and Freeman-Sheldon syndrome, based either on the probable mode of inheritance in their family, the lack of mental retardation, deafness, or broad distal digits with short nails, and the distinctive facial appearance, finger/toe abnormalities, and radiographic findings in their patients.

Adducted thumbs and club foot as well as downward slanting palpebral fissures, telecanthus, and abnormal ear placement were reported in autosomal recessively inherited Christian-type adducted thumb syndrome.⁴ These features as well as hirsutism, craniosynostosis, and a fatal course of the disease in our first patient are shared in our cases. Therefore, a significant overlap of the adducted thumb syndrome and the adducted thumb-club foot syndrome exists. Most patients classified with this diagnosis, however, presented with additional non-specific findings, such as microcephaly, bifid uvula/cleft or highly arched palate, generalised severe muscular hypotonia, myopathic face, and impaired swallowing.^{4,5} Myopathic changes in a muscle biopsy were observed in a patient with Christian-type adducted thumb syndrome by Kunze *et al*⁶ and dysmyelination was observed in one of the patients originally reported by Christian *et al*.⁴ Information as to the aetiology of the disorder is not available in the other cases with that syndrome or in our patients. The existence of a distinctive adducted thumb-club foot syndrome is largely emphasised by the reports of this recognisable dysmorphic condition in three consanguineous families of different ethnic origin. Moreover, the disorder differs significantly from similar established disease entities by the absence of mental retardation and most likely autosomal recessive inheritance. On the other hand, some intra- and interfamilial variability of the syndrome is described.

Finally, our very recent review of published reports, the London Dysmorphology Database,⁶ and the POSSUM Database did not show up any other known syndrome equalling or approximately matching the adducted thumb-club foot syndrome proposed by Dundar *et al*¹ or the syndrome present in the patients reported by Sonoda and Kouno³ and considered to represent a new type of distal arthrogryposis. There were some similarities with the patients reported by Moore and Weaver,⁷ who presented with probably autosomal dominant inherited distal arthrogryposis and craniofacial abnormalities and who were considered to have a new subtype of type II arthrogryposis.

We conclude that adducted thumb-club foot syndrome most likely presents a distinct clinical entity. Parental consanguinity observed in our family as well as in the Turkish and Japanese families, strongly supports autosomal recessive inheritance of this syndrome, although we cannot exclude X linked inheritance or parental germline mosaicism, which has been shown in CCA.⁸ Genome scans in the families with the adducted thumb-club foot syndrome might enable the mapping of the disease causing gene that exerts pleiotropic effects at least in organogenesis and prenatal development.

We wish to thank the family for their cooperation.

ANDREAS R JANECKE*
KARIN UNSINN†
ALFONS KRECZY‡
IVO BALDISSERA§
INGMAR GASSNER†
NIKOLAUS NEU†
GERD UTERMANN*
THOMAS MÜLLER†

*Institute of Medical Biology and Human Genetics, University of Innsbruck, Schöpfstrasse 41, A-6020 Innsbruck, Austria

†Department of Paediatrics, University of Innsbruck, Austria

‡Institute of Pathology, University of Innsbruck, Austria

§Department of Ophthalmology, University of Innsbruck, Austria

Correspondence to: Dr Janecke, Andreas.Janecke@uibk.ac.at

- 1 Dundar M, Demiryilmaz F, Demiryilmaz I, Kumandas S, Erkilic K, Kendirci M, Tuncel M, Ozyazgan I, Tolmie JL. An autosomal recessive adducted thumb-clubfoot syndrome observed in Turkish cousins. *Clin Genet* 1997;51:61-4.
- 2 Online Mendelian Inheritance in Man, OMIM (TM). Center for Medical Genetics, Johns Hopkins University, Baltimore, MD, and National Center for Biotechnology Information, National Library of Medicine, Bethesda, MD, 1999. World Wide Web URL: <http://www.ncbi.nlm.nih.gov/omim/>
- 3 Sonoda T, Kouno K. Two brothers with distal arthrogryposis, peculiar facial appearance, cleft palate, short stature, hydronephrosis, retentio testis, and normal intelligence: a new type of distal arthrogryposis? *Am J Med Genet* 2000;91:280-5.
- 4 Christian JC, Andrews PA, Conneally PM, Muller J. The adducted thumbs syndrome. An autosomal recessive disease with arthrogryposis, dysmyelination, craniosynostosis, and cleft palate. *Clin Genet* 1971;2:95-103.
- 5 Kunze J, Park W, Hansen KH, Hanefeld F. Adducted thumb syndrome. Report of a new case and a diagnostic approach. *Eur J Pediatr* 1983;141:122-6.
- 6 Winter RM, Baraitser M. *The London Dysmorphology Database*. Oxford: Oxford University Press, 1993.
- 7 Moore CA, Weaver DD. Familial distal arthrogryposis with craniofacial abnormalities: a new subtype of type II? *Am J Med Genet* 1989;33:231-7.
- 8 Putnam EA, Park ES, Aalfs CM, Hennekam RC, Milewicz DM. Parental somatic and germ-line mosaicism for a FBN2 mutation and analysis of FBN2 transcript levels in dermal fibroblasts. *Am J Hum Genet* 1997;60:818-27.

