

Silver-Russell phenotype in a patient with pure trisomy 1q32.1-q42.1: further delineation of the pure 1q trisomy syndrome

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Partial duplication of the long arm of chromosome 1 has been described in more than 200 patients. In most of these cases, the duplication is the result of an unbalanced segregation of a parental balanced translocation. Patients with duplications of 1q are therefore monosomic for the other chromosomal material involved in the translocation. The phenotypic result of such chromosomal abnormalities is difficult to predict. We present a patient with a pure de novo duplication of chromosome 1q32.1-q42.1. The phenotype described here is solely the result of the trisomy 1q32.1-q42.1. Our patient has many features in common with Silver-Russell syndrome and several previously reported patients with chromosomal abnormalities have had features suggestive of Silver-Russell syndrome.¹ To our knowledge this is the first description of a patient with a pure de novo trisomy of chromosome 1q32.1-q42.1. Pure trisomy 1q32.3-q42 has been reported once and pure trisomy 1q32-q42 has been reported twice before.²⁻⁴ More reports of patients with this cytogenetic abnormality are needed for further delineation of the phenotype.

CASE REPORT

The proband, 28 years of age, is the second child of healthy, unrelated, Dutch parents. The pregnancy was complicated by oligohydramnios. He was born at 37 weeks of gestation following a normal delivery. At birth, weight was 1960 g (<3rd centile) and length was 45 cm (<3rd centile). The placenta was small and showed infarctions. He had two healthy sisters. Family history was positive for short stature; his mother and maternal grandmother had a height of 1.49 m and 1.48 m, respectively (both below the 3rd centile). His father had a horseshoe kidney and slight hydronephrosis. A paternal uncle had a club foot for which he was operated on. A maternal uncle had a heart defect.

Feeding problems and repeated infections were noted in infancy. Psychomotor development was delayed. At 19 months he could sit without support and he started to walk at 3 years but could not talk. At the age of 3.5 years he was evaluated for the first time because of his retardation. Physical examination at that time showed a small toddler. He had a triangular face with downturned corners of the mouth, a small, pointed chin, and a flat nasal bridge (fig 1A). Height and weight were below the 3rd centile. He had an odd gait with flexed knees. A systolic grade II murmur was heard on auscultation. The penis was small and the right testicle was not palpable in the scrotum. There was slight hypotonia of the extremities and asymmetry of the legs; his left leg was 1 cm longer and the circumference of the upper left leg was larger than the right one. Congenital dislocation of the hips was excluded as a cause of the asymmetry. He had genua valga, partial cutaneous syndactyly of the 2nd and 3rd toes of both feet, and an evident thoracolumbar scoliosis. Additional investigations (fundoscopy, electroencephalography, neurological examination, and cerebro-

