

## ELECTRONIC LETTER

## A novel atypical 22q11.2 distal deletion in father and son

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*J Med Genet* 2002;**39**:e62(<http://www.jmedgenet.com/cgi/content/full/39/10/e62>)

Interstitial deletions of chromosome 22q11.2 are associated with several birth defects and malformations, which include DiGeorge, velocardiofacial, and conotruncal anomaly face syndromes. These were all initially described as separate entities, but are now considered to be part of the spectrum of the same condition. The CATCH22 acronym was proposed to encompass this phenotypic variability,<sup>1</sup> but the term "22q11 deletion syndrome" is considered to be more appropriate.<sup>2</sup>

22q11.2 deletions are estimated to occur at a frequency of 1 in 4000 live births, and it is considered to be the most common known deletion disorder in humans.<sup>3</sup> Around 90-95% of 22q11 deletion syndrome cases are sporadic, suggesting that this region is prone to deletions.<sup>3,4</sup> The finding that most deletions were similar suggested that there might be sequences at the breakpoints that confer susceptibility to chromosome rearrangements. Edelmann *et al*<sup>5</sup> reported the presence of highly homologous low copy repeats in the 22q11 region (LCR22s), which mapped to the proximal and distal interval breakpoints of the common 3 Mb deletions in patients with velocardiofacial syndrome. This finding suggested that misalignment in intrachromosomal homologous recombination events could lead to the 3 Mb deletion.

Around 90% of 22q11 deletion syndrome patients are found to have a 3 Mb deletion, known as the common or "typical deleted region", which may contain about 30 functional genes. About 7% have a smaller 1.5 Mb deletion. Atypical or unique deletions or translocations have also been found in a few rare patients.<sup>6</sup> Deletion studies have narrowed down the "minimal DiGeorge critical region" to the proximal 250 kb of the typical deleted region.<sup>7</sup> However, to date seven patients have been reported with atypical deletions that show no overlap with this critical region.<sup>8-14</sup> These cases are extremely valuable as

they may provide some insight into the underlying molecular mechanisms and may help to identify potential gene(s) involved.

We report on a further case with a novel deletion in the distal half of the typical deleted region that does not overlap the MDGCR. The deletion could not be seen by the use of commercial probes. This child presented with tetralogy of Fallot and showed a mild facial phenotype. The deletion was also present in his asymptomatic father.

**CASE REPORT**

The proband was a male infant born to a 21 year old mother at 39 weeks' gestation after an uneventful pregnancy. The baby was delivered by caesarean section because of fetal distress. Apgar scores were 9 at one and five minutes. Birth weight was 3250 g, length 47 cm, and head circumference 34.5 cm. Physical examination at birth was normal and unremarkable. On day 1 a loud systolic murmur was noted on auscultation. The baby was otherwise well, well perfused, and neither tachypnoeic nor cyanotic. Oxygen saturation by pulse oximeter was 97% in air. Sucking reflex was good although he fed slowly. Chest x ray was normal. ECG was normal, but showed an upturned T wave at V1. At 15 days he was seen by the cardiologist. The diagnosis of tetralogy of Fallot was suspected and the possibility of 22q11 deletion syndrome was raised based on the heart defect and his facial appearance. Echocardiography at the age of 2 months confirmed the diagnosis of tetralogy of Fallot. Given his stable condition, a conservative approach was taken, postponing surgical correction until later in the first year of life. The thymus was present. Serum calcium was normal.

He was seen again at the age of 5 months. Height was 65 cm (10-25th centile), weight 5950 g (0.4th centile), and head circumference 41.2 cm (2nd centile). Development was adequate for age, both in motor and social areas, although it was still too early to detect any signs of speech delay. On physical examination he had a broad forehead, a small mouth, and distinctive ears, posteriorly rotated with deficient upper helices. The palate and uvula were normal, and the rest of the examination was unremarkable. He was reviewed at the age of 9 months, when photographs were taken (fig 1), but no significant phenotypic changes were noted. Neither of the parents was initially considered to show findings suggestive of being a carrier for the same deletion. His mother reported speech delay needing speech therapy in childhood, and his father (fig 2) had some learning difficulties at school. They were otherwise healthy.