J Med Genet 2001;38:269-271

Diaphragmatic hernia, hydrocephalus, and cardiac malformations in four pregnancies of a non-consanguineous couple

EDITOR—Diaphragmatic hernia occurs with an incidence of 1/4000-1/5000 newborns.^{1,2} About half of the cases occur as isolated malformations; anomalies of the central nervous system are well known associated defects, as are midline malformations such as cleft lip and palate and heart defects.^{1,2} Among syndromic causes of diaphragmatic hernia are numerous chromosomal imbalances (4p deletion, trisomy 18, i(12p)), and some single gene defects such as the autosomal recessive Fryns syndrome³ and an X

linked form, the thoracoabdominal syndrome.^{4,5} Fryns syndrome is probably the most frequent non-chromosomal malformation syndrome associated with diaphragmatic hernia,^{3,6} but this disorder presents with typical dysmorphic features, and both heart and CNS malformations are infrequent in Fryns syndrome.

The family reported here, along with several other published reports, combining CNS, heart, and diaphragmatic defects, may help to delineate a distinct syndromic form of diaphragmatic hernia.

Healthy, non-consanguineous parents, of French origin and with unremarkable family histories, had six unsuccessful pregnancies. Two resulted in first trimester spontaneous abortion. The other four led to pregnancy terminations between 15 and 23 weeks' gestation because of malformations detected on ultrasound (table 1). Left diaphragmatic hernia was the earliest observed and most constant feature. Cardiac malformations, present in all cases, were of varying

Table 1 Summary of malformations in affected fetuses

	Fetus 1	Fetus 2	Fetus 3	Fetus 4
Gestational age, sex	23 wk, M	24 wk, M	18 wk, F	16 wk, F
Ultrasound (anomalies)	Brain, diaphragm	Diaphragm, heart	Hydrocephalus, diaphragm	Diaphragm
CNS	Hydrocephalus, 3–4 vent	No brain histology done	Tetравentricular hydrocephalus	Tetравentricular hydrocephalus
Cardiac	VSD	Hypoplastic left heart	VSD, ASD	Complex heart malformation
Gastrointestinal	—	Imperforate anus	—	—
Abdominal wall	Diaphragmatic hernia, left	Diaphragmatic hernia, left	Diaphragmatic hernia, left	Diaphragmatic hernia, left

types: VSD/ASD was seen twice and hypoplastic left heart and a complex heart malformation once each. Hydrocephalus was also constant on morphological examination of the fetus, although not yet visible on ultrasound in the pregnancy terminated at 15 weeks. In cases 3 and 4, examined by the same neuropathologist, this was a tetra-ventricular, non-obstructive hydrocephalus. The only inconstant malformation was imperforate anus, described in one male fetus. Muscle histology was normal in the two cases investigated in detail.

We examined the last two fetuses personally. No major dysmorphic features were present (fig 1). Specifically, the craniofacial features and nail/distal digit hypoplasia typical of Fryns syndrome were lacking.