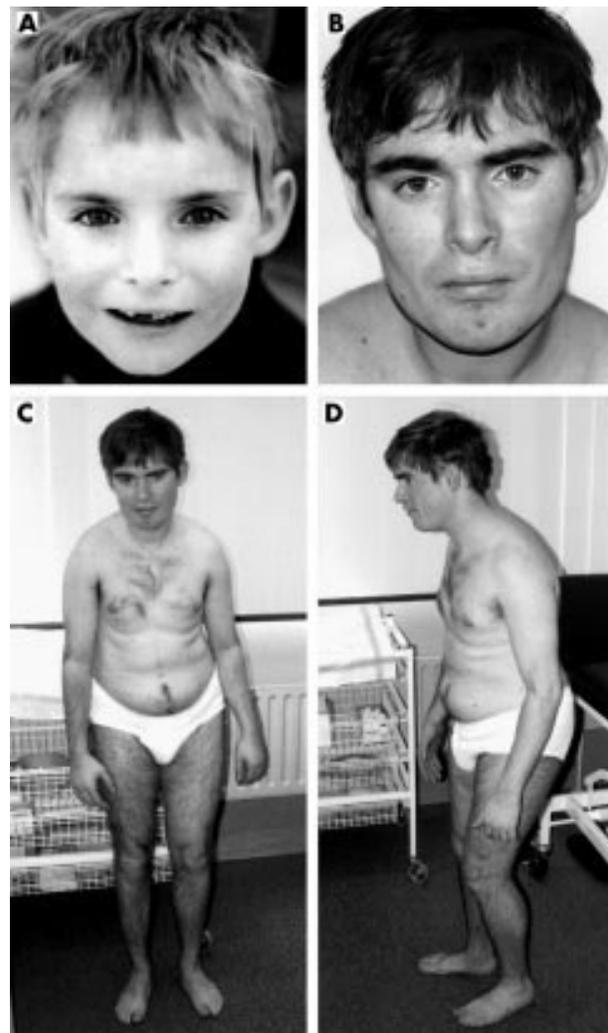


Figure 1 (A) Patient aged 3.5 years showing a triangular face, downturned corners of the mouth, and small pointed chin. (B) Patient aged 28 years. (C) Patient aged 28 years showing short stature, hypertrichosis, and kyphoscoliosis. (D) Side view of patient.

spinal fluid analysis) were all normal. There was a developmental speech delay with normal hearing test results. Total skeletal radiological investigation showed a two year delay in bone maturation and confirmed the thoracolumbar scoliosis, but showed no other abnormalities. The typical clinical features were compatible with Silver-Russell syndrome.