**MATERIAL AND METHODS****Methods for microsatellites**

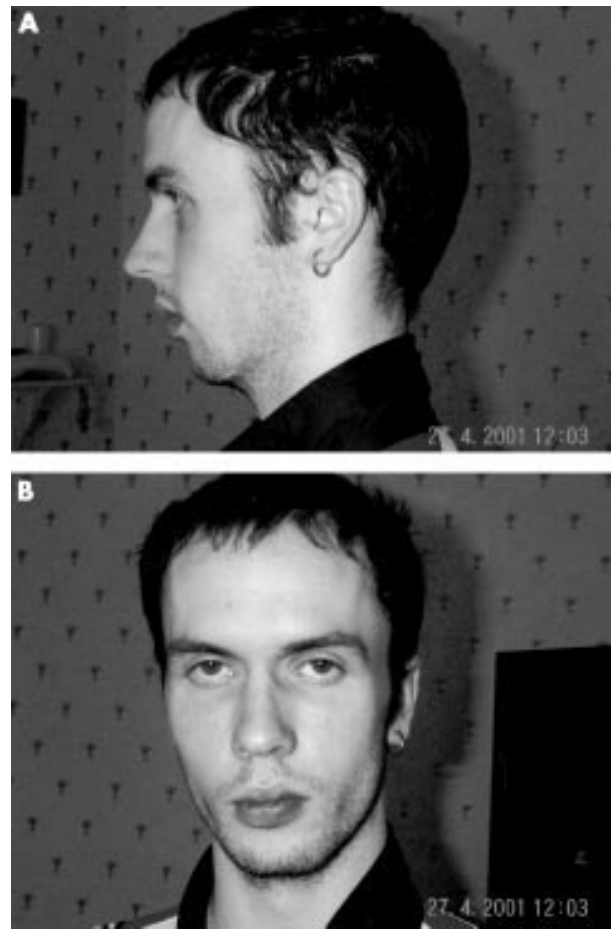
PCR reactions were performed in 25 µl volumes using standard reagents and resolved by electrophoresis on 36 cm denaturing polyacrylamide-urea gels using a Pharmacia ALF laser fluorescent sequencer, as previously described.<sup>15</sup> The PCR primer sequences and cycling conditions for the microsatellite markers

**Key points**

- A child presented with tetralogy of Fallot and a mild facial phenotype suggestive of 22q11 deletion syndrome.
- The commercial FISH probe (N25) for DiGeorge syndrome failed to show a deletion in this region.
- DNA analysis using microsatellite markers showed loss of heterozygosity with no paternal contribution for a number of markers on the distal half of the "typical deleted region".
- FISH using PACs containing these markers confirmed a heterozygous deletion that was also present in the asymptomatic father.
- Patients with a suggestive 22q11 deletion syndrome phenotype but normal FISH results with commercial probes should be further investigated for atypical deletions.



**Figure 1** (A, B) Proband aged 9 months. Note mild phenotype: broad forehead, small mouth, and distinctive ears, posteriorly rotated with deficient upper helices.



**Figure 2** (A, B). Proband's father. Subtle features include a small chin and malar flattening, more noticeable on the side view.

D22S1638, D22S1648, D22S944, D22S941, D22S264, D22S311, D22S1709, D22S938, and D22S308 can be found at <http://www.gdb.org/>. The forward primers for each pair were labelled with 6 FAM. The following alternative primer pair for D22S944-D22S944B was also used: 5' CGA CCA TAA CTA CTG AAA ATA AAG G 3' and 5' CTT CCA TGC TGA CAG CCC AT 3'. This primer set resolves the frequent non-amplification of some alleles caused by a variant base under one of the original primers.

