Short Report

‘Deletion rescue’ by mitotic 11q uniparental disomy in a family with recurrence of 11q deletion Jacobsen syndrome


We describe a family with recurrent 11q23-qter deletion Jacobsen syndrome in two affected brothers, with unique mosaic deletion ‘rescue’ through development of uniparental disomy (UPD) in the mother and one of the brothers. Inheritance studies show that the deleted chromosome is of maternal origin in both boys, and microarray shows a break near the ASAM gene. Parental lymphocyte chromosomes were normal. However, she is mosaic for the 11q deletion seen in her sons at a level of 20–30% in skin fibroblasts. We hypothesize that one of her #11 chromosomes shows fragility, that breakage at 11q23 occurred with telomeric loss in some cells, but ‘rescue’ from the deletion occurred in most cells by the development of mitotic UPD. She apparently carries the 11q deletion in her germ line resulting in recurrence of the syndrome. The older son is mosaic for the 11q cell line (70–88%, remainder 46,XY), and segmental UPD11 ‘rescue’ apparently also occurred in his cytogenetically normal cells. This is a novel phenomenon restoring disomy to an individual with a chromosomal deletion.

Conflict of interest

The authors have nothing to disclose related to this article.

Jacobsen syndrome, (MIM# 147791), includes characteristic neurodevelopmental and physical birth defects, and thrombocytopenia, associated with deletion of the 11qter region (1, 2). The chromosomal region conferring specificity for the syndrome is the 11q24.2 band, with more distal deletions showing a different phenotype (3). Patients show a variety of breakpoints within the 11q23-qter region, with different clinical outcomes depending on the extent of the deletion (4, 5).

In 11q23 region, there is a folate deficiency-inducible heritable fragile site, FRA11B (MIM #600651), produced by a CCG expansion located within the CBL2 gene (6, 7). Chromosomal deletions in the Jacobsen syndrome can originate near this locus; however, the breakpoints in most patients are telomeric to FRA11B (8).

A series of CGG expansions in the 11q23 region has been mapped by Jones et al. (9). Breakpoints in many Jacobsen syndrome patients cluster near these sites. Of 14 patients described by Jones et al. (9), FRA11B was near the breakpoint in only 2, with breakpoints in the other 12 patients located near six novel CGG repeats.
Recurrence of Jacobsen syndrome has been observed in families with chromosome translocations (10, 11). However, in those affected siblings, clinical findings are determined not only by 11q deletion but also by trisomy of the translocation partner chromosome.

We describe a family with two affected children, not associated with a translocation in the parents, with one child being mosaic for 11q23-qter deletion. However, the mother is homozygous in her lymphocytes for all loci within the deleted region in her sons, and apparently has uniparental disomy (UPD) for 11q23qter. She apparently experienced chromosome 11q23 breakage, and then ‘rescue’ by development of mitotic distal 11q UPD, but with deleted cells found in skin fibroblasts. Her sons inherited this fragile chromosome, with one brother showing a deletion and the other mosaicism for the deletion, with partial ‘rescue’ by development of mitotic distal 11q UPD, as for the mother.

Materials and methods

Clinical evaluation

The older brother had significant neonatal complications including hypoglycemia, respiratory distress, and thrombocytopenia, with platelet counts as low as 100,000, but only minimal associated purpura and petechiae.

A bone marrow karyotype showed a deletion of 11q23.3qter in 100% of bone marrow cells, explaining the thrombocytopenia. A subsequent peripheral lymphocyte karyotype showed 70% of cells with the deletion, and 30% normal 46,XY. At that time, the parents were told that a diagnosis of Jacobsen syndrome was probable, and based upon the mosaicism detected, that the condition was unlikely to recur.

About a year and a half later, the parents had their second son. He had undescended testes and thrombocytopenia, with a small and insignificant ventricular septal defect.