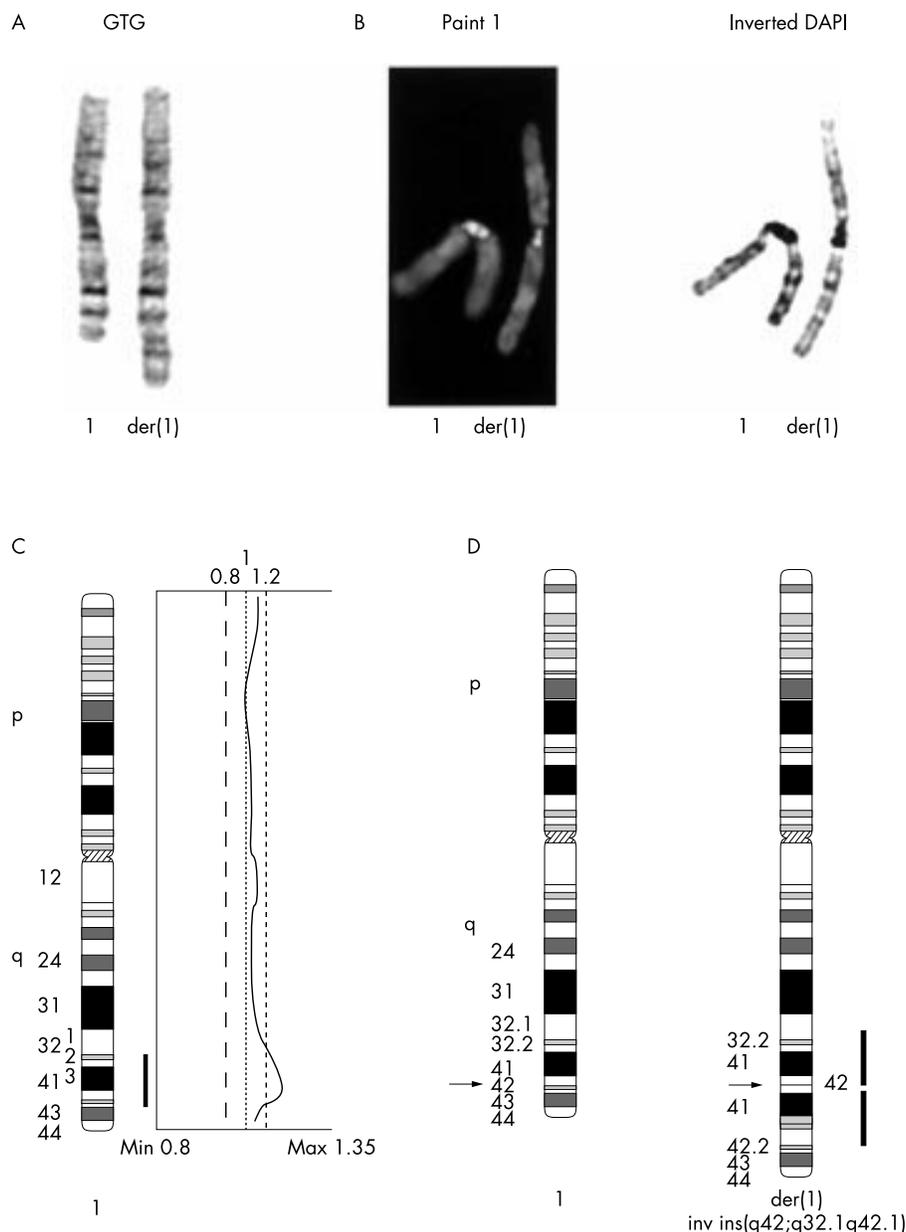


Figure 2 (A) GTG banded partial karyotype of the normal chromosome (left) and the abnormal chromosome (right) of the patient. (B) Whole chromosome 1 paint (Cambio), showing total covering of both the normal (left) and abnormal (right) chromosome 1. The inverted DAPI image is shown on the right. (C) Ratio profile of the abnormal chromosome 1 (CGH results). Threshold setting 0.8-1.2. The bar indicates the duplicated region (q32.1-q42.1). (D) Ideogram of the normal chromosome 1 (left) and abnormal chromosome 1 (right). The arrow indicates the insertion point at q42. The two bars indicate the inverted duplication.

At the age of 11 years, he received hormone therapy for bilateral cryptorchidism. Since his right testis remained undescended after treatment, an orchidopexy was performed. On review at 12 years, he had a progressive thoracolumbar scoliosis.

At referral, he was 28 years of age and was re-evaluated because of apparently syndromal retardation. He showed aggressive and autistic-like behaviour. Since the age of 24, he had problems of enuresis nocturna. Physical examination showed a small man with severe thoracolumbar scoliosis, multiple naevi, hypertrichosis, and dysmorphic features as previously described (fig 1B, C, D). Height was 155 cm (−3 SD), weight 58 kg (+2.6 SD), and head circumference 55.5 cm (50th centile). His legs were asymmetrical, the length and the circumference of the left leg being 4 cm and 5 cm respectively larger than those of the right leg.

METHODS

Whole blood lymphocyte cultures were performed according to standard procedures. Cytogenetic analysis of metaphase chromosomes was performed by GTG banding (G banding by trypsin using Giemsa).

To identify the origin of the extra chromosomal material, a whole chromosome paint was performed for chromosome 1 (Cambio). Additionally, comparative genomic hybridisation (CGH) was used to elucidate the origin of the extra chromosome 1 material.^{5,6} This was performed according to standard protocols.⁷

Fluorescence in situ hybridisation was applied to exclude a duplication of chromosome 15q11 (sometimes associated with autistic-like behaviour).⁸ DNA analysis was performed to exclude fragile X syndrome and to exclude uniparental disomy for chromosome 7 (detected in some cases with Silver-Russell syndrome).⁹

Table 1 Clinical features of our case compared to published data

	1q32.3-q42 ²	1q32-q42 ^{3,4}	1q32-qter ¹²⁻¹⁵	1q32.16-42.1*	SRS features ^{9,10}
Young gestational age	-	2/2	0/4	+	+
Wide sutures and fontanelles	?	1/1	4/4	+	+
Postnatal growth retardation	+	2/2	1/1	+	+
Asymmetry	+	1/1	?	+	+
Relative macrocephaly	-	0/2	2/2	+	+
Prominent/wide forehead	-	2/2	3/4	+	+
Downturned mouth corners	?	?	?	+	+
Triangular face	?	?	2/2	+	+
Broad, flat nasal bridge	-	1/2	3/4	+	?
Low set ears/ear anomalies	-	1/2	4/4	-	+
Cryptorchidism/small testes	+	1/2	3/3	+	+
Abnormal fingers or toes or both	+	2/2	4/4	+	+
Psychomotor/mental retardation	+	2/2	2/4	+	+
Spine defects	+	1/2	?	+	+

* = present case, + = presence of a symptom, - = absence of a symptom, ? = absent or not mentioned.

