ELECTRONIC LETTER

A rare case of a de novo dup(19q) associated with a mild phenotype

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Partial trisomy of the long arm of chromosome 19q is an uncommon aneusomy and has been reported in only 18 cases. Fourteen of these were the result of unbalanced translocations. Only four cases were the result of pure duplications.¹⁻⁴ The phenotype described includes microcephaly, heart malformations, anomalies of the genitourinary tract or gastrointestinal system, and growth retardation. Developmental delay is common (table 1) and the prognosis usually poor owing to the severity of the anomalies.

We present a child with a dir dup(19)(q13.1q13.3) de novo direct duplication. The origin of the extra material was confirmed by fluorescence in situ hybridisation (FISH) using a whole chromosome paint probe for chromosome 19. The patient's phenotype is less severe than previously reported and possibly reflects the different rearrangement breakpoints and concomitant extent of duplication.

CASE REPORT

The proband was a female, born at 39 weeks of gestation to non-consanguineous, Caucasian parents. She was delivered by caesarean section for maternal reasons. Birth weight was 3555 g (>50th centile), length 52 cm (90th centile), and OFC 33.3 cm (>10th centile). Her Apgar scores were 9 at one minute and 10 at five minutes. She was the couple's first child. Clinical examination at birth was normal. She had some difficulty breast feeding but managed well with bottle feeding. At 6 months of age there were concerns about her development. She was referred for assessment at the age of 11 months. Although she had good head control, was able to sit supported, and take weight on her forearms, she could not weight bear and had no words. She had an immature grasp. She appeared to respond appropriately to visual and auditory stimuli. At 14 months, she was reassessed and a number of investigations including a karyotype performed. Full blood count, blood gas, and urinary organic and amino acids were normal. The karyotype showed an abnormality on chromosome 19q.

At 17 months of age she was noted to have global developmental delay. In personal and social areas of development and fine motor skills she functioned at 13-14 months of age. Her gross motor skills were at around the 10-11 month level and in language she functioned at around a 6 month level. Orthopaedic, ophthalmology, and audiology reviews were all unremarkable.

On review at 2 years 3 months, she was able to stand and cruise around furniture. She had no speech and made occasional sounds, although she understood commands. She had problems with chewing food and swallowing and had to eat pureed food. She had constipation, which required treatment with a laxative. Otherwise she was a healthy child with no behavioural problems and no history of seizures. On examination, her height was 85.9 cm (>25th centile), weight 13.9 kg (>75th centile), and OFC 46.5 cm (25th centile). Her hands were normal. On examination of the head and face, her hair had a double crown, and her palate was slightly higher than normal. The remainder of the examination was unremarkable except for a crease running from between the first and second toes underneath the other toes.

Figure 1 Partial karyotype of a dup(19)(q13.1q13.3) direct duplication. Arrows indicate the region of duplication.

METHODS AND RESULTS

Cytogenetic G banded studies undertaken on stimulated peripheral blood lymphocytes using conventional techniques showed a de novo, non-mosaic duplication of chromosome 19 between bands q13.1 to q13.3 (fig 1). The 60 cells examined excluded 5% mosaicism with 95% confidence.⁵ Parental chromosomes were normal. Fluorescence in situ hybridisation (FISH) studies with a whole chromosome 19 paint (wcp19) probe (Boehringer Mannheim) confirmed the G banding analysis. The final karyotype was interpreted as 46,XX,dir dup(19)(q13.1q13.3) de novo.ish dir dup(19)(q13.1q13.3) (wcp19+).

