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.

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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

Strong,⁹ and Takao *et al*,¹⁰ respectively. With medical and scientific publications dominated by the English language, the publication of Sedláčková's work in her native Czechoslovakian was always likely to pass unnoticed, a problem compounded by the consequences of cold war politics. However, the similarity of Sedláčková's cases to VCFS has previously been noted by one of us (RWP)¹¹ and also acknowledged in a major text.¹² Sedláčková herself, who died in 1976 aged 62, attempted to achieve some recognition for describing the condition that subsequently became known as VCFS (R J Gorlin, personal communication).

In the first and most important description of a syndrome with congenitally short velum,⁴ Sedláčková highlighted many of the features characterising deletion 22q11 syndrome. Between 1950 and 1954, 26 children, 11 boys and 15 girls, were identified with a shortened soft palate and a sufficiently long hard palate but no clefting. They ranged in age from 2 to 16 years and their appearance was so distinctive that it was known the child would "snuffle" even before it spoke. Nine of the children were poor feeders because of a weak suck and motor development was delayed in all but two. Only seven began speaking at the normal age, while the others typically began to speak in their third or fourth years. The facial features were described as striking, with narrow, slanting eye slits, a degree of telecanthus, an open mouth, a wide base to the nose, and a fairly flat nose with small nostrils. The upper lip was described as being short and drawn up, the philtrum somewhat smooth, and there was a degree of micrognathia. In addition, ear lobes were described as small, the entrance to the auditory meatus narrow, and otitis media was common. In 22 of the 26 children the hands were described as small and slender, the fingers being short and slim with pointed ends. Terminal phalanges, in particular, were short. Growth was generally satisfactory, with the exception of three cases who were noticeably shorter and weaker than their sibs. Occasional abnormalities included mild contraction of the fingers (n=1), overlapping toes (n=2), unilateral oligosyndactyly of the right hand (n=1), congenital subluxation of the hip (n=2), Sprengel deformity (n=1), and undescended testes (n=3). Mental retardation to some degree was noted in nine of the 26. By the time of her second paper,⁵ Sedláčková had gathered 48 cases, noted an imperfect closure of the eyelids in some, and added congenital heart disease to the list of associated anomalies. Her syndrome became known as velofacial hypoplasia.¹³

Most significantly, Sedláčková provided illustrations of typical cases with a congenitally shortened velum in her first paper,⁴ including two examples with frontal portrait view. In her second paper a further portrait of a typical case is provided.⁵ Clinicians who know deletion 22q11 syndrome could surely not dispute the patients having facies well within the spectrum with which we are now familiar. It seems likely she described children across the DiGeorge-VCFS spectrum, as a short philtrum with tented upper lip tends to be part of DiGeorge syndrome, while slender, tapering fingers tend to be associated with VCFS. However, she made no mention of long fingers, which is

generally the pattern in VCFS, and herein lies the only obvious discrepancy. Nevertheless, the illustrations of hands from typical cases⁴ is acceptably within the spectrum for deletion 22q11 syndrome. She has not included children with overt clefting but this probably reflects her ascertainment of cases, perhaps not wanting to potentially "contaminate" the cohort by including those operated on for cleft palate. She does, however, refer to 10 cases with congenitally short palate, operated on for cleft palate, from the huge series of more than 2600 cases operated on by the late Professor Burian.⁴ One cannot, of course, exclude the possibility that she described some non-deletion 22q11 cases because today, with the benefit of a reliable test, phenocopies are sometimes observed in genetic clinics.

Overall, the close overlap of Sedláčková's description, together with the illustrative material, is convincing, but expert readers must decide for themselves whether she has reported what we now know as deletion 22q11 syndrome. If the subjects could be revisited and FISH tested, the controversy would be resolved but the passage of time perhaps makes this unlikely. There has been work showing a common aetiology of velofacial hypoplasia and VCFS,¹⁴ but no suggestion that any of Sedláčková original cases were included. Given the prevalence of deletion 22q11 syndrome, any clinician with a substantial case load of velopharyngeal insufficiency is bound to have a cohort with the condition; it is then a matter of distinguishing these from other cases. We suggest that Sedláčková successfully achieved this, provided a good clinical description, and should be acknowledged for the accomplishment.

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Do patients with maternal uniparental disomy for chromosome 7 have a distinct mild Silver-Russell phenotype?