Genetic analyses included karyotyping of fetuses 2–4 on amniocentesis (one) or fibroblasts post-termination (one), or both (one). Cytogenetic studies using RHG, RTBG, and GTBG banding were normal at the 550–600 band resolution level. Standard karyotypes of both parents were also normal, 46,XX and 46,XY. A 22q11 microdeletion was also excluded in the parents and one fetus by fluorescence in situ hybridisation using a critical region probe (Oncor). The parents were investigated with a probe set covering 41 subtelomeric regions (Cytocell Telomeric Multiprobe), which confirmed the presence of all telomeres. Analysis of fetus number 4 with the MultiFish Spectra Vision set (Vysis) was also normal.

We present here a couple whose six pregnancies resulted in two spontaneous abortions and four pregnancy terminations for multiple malformations. The malformed fetuses, two male and two female, presented with a remarkably similar malformation syndrome comprising left diaphragmatic hernia, heart malformation, and non-obstructive hydrocephalus of early onset. The diaphragmatic hernia was suspected as early as 12 weeks on ultrasound and confirmed by 15–16 weeks; the hydrocephalus developed somewhat later but was clearly present on echographic examination at 19–20 weeks' gestation.

A chromosomal anomaly could have explained the combination of first trimester miscarriage and malformed fetuses in the same family, but cytogenetic and molecular cytogenetic studies, including the use of telomeric probes for detection of a cryptic translocation, were repeatedly normal. We considered a mitochondrial disorder, given that all six pregnancies were abnormal. However, we know of no precedent for such an aetiology in malformation syndromes and fetal muscle histology was normal.

An autosomal recessive aetiology seems the most likely, given four affected fetuses of both sexes born to normal parents. The constancy of the phenotype is anecdotal evidence for a recessive disorder, as is the resemblance to Fryns syndrome, which follows this hereditary transmission. Among syndromic causes of diaphragmatic hernia,

Figure 1 Fetuses 3 (A) and 4 (B) after pregnancy termination (18 and 16 weeks' gestation). Note lack of distinct dysmorphic features.

Table 2 Differential diagnosis

	Fryns	"Fryns-like" cases*	Thoraco-abdominal	Current cases
Diaphragmatic hernia	++	++	++	++
Hydrocephalus	+	++	++	++
Heart malformation	+	+	++	++
Anal anomaly (imperforate)	—	—	—	+

*See text for discussion of cases reported in references 2, 10, and 11.

Fryns syndrome is the closest clinically. However, the typical dysmorphic features of facies and limbs were lacking in the fetuses and CNS pathology is not frequent in this disorder. Heart malformations are known but are rarely severe and imperforate anus is rarely, if ever, described.^{3 6 7}

The thoracoabdominal syndrome^{4 5} combines diaphragmatic defects with CNS anomalies, including hydrocephalus in some cases, but there are other midline defects (omphalocele, clefts of lip and palate) and inheritance is X linked recessive.⁵ The family reported here had similarly affected fetuses of both sexes. We also considered the CHARGE association and the hydrolethrus syndrome^{7 8} in the differential diagnosis, but excluded them given inadequate clinical fit (table 2).

Several other families, some of which are described within the Fryns syndrome entry (MIM 229850) in the catalogue of *Mendelian inheritance in man*,⁹ have been reported with a malformation complex similar to that of our patients. Fitch *et al*¹⁰ reported a child with absent left hemidiaphragm, arhinencephaly, and cardiac malformations born to consanguineous parents; as distal digital hypoplasia was described, it is possible that their case represents Fryns syndrome, which was not delineated nominally until the following year. However, other publications also report the association of diaphragmatic hernia and CNS anomalies, sometimes in association with heart defects.¹¹ Bieber *et al*² presented a family in which two sibs, of different sexes, had a right diaphragmatic hernia, pulmonary hypoplasia/agenesis, and hydrocephalus. Their family differs from the one we report in that the hernias were right sided (the rarer form), there was no cardiac defect, and the hydrocephalus was obstructive.

Therefore, although we are not aware of another reported family with exactly the same combination of anomalies, there is some precedent for the combination of heart, CNS, and diaphragmatic defects outside Fryns syndrome. We strongly suggest, based on the family reported here, the existence of a monogenic, probably autosomal recessive aetiology for this combination. Whether this disorder will prove to be the result of a distinct mutated gene, or might perhaps be allelic with that for Fryns syndrome,

will await identification of the gene or genes responsible. In the meantime, descriptions of additional families would greatly aid genetic counselling and prenatal diagnosis in severe cases such as the family presented here.