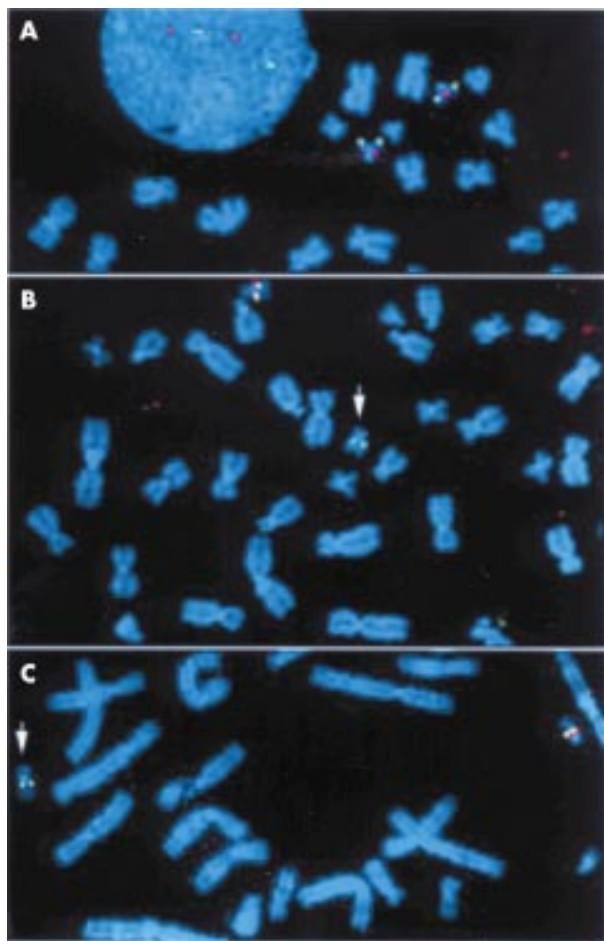
### FISH

Chromosome preparations were made from peripheral blood cultures using standard protocols. The N25 commercial probe (Vysis Inc, Downers Grove, IL) was used according to the protocol supplied by the manufacturer. P1-derived artificial chromosome (PAC) clones were obtained from BACPAC Resources (Oakland, CA). DNA was prepared by a standard mini-prep method and labelled with biotin-16-dUTP or digoxigenin-11-dUTP (Roche, Indianapolis, IN) by nick translation. Probe labelling, DNA hybridisation, and antibody detection were carried out using methods described previously.<sup>16</sup> FISH slides were analysed using a Zeiss Axioplan 2 microscope with the appropriate filters (83000 for DAPI, FITC, and rhodamine; Chroma Technology, Brattleboro, VT). Images were collected and merged using a cooled CCD camera (Princeton Instruments Pentamax camera, Roper Scientific, Trenton, NJ) and IP Lab software (Signal Analytics, Vienna, VA).

### RESULTS

A standard G banded karyotype at 400-550 band resolution level was normal in this child. Using a commercial FISH probe

(N25) for DiGeorge syndrome, no deletion could be seen (fig 3A). Haplotypes were produced using 14 fluorescent microsatellite markers spanning the 3 Mb common deleted region. There was evidence for loss of heterozygosity with no paternal contribution for markers D22S264, D22S311, or D22S1709. This identifies an atypical deletion between markers D22S944 and D22S308 (fig 4). The father had only one allele for the markers deleted in the child, and it was therefore impossible to distinguish true homozygosity from a possible deletion using this technique. To confirm the presence of a deletion in the proband we identified PACs containing microsatellite markers from published maps of the region, choosing PACs that were outside the 200 kb low copy repeats (LCR22s), which mediate rearrangements on chromosome 22q11.<sup>5</sup> Fig 5 shows the position of the clones used for FISH in this study. PAC 353B13 contains *ZNF74* as well as D22S264,<sup>17</sup> and therefore lies ~15 kb telomeric to the 1.5 Mb distal deletion breakpoint.<sup>6</sup> D22S1709 is contained in PAC 988B13,<sup>5</sup> which is ~35-70 kb centromeric to the 3 Mb distal deletion breakpoint. No PAC could be identified for D22S311. We also identified PACs that flank the 1.5 Mb and 3 Mb distal breakpoints: PAC 515J12 contains D22S944 as well as *TBX1*, but maps at least 300 kb from the 1.5 Mb distal breakpoint<sup>18</sup>; PAC 201M18 is adjacent to the sc11.1 repeat, close to the LCR22 repeat at the distal 1.5 Mb breakpoint; and PAC 182G20 contains D22S938 and is ~500 kb telomeric to the distal 3 Mb breakpoint.<sup>5</sup> We found that signals from PAC 353B13 and PAC 988B13 were deleted on one chromosome 22 in the proband, while the flanking PACs (515J12, 201M18, and 182G20) were present on both homologues and are therefore not deleted.