EDITOR—Silver-Russell syndrome (SRS) is characterised by severe intrauterine growth retardation (IUGR), postnatal short stature, asymmetry of the face, body, and limbs, short and incurved fifth fingers, and a characteristic triangular face with a prominent and bossed forehead, a small lower jaw, and downturned corners of the mouth.^{1,2} Many other slightly dysmorphic features are seen in SRS patients (table 1) and these have been regarded mostly as confirmatory, not obligatory, for the diagnosis.³⁻⁵ Any one feature is not consistently observed in all SRS patients and the expression of features tends to vary greatly among subjects leading to considerable heterogeneity.^{3,4} Straightforward criteria for the evaluation of the severity of SRS characteristics have not been set and it has been proposed that SRS might in fact comprise different subgroups.^{4,6} Most SRS cases are sporadic, but different monogenic modes of inheritance have been proposed.⁷⁻⁹ Abnormalities of chromosomes 8, 15, 17, and 18 have also been associated with SRS.¹⁰⁻¹⁵

Maternal uniparental disomy of chromosome 7 (matUPD(7)), the inheritance of both copies of chromosome 7 exclusively from the mother, occurs in approximately 10% of Silver-Russell syndrome (SRS) patients.¹⁶⁻¹⁹ Altogether, 21 cases of matUPD(7) have been reported¹⁶⁻²⁴ and at least 14 of these have been diagnosed with SRS.^{6,16-19} All matUPD(7) patients have pre- and postnatal growth retardation, except one case who had short stature only postnatally.²³ Paternal uniparental disomy of chromosome 7 has no effect on growth and development.²⁵ It has been suggested that there is at least one imprinted gene influencing growth and development on chromosome 7. MatUPD(7) patients presumably end up with two copies of the maternally imprinted gene and thus lack the effects of a growth promoting gene. To date, three imprinted genes, *PEG1/MEST*, *γ2-COP*, and *GRB10*, are known on chromosome 7, but their role in SRS remains undecided.²⁶⁻²⁹

In a systematic screening for cases of matUPD(7) among patients with SRS, we have identified four matUPD(7) cases

out of 32 SRS patients studied, consistent with a frequency of approximately 10%. These four matUPD(7) patients present with many common characteristics and seem to form a phenotypically homogeneous group. They consistently lack some classical features of SRS, such as a significantly triangular face, micrognathia, and downturned mouth corners. However, all present with additional specific features such as speech delay, severe feeding difficulties, and excessive sweating. We sought to evaluate which typical SRS features are most predominant in matUPD(7) patients and if these features differentiate a matUPD(7) phenotype from non-matUPD(7) SRS patients.

Patients were recruited from the outpatient clinic for growth disorders at the Hospital for Children and Adolescents, University of Helsinki, Finland. The diagnosis of SRS was confirmed in all patients either by a paediatric endocrinologist or by a medical geneticist. Patients were included in this study using the following criteria: (1) intrauterine growth retardation and/or born small for gestational age, (2) postnatal growth retardation exceeding -2.5 SD, and (3) at least three of the following facial characteristics: triangular face, micrognathia, frontal bossing, craniofacial disproportion in early infancy, and relative macrocephaly, and (4) at least one of the following relative criteria: asymmetry, hemihypertrophy, clinodactyly/brachydactyly of the fifth digits, low set ears, and hypospadias/cryptorchidism. All patients were also required to have normal karyotype, growth hormone excretion, and thyroid function. Patients and their parents provided written informed consent and blood samples were obtained from the patients and parents. The study was approved by the ethical review board of the Hospital for Children and Adolescents, University of Helsinki, Finland.

We genotyped all SRS patients on blood DNA with 14 chromosome 7 specific fluorescent tetra- and dinucleotide repeat microsatellite markers by PCR and an automated sequencer (ABI). Maternal only inheritance of chromosome 7 was detected in four SRS patients out of 32 studied (12.5%). Complete isodisomy was observed in case I and mixed hetero- and isodisomy in the other three cases (fig 1). Correct paternity was verified for all matUPD(7) patients by genotyping 12 chromosome 18 microsatellite markers in a similar way.

We evaluated the patients by reviewing medical data and growth charts. Nine patients were further evaluated by

Table 1 Occurrence of SRS features. Categorisation is based on multiple published reports of SRS features, on the general emphasis stated in these reports for inclusion criteria in SRS studies, and on our own observations

	Diagnostic characteristics (generally observed)	Confirmatory characteristics (frequently observed)	Miscellaneous characteristics (rarely observed in single cases)
Growth	Small for gestational age Short stature postnatally >-2 SD	Delayed bone age	Delayed fontanelle closure
Craniofacial appearance	Triangular face Frontal bossing Micrognathia Downturned mouth Craniofacial disproportion Relative macrocephaly	Low set ears/ear anomalies Irregular teeth High arched/cleft palate	Anteverted nares Blue sclerae Epicanthic folds Congenital ptosis Eyebrows meeting in midline
Limbs & body	Clinodactyly of fifth digits Brachydactyly of fifth digits Asymmetry of limbs Hemihypertrophy trunk/limbs	Syndactyly of toes II/III Muscular hypotrophy/tonia Hypospadias Cryptorchidism Scoliosis-lordosis Absent sacrum Absent coccyx Vertebral abnormalities	Café au lait spots Short neck Simian crease Calcaneovalgus deformities Ambiguous genitalia Second metacarpal pseudoepiphysis Hepatomegaly Splenomegaly
Development & behaviour		Delayed psychomotor development High pitched/squeaky voice Excessive sweating Feeding difficulties	Raised urinary gonadotrophins Precocious puberty