When the boys were seen later, both were found to have decelerated growth, with brachycephaly, epicanthal folds, mild hypertelorism, a broad nasal bridge, upturned nares, and underdeveloped superior helices. Both showed fifth finger clinodactyly, fifth metacarpal shortening in the older brother, and both had a predominance of arches on the fingertips, though an increased number of arches was also observed in both parents. The brothers showed developmental delays predominantly in speech and language, with the older brother also having a motor delay. A karyotype on the younger brother showed a deletion of 11q23qter in all cells. Both brothers were maintaining platelet counts in the 100,000/mm³ range without the need for transfusions.

Of interest, in retrospect, the mother had difficulty with speech and language in school, and has hearing loss as an adult. She shows strong facial resemblance to her sons, and has short fifth metacarpals.

Cytogenetic and molecular studies

In addition to routine karyotypes as described above, both brothers and parents were tested for the presence of FRA11B. Treated cells were scored for breakage at 11q23 and a variety of folate deficiency inducible fragile sites. The family was also tested by fluorescent in situ hybridization (FISH) with three probes derived from chromosome 11 (Vysis, Abbott Laboratories, Sun Valley, CA): CEP 11, a specific 11q subtelomeric probe, and a probe for the Myeloid/lymphoid mixed lineage leukemia (MLL) locus (11q23).

For molecular inheritance studies, DNA samples were obtained from leukocytes and then amplified using the polymerase chain reaction for a variety of chromosome 11 loci. The markers tested are listed in Table 1. Alleles were determined using fluorescent high-resolution capillary electrophoresis (ABI, Life Technologies Corporation, Grand Island, NY).

Finally, DNA from maternal leukocytes was analyzed by chromosomal microarray on the CytoChip Affymetrix Cytogenetics Solution platform, with hybridization to approximately 2.7 million 40mers.

Results

The parents and sons did not show a FRA11B, though other common sites (3p14, 6q21, 7p14, etc.) demonstrated the expected level of fragility. FISH studies in blood showed normal results for both parents for all three chromosome 11 loci. Both brothers showed normal patterns for CEP 11 and MLL (11q23), but showed a deletion for the 11q subtelomeric specific probe (100% in the older and 75% for the younger brother). The deletion occurred distal to MLL, was apparently terminal, and was designated 46,XY, del 11q2311qter (Fig. 1, Table 1).

Following these results, the mother graciously consented to a skin biopsy for chromosome analysis. In her fibroblasts, 22% of metaphase and 30% of interphase cells showed a deletion of 11q23qter. A repeat FISH study of her lymphocytes did not detect the deleted chromosome in 120 metaphase cells examined.

Table 1. Summary of cytogenetic results in the family

<table>
<thead>
<tr>
<th>Normal 11q lymphocytes</th>
<th>11q deletion</th>
<th>11q deletion FISH</th>
<th>FRA 11B breakage (%)</th>
<th>Breakage controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brother A 12% (12/83)</td>
<td>88% (71/83)</td>
<td>75% (30/40)</td>
<td>0</td>
<td>4/33</td>
</tr>
<tr>
<td>Brother B 0%</td>
<td>100% (23/23)</td>
<td>100% (50/50)</td>
<td>0</td>
<td>7/53</td>
</tr>
<tr>
<td>Mother 100%</td>
<td>0% (0/106)</td>
<td>0% (0/100)</td>
<td>0</td>
<td>25/106</td>
</tr>
<tr>
<td>Father 100%</td>
<td>0% (0/101)</td>
<td>0% (0/100)</td>
<td>0</td>
<td>26/101</td>
</tr>
</tbody>
</table>

FISH, fluorescent in situ hybridization.
In the family study, both brothers show lack of inheritance for maternal DNA markers from D11S1353 (localized to 11q23.3q24) to the terminus, with 9 of 13 markers informative. Inheritance of 11 markers showed biparental inheritance proximal to and including D11S925 (11q23.3), with a few markers uninformative (Table 2).