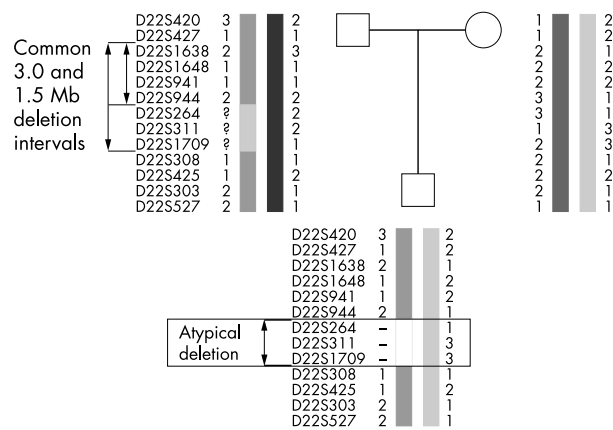


**Figure 3** (A) Hybridisation of N25 commercial DiGeorge probe to metaphase chromosomes from the proband. Signals from N25 and control probe are visible on both chromosome 22 homologues. Note the two red and two green signals in the interphase nucleus. (B) Hybridisation of P988B13, labelled with digoxigenin, detected by rhodamine anti-digoxigenin (red) and P182G20, labelled with biotin and detected with avidin-FITC (green) to metaphases from the same person. P988B13 is deleted on one chromosome 22 (arrowed) but P182G20 is present on both. (C) Hybridisation of P988B13 and P182G20 to the father of the proband. One chromosome 22 is deleted for P988B13 (arrowed), but P182G20 is present on both homologues. Father and son appear to have the same deletion.

This result confirms the results obtained using microsatellite markers. An example is shown in fig 3B, where PAC 988B13 is deleted on one chromosome 22 (arrowed) and PAC 182G20 is present on both. Using the same PACs we showed that the same deletion was present in the father (fig 3C). In this family the proband has inherited a heterozygous deletion of the distal half of the typical deleted region from his father, who was asymptomatic and did not show overtly characteristic phenotypic features. A more detailed analysis, however, showed subtle features, such as small chin and malar flattening, which was more noticeable on the side view (fig 2).

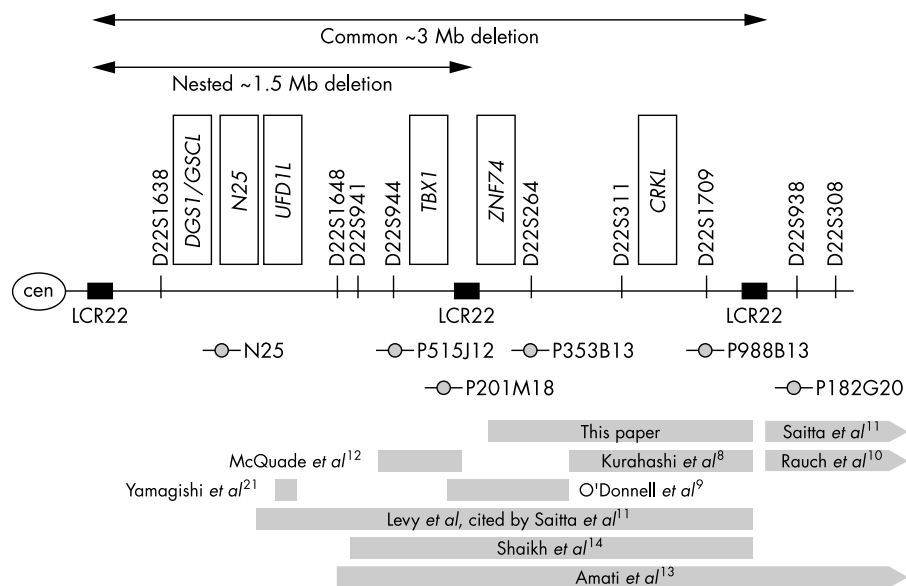
## DISCUSSION

Most 22q11 deletion syndrome patients are found to have a 3 Mb deletion, known as the “common” or “typical” deleted region. Atypical or unique deletions or translocations have also been found in a few rare patients.<sup>6</sup> Studies in patients carrying smaller deletions and rare rearrangements, including the ADU translocation, have made it possible to narrow down the minimal DiGeorge critical region to the proximal 250 kb of the typical deleted region.<sup>7</sup>



**Figure 4** Haplotype analysis. Loss of heterozygosity in the proband with no paternal contribution for the markers D22S264, D22S311, or D22S1709. This identifies an atypical deletion between markers D22S944 and D22S308. The father had only one allele for the markers deleted in the child, and it was therefore impossible to distinguish true homozygosity from a possible deletion using this technique.