DISCUSSION

Pure duplications of 19q are rare; two of the four previously reported cases were live born¹⁻⁴ (table 1). Two cases^{2,3} were detected prenatally and there is minimal phenotypic information. In the case described by Cotter *et al*,² a dup(19)(q13.2q13.4) was found on chorionic villus biopsy performed for advanced maternal age. Following the discovery of a cystic hygroma on scan, a suction termination of pregnancy was carried out at 13 weeks. No phenotypic characterisation was possible. The second case found prenatally was described by Tercanly *et al*.³ During the index pregnancy, an ultrasound scan had shown the presence of mild hydrops fetalis with ascites and nuchal oedema. There was a single large cystic dysplastic kidney. There were congenital heart anomalies including a ventricular septal defect, aortic coarctation, and an anomaly of the aortic arch. A chorionic villus biopsy was performed and the fetus found to have dir dup(19)(q13.1qter). Termination of the pregnancy at 21 weeks of gestation was performed. Post mortem examination confirmed the scan findings and showed that there was a fused kidney with bilateral absence of ureters. The case described by Bhat *et al*¹ with "pure distal trisomy 19q" showed a dup(19)(q13.3q13.4) inverted duplication, confirmed by FISH. The child was growth retarded with all parameters below the 3rd centile. He had a flat face, hypertelorism, epicanthic folds, and a left choanal stenosis. His mouth was downturned, and he had micrognathia. His neck was short with redundant skin folds. He had several skeletal anomalies including bilateral subluxated and stiff shoulder joints and

Table 1 Clinical findings of live born partial trisomy 19q

Clinical characteristics	Bhat <i>et al</i> ¹	Quack <i>et al</i> ⁴	Present case
Aneusomic segment	q13.3-q13.4	q11.05-q13.2	q13.1-13.3
Low birth weight	+	–	–
Growth retardation	+	–	–
Psychomotor retardation	+	+	+
Flat facies	+	–	–
Downturned mouth	+	+	–
Abnormal ear	+	+	–
Short neck with excess skin fold	+	NR	–
Congenital heart malformations	+	–	–
Congenital hip dislocation	+	–	–
Joint stiffness and flexion contractures	–	–	–

Adaptation from Bhat *et al.*¹
NR = not reported.

Figure 2 Summary of published reports concerning the size of the duplicated regions of dup(19q). The numbers below the vertical lines indicating the size correspond to the reference numbers. PC = present case.

ulnar deviation of both wrists. His fingers were long and thin with flexion contractures of both thumbs. He had bilateral dislocated hips and rocker bottom feet with camptodactyly of the fourth and fifth toes. Echocardiography showed the presence of a patent ductus arteriosus, moderate tricuspid regurgitation, and a left superior vena cava. Seizures developed at 7 months of age. He continued to have poor weight gain and at the age of 18 months his overall development was around the 4 month level.

An unusual dup(19q) presented by Quack *et al*⁴ described a supernumerary ring chromosome in an overweight boy with dysmorphic facies and mental retardation. On physical examination, he had macrocephaly, hypertelorism, downward slanting palpebral fissures, and a bluish ring around the eyes. He also had a prominent nose and an unusually shaped mouth. FISH studies showed the ring to be derived from the long arm of chromosome 19, r(19)(q11.05q13.2). The mother showed the same extra r(19) chromosome. Her phenotype was unremarkable.

Our patient is the fifth case of pure duplication 19q, only the third case of a liveborn, and also the first case with a direct duplication in that region. In the other cases where information is available, psychomotor and mental retardation was present. Our patient has global developmental delay and delayed speech but has no congenital anomalies. She is well grown with no microcephaly. Therefore, this case appears to show only one of the physical features commonly associated with partial dup(19q). This is similar to the case reported by Quack *et al*⁴ where the phenotype of both mother and child is mild. Therefore, duplications that are proximal or involve only a small portion of 19q13.3 appear to show a milder phenotype than those with more distal duplications and involve a larger region of band 19q13.3 (fig 2). However, explanations for phenotypic variability include apparent inconsistencies in report-

ing the karyotype, involvement of regulatory and structural genes on the chromosomes, position effects resulting from altered location of chromosome segments, and variability in the length of trisomic segment at submicroscopic level.⁶

The mechanism for the formation of duplications is not known. In theory, duplications are thought to result from an insertion or translocation involving the other homologue, or unequal crossing over or sister chromatid exchange at meiosis.^{7,8} Our patient presented with a pure *de novo* direct duplication. Her phenotype is mild, possibly because of the genetic content and the size of the trisomy 19q, and may result in a less severe phenotype associated with more proximal duplication. It appears that the patient has essentially pure trisomy 19(q13.1-q13.3). Ideally, to provide further characterisation of the breakpoints, locus specific probes could be used. This may delineate more clearly a critical region associated with the milder phenotype. However, there was insufficient specimen to carry this out and the parents have declined to have any further blood tests.

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