Unexpectedly, the mother also showed interesting results. She has only one apparently duplicated allele for all 13 markers within the 11q region deleted in her sons. In contrast, the father shows two alleles for 10 of these 13 loci. The probability that the mother is homozygous for all these polymorphic markers by chance is negligible, and we assume, given her normal lymphocyte chromosomal results, that she has UPD for this region.

The chromosomally mosaic brother also shows apparent homozygosity/hemizygosity for 11q alleles. It is probable, given the lack of maternal alleles detected in at least 10% of his cells having an intact chromosome 11, that this brother also has paternal UPD for this region.

Microarray analysis of the mother’s leukocyte DNA showed loss of heterozygosity and deletion of 11q24.1qter. The approximate breakpoint is near bp 122,910,000 (HG 19) (12), possibly within the ASAM gene (122,943,033 - 123,066,007, HG19), with the adjacent gene GRAMD1B clearly being within the deleted and homozygous region (Fig. 2). This compares well
with results from D11S1345, which is the most distal biparental marker, starting at 118,244,336 (RefSeq), and D11S1336, the first distal homozygous marker, which starts at bp 122,639,022 (RefSeq), a region of some 4 Mb encompassing breakpoint #5 in Jones et al. (9), which is adjacent to D11S1336 (Fig. 2).

**Discussion**

We believe this is the first report of recurrence of the 11q-Jacobsen syndrome in the absence of a translocation. There has been speculation, without corroboration, that recurrence could occur due to parental chromosome 11q fragility (13, 14). However, this has not been observed for FRA11B, where most patients carrying the fragile site do not have affected children, and the syndrome has not recurred in two families in whom the mother carries a FRA11B (8). There is one curious family with two affected siblings showing a deletion of 11q23.3ter where parental studies were normal. No explanation for the recurrence is given other than speculated involvement of FRA11B (15).

This is also the first report of ‘deletion rescue’ by presumed UPD, as found in most cells in the mother of the affected boys. Mosaic paternal UPD for distal chromosome 11p (of mitotic origin) is often observed in the Beckwith–Wiedemann syndrome (BWS) (16). Complete paternal UPD 11 is postulated to be lethal if not mosaic (17). We here describe a patient (the mother) with complete UPD restricted to the 11q23qter region, of unknown parental origin. There are some minor findings of Jacobsen syndrome in the mother, such as similar facial appearance and fifth metacarpal shortening, in addition to hearing loss. Her deletion or the UPD could be contributing to her phenotype.

There are at least two reports describing somewhat similar chromosomal rescues. Saitoh et al. (18) postulated that the Prader–Willi phenotype was modified or ‘partially rescue(d)’ in a patient with maternal UPD 15 by inheritance of an active paternal inv dup (16) in about 20% of cells. In this case, mosaic trisomy perhaps compensated for otherwise absent paternal chromosome 15 alleles in most cells. A second report by Gradek et al. (19) describes a patient with a 46,XYr(8)/46,XY mosaic karyotype. The disomic cells showed UPD of the paternal chromosome 8, with the ring being maternal in origin. The patient was minimally affected, and the authors suggest that this is because many of his cells became disomic by loss of the ring and duplication of the paternal chromosome 8. In this case, monosomy perhaps rescued trisomy.

In conclusion, care should be taken with genetic counseling regarding recurrence of Jacobsen syndrome. Recurrences without unbalanced translocations have been reported (15, 20). We wonder if there are other Jacobsen syndrome patients who have parents with UPD of 11q, or who are mosaic for 11q deletion themselves. However, this has not been previously reported in the literature, and will likely only be recognized if a subtle parental Jacobsen syndrome phenotype is investigated further with FISH, family DNA, and chromosomal microarray testing. Perhaps, there are other patients with similar ‘escape’ from another deletion syndrome through development of segmental mitotic UPD.

**References**


12. http://genome.ucsc.edu/cgi-bin/