Several reports have described patients with unique distal deletions that show no overlap with the minimal DiGeorge critical region.<sup>8–14</sup> These are either nested within the large 3 Mb typical deleted region, or they are distal to and do not overlap with it. The phenotype of patients with distal deletions not overlapping the minimal DiGeorge critical region seems to be indistinguishable from that of patients with the common large deletion. Kurahashi *et al*<sup>8</sup> described such a deletion in a patient with tetralogy of Fallot, pulmonary atresia, and typical facial features. This unique deletion comprised most of the distal half of the typical deleted region, and delineated the “type 3 deletion”, which showed no overlap with previously reported proximal deletions. The authors suggested that this represented a second critical region located distally in the typical deleted region. O’Donnell *et al*<sup>9</sup> reported a patient with ventricular septal defect and mild facial phenotype, who was also found to have a deletion distal to the minimal DiGeorge critical region and overlapped the proximal end of the deletion reported by Kurahashi *et al*.<sup>8</sup> Rauch *et al*<sup>10</sup> reported a patient with an interrupted aortic arch (type B), truncus arteriosus, and craniofacial abnormalities. He had a novel deletion distal to and not overlapping the typical deleted region. Interestingly, the deletion was also present in his mother and sister, who were asymptomatic but showed mild characteristic facial features. Saitta *et al*<sup>11</sup> reported a child with the same congenital heart defect and a similar extension of the deletion. He also had hypospadias and the phenotype showed some overlap with the Opitz G/BBB syndrome, a genetically heterogeneous disorder linked to the X chromosome and 22q11.<sup>19</sup> McQuade *et al*<sup>12</sup> reported a patient with cleft palate, velopharyngeal insufficiency, schizophrenia, and normal cardiovascular findings. This patient had a 750 kb deletion located between the minimal DiGeorge critical region and the deletion described by Kurahashi *et al*,<sup>8</sup> but showing no overlap with either of them. Amati *et al*<sup>13</sup> reported a patient (JK) with tetralogy of Fallot, right aortic arch, and typical facial phenotype. She had a large deletion, distal to the minimal DiGeorge critical region, which included the distal critical region described by Kurahashi *et al*<sup>8</sup> and the adjacent region outside the typical deleted region reported by Rauch *et al*.<sup>10</sup> Based on previously reported deletions these authors postulated the existence of five different intervals within the deleted area, which would argue against the involvement of a unique major gene responsible for the primary defect in all patients. Shaikh *et al*<sup>14</sup> studied a large series of 200 patients with DiGeorge and velocardiofacial syndrome. In an attempt to characterise the chromosome 22



**Figure 5** Composite breakpoint map of 22q11, illustrating the relative locations of several atypical deletions, redrawn from fig 2 in Saitta *et al.*<sup>11</sup> The common 3 Mb and the nested 1.5 Mb deletion are also shown, as well as the location of the LCR22 repeats at the proximal and distal VCFS breakpoints (filled boxes). Microsatellite markers and the PACs used for FISH characterisation of the deletion described in this paper are depicted, together with selected genes (boxed).

specific LCR22s they constructed a cosmid bacterial artificial chromosome (BAC) and P1 derived artificial chromosome (PAC) contig between markers flanking the 3 Mb typical deleted region. Analysis of the sequence of the entire 3 Mb typical deleted region showed four LCR22s. These authors further showed the involvement of these LCR22s not only in recurrent common 3 Mb deletions but also in a unique smaller 1.5-2 Mb deletion, which comprised the distal half of the typical deleted region. The proximal end point of this deletion lay within the proximal half of the typical deleted region but outside the minimal DiGeorge critical region.