RESULTS

An unbalanced male karyotype containing an abnormal chromosome 1 with extra, unidentified chromosomal material on the long arm was detected, resulting in the following karyotype: 46,XY,add(1)(q44) (fig 2A). Parental karyotypes from peripheral blood lymphocytes were both normal, indicating that the origin of the chromosomal abnormality was de novo in the proband. No paternity testing was performed. To exclude the involvement of other chromosomes, a whole chromosome 1 paint was performed, resulting in total coverage of the abnormal chromosome 1 (fig 2B). The CGH technique showed that the region from 1q32.1 to 1q42.1 was duplicated (fig 2C). The combination of GTG banding of the abnormal chromosome 1 and the region of duplication defined by CGH led to the following description of the cytogenetic abnormality: 46,XY,inv ins(1)(q42;q32.1q42.1) (fig 2D).

Fluorescence in situ hybridisation to exclude a duplication of chromosome 15q11 showed no abnormalities. DNA analysis did not indicate fragile X syndrome and uniparental disomy for chromosome 7 was excluded.

DISCUSSION

Our patient meets the clinical criteria for Silver-Russell syndrome described by Price *et al.*¹⁰ Although constitutionally short stature cannot be excluded in our case, his dysmorphic features are compatible with Silver-Russell syndrome. He also had the classical phenotype in infancy: birth weight and postnatal growth below -2 SD of the mean, with a normal OFC (50th centile), a triangular face with a small, pointed chin, and asymmetry of the legs.

A de novo duplication of chromosome 1q32.1-q42.1 without monosomy for other chromosomal material was found by chromosomal analysis. This has not been reported previously. Only two patients with a pure de novo duplication of chromosome 1q32-q42 and one with a pure de novo duplication of chromosome 1q32.3-q42 have been previously published.²⁻⁴ To our knowledge there is only one previously described patient with a pure trisomy 1q where the authors had considered the diagnosis of Silver-Russell syndrome.¹¹ In that particular case, however, the trisomic region was limited to 1q42-qter.

Pure de novo duplication involving chromosome bands 1q32.1-qter have been reported four times before.¹²⁻¹⁵ In all other cases, an accompanying monosomy owing to unbalanced translocations may have influenced the clinical features.¹⁶⁻¹⁹

The clinical findings and cytogenetic results of our patient are compared with the previously reported patient with pure trisomy 1q32.3-q42, two cases with a de novo pure trisomy 1q32-q42, the four patients with a de novo pure trisomy 1q32-qter, and the characteristics of Silver-Russell syndrome in table 1.

The most frequently reported abnormalities were low birth weight, prenatal growth retardation, delayed psychomotor development, wide sutures and fontanelles, prominent and wide forehead, broad and flat nasal bridge, and low set, posteriorly rotated, malformed ears. Since most of these symptoms are commonly seen in patients with other chromosome aberrations, it is impossible to delineate a pure trisomy 1q syndrome solely based on these features. Taking all the features in our patient into account, however, he shows a Silver-Russell phenotype. This confirms that this phenotypic syndrome is genetically heterogeneous.²⁰

Determination of the breakpoints in the previous reports was not as accurate as in the present case. The relatively new cytogenetic techniques (FISH and CGH) provide important additional information, leading to a more detailed description of a pure de novo trisomy 1q syndrome.

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ECHO

APC gene mutation does not predict duodenal cancer



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Progression to duodenal cancer cannot be predicted from germline mutation of the *APC* gene in patients with familial adenomatous polyposis (FAP), a 10 year prospective study has shown. The researchers made the discovery during their assessment of how endoscopic surveillance for the presence and severity of duodenal polyps in FAP related to progression to duodenal cancer and its management and outcome.

Among 90 patients with duodenal polyps due to FAP, 19 did not have *APC* gene mutation and five had a mutation on exon 15 that could not be characterised by standard techniques. Data on the remaining 66 patients (73%) from 26 of 44 families (60%) showed that 5 base pair deletions at codons 1061 (14 patients, eight families) and 1309 (10, five) on exon 15 were the most common mutations. A similar proportion of patients with severe duodenal polyps (stage III, IV, and duodenal cancer) had mutations on exons 1-14 (53%) as on exon 15 (54%). The proportion of these patients with or without *APC* mutation was also similar statistically (54% v 39%, respectively).

The study included 114 patients with FAP undergoing endoscopy of the upper gastrointestinal tract to ascertain size and position of gastric and duodenal polyps and reviewed prospectively over 10 years. Ninety patients were tested for *APC* germline mutation.

▲ *Gut* 2002;**50**:636-641.