Note added in proof

The couple's seventh pregnancy resulted in the term birth of a normal boy.

We would like to thank the couple for their cooperation in the face of a devastating situation. We appreciate the collaboration of Drs Jean Ouziel and Gianpaolo Pizzolato, as well as that of colleagues in obstetrics, ultrasound, and cytogenetics. Mr Tom Warren's help with graphics is gratefully acknowledged.

C D DELOZIER-BLANCHET*

J LESPINASSE†

M A BRUNDLER‡

P EXTERMANN§

*Division of Medical Genetics, Geneva University Hospital, 1 rue Michel-Servet, CH-1211 Geneva 4, Switzerland

†Cytogenetics Laboratory, Central Hospital, Chambéry, France

‡Department of Pathology, Geneva University Hospital, Switzerland

§Fetal Medicine Unit, Department of Obstetrics and Gynecology, Geneva University Hospital, Switzerland

Correspondence to: Dr DeLozier-Blanchet, delozier@cmu.unige.ch

- David TJ, Illingsworth CA. Diaphragmatic hernia in the south west of England. *J Med Genet* 1976;13:253-62.
- Bieber FR, Dawson AE, Holmes LB. Etiologic complexities of diaphragmatic defects: right diaphragmatic hernia, pulmonary hypoplasia/agenesis and hydrocephalus in sibs. *Am J Med Genet* 1991;41:164-8.
- Fryns JP, Moerman F, Goddeeris P, Bossuyt C, Van den Berghe H. A new lethal syndrome with cloudy cornea, diaphragmatic defects and distal limb deformities. *Hum Genet* 1979;50:65-70.
- Parmi R, Meizner I, Katz M. Familial congenital diaphragmatic defect and associated midline anomalies: further evidence for an X-linked midline gene? *Am J Med Genet* 1990;36:313-15.
- Parvari R, Carmi, Weissenbach J, Pilia G, Mumm W, Weinstein Y. Refined genetic mapping of X-linked thoracoabdominal syndrome. *Am J Med Genet* 1996;61:401-2.
- Cunniff C, Jones KL, Saal HM, Stern HJ. Fryns syndrome: an autosomal recessive disorder associated with craniofacial anomalies, diaphragmatic hernias and distal digital hypoplasia. *Pediatrics* 1990;85:499-504.
- Jones KL. *Smith's recognizable patterns of human malformation*, London: Saunders, 1997:857.
- Winter RM, Baraitser M. *London dysmorphology database*. Oxford Medical Databases. Oxford: Oxford University Press, 1996.
- McKusick VA. *Mendelian inheritance in man*. On-line edition. Baltimore: The Johns Hopkins University Press, 2000.
- Fitch N, Srolovitz H, Robitaille Y, Guttman R. Absent left hemidiaphragm, arhinencephaly, and cardiac malformations. *J Med Genet* 1978;15:399-401.
- Landau J W, Barry JM, Koch R. Arhinencephaly. *J Pediatr* 1963;62:895-900.

J Med Genet 2001;38:271-272

Deletion 22q11 syndrome: acknowledging a lost eponym as we say farewell to an acronym

EDITOR—Time may be closing on use of the acronym "CATCH22" for "deletion 22q11 syndrome",¹ but it is likely to be a good while before it has finally run out. Many will prefer to retain their personal preference and "deletion 22q11 syndrome" does not easily roll off the tongue (and it really needs to be stated in full to distinguish it from the separate and emerging "deletion 22q13 syndrome"^{2 3}). Besides this, any consensus accepted by geneticists will

take time to filter through to colleagues in other disciplines who, carrying most of the clinical burden for managing the patients' medical problems, may reasonably question the value of so much discussion about a name. Before (if ever) the relatively unambiguous "deletion 22q11 syndrome" achieves universal acclaim, and/or "velocardiofacial syndrome" (VCFS), the history of medical genetics should record that a little known otolaryngologist from Prague, Dr Eva Sedláčková, almost certainly described the syndrome in 1955,⁴ and subsequently in 1967,⁵ as a result of good clinical observation on a cohort of patients with congenital shortening of the soft palate. The findings are further referred to in a paper on soft palate innervation.⁶ The first paper, of course, appeared some 10, 13, 23, and 25 years before publications by DiGeorge,⁷ Shprintzen *et al*,⁸