We have found a novel deletion at 22q11.2 involving the distal half of the typical deleted region, to our knowledge not previously reported. The proximal deletion breakpoint is defined by two PACs which map very close to the nested 1.5 Mb distal deletion breakpoint, suggesting that the proximal breakpoint of this novel deletion lies within the distal 1.5 Mb LCR22 repeat. The distal deletion breakpoint is likely to map within the distal 3 Mb LCR22 repeat, although one of the flanking PACs used for FISH lies some distance away from the LCR22 sequence. It is possible that the novel deletion that occurred in this patient is mediated by homologous recombination between the two LCR22s. This deletion is larger than the one described by Kurahashi *et al.*<sup>8</sup> and extends proximally, although it does not overlap with the minimal DiGeorge critical region. This child presented with tetralogy of Fallot and showed mild characteristic facial features. The deletion was also present in the asymptomatic father, who refused echocardiographic studies. This is the eighth reported patient with a distal deletion that shows no overlap with the minimal DiGeorge critical region. This patient's deletion is a novel and unique deletion not previously reported. It includes interval 4, as defined by Amati *et al.*,<sup>13</sup> and can also be considered as a B-D deletion, according to Shaikh *et al.*<sup>14</sup> These authors hypothesise that the small size (<15 kb) of the LCR22s that mediate deletions both in the patient of Kurahashi *et al.*<sup>8</sup> and in ours may explain the rarity of these distal deletions.

All but two patients with more distal deletions (that is, excluding the cases reported by McQuade *et al.*<sup>12</sup> and O'Donnell *et al.*<sup>9</sup>) presented with a characteristic conotruncal heart defect (tetralogy of Fallot or interrupted aortic arch with truncus arteriosus). However, they showed very mild characteristic

facial features, with the exception of patients reported by Kurahashi *et al.*<sup>8</sup> and Amati *et al.*<sup>13</sup> However, phenotypic variability of 22q11 deletion syndrome patients does not seem to correlate with the extent or position of the deletions.<sup>20</sup> It is generally accepted that while 22q11 deletion syndrome is caused by identical gene(s) in the common deletion, other factors may influence phenotypic variability.<sup>13</sup> Indeed, both the family reported by Rauch *et al.*<sup>10</sup> and ours have asymptomatic members who are also carriers for the same deletion. This intrafamilial phenotypic variability was ultimately illustrated by the report of monozygotic twins who showed a discordant phenotype.<sup>21</sup>

Structural heart abnormality is a very common feature in 22q11 deletion syndrome. It was present in 75% of patients seen in the European Collaborative Study.<sup>22</sup> Of these, tetralogy of Fallot was the most frequent heart defect, present in 23.3% of patients with significant cardiac pathology. A recent study showed that 13% of patients with tetralogy of Fallot had a 22q11.2 deletion. In these cases, tetralogy of Fallot was more frequently associated with pulmonary atresia plus major aortopulmonary collateral atresia, and all deleted patients were more likely to have one or more extracardiac anomalies.<sup>23</sup>

Ryan *et al.*<sup>22</sup> observed a less severe phenotype in transmitting parents, particularly regarding cardiac anomalies. This may be partly because of infant mortality associated with severe cardiac anomalies and decreased reproductive fitness for those who survive.<sup>24</sup>

Recent studies of the cognitive and psychoeducational profiles of children with 22q11 deletion syndrome have confirmed a wide variation in intelligence. The same range of developmental outcomes was observed regardless of the presence of other associated anomalies, indicating that variations in intelligence were directly related to the 22q11.2 deletion.<sup>25</sup> It has also been reported that patients with a deletion inherited from one parent have lower mean full scale IQS compared with patients with a de novo deletion. This may be partly explained by the lower educational level of affected parents compared to unaffected ones.<sup>25</sup>

Patients with phenotypes consistent with 22q11 deletion syndrome in whom a deletion could not be found have been extensively screened for mutations within candidate genes, but none has been found so far.<sup>3</sup> *TBX1* has recently been identified as a potential key gene underlying 22q11 deletion

syndrome. Heterozygous mouse embryos for a null mutation of this gene have a high incidence of aortic arch abnormalities.<sup>26</sup> However, the *TBX1* locus is not always included in 22q11.2 deletions. It has been suggested by these authors that regulatory elements or modifier genes located at a distance may affect *TBX1* expression. Alternatively, haploinsufficiency of other genes may independently affect the same developmental pathway. The *CRKL* gene has also been implicated in the underlying molecular mechanism of 22q11 deletion syndrome.<sup>27</sup> Interestingly, *CRKL* maps to the distal half of the typical deleted region, suggesting that it may be responsible for those cases with the most distal deletions.

This case illustrates the need to investigate further those patients with a suggestive phenotype but a normal FISH result with commercial probes.

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