Translocations and Deletions of 5q13.1 in Myelodysplasia and Acute Myelogenous Leukemia: Evidence for a Novel Critical Locus

By Jeffery Fairman, Rui Yu Wang, Hong Liang, Lian Zhao, David Saltman, Jan C. Liang, and Lalitha Nagarajan

Acquired partial and complete deletions of chromosome 5 (5q−) are common cytogenetic anomalies associated with myelodysplasia (MDS) and acute myeloid leukemia (AML). A critical region of consistent loss at 5q31.1 (in >90% of cases) has led us and others to postulate the presence of a key negative regulator(s) of leukemogenesis. Although the interstitial deletion limits vary among patients, del(5)(q13q33) and del(5)(q22q33) constitute major subsets. Furthermore, it is not rare to encounter deletions, translocations, or paracentric inversions involving 5q11 to 5q13, which indicates inactivation or disruption of important gene(s) at that locus. In this report, we have localized a novel locus at 5q13.1 to a 2.0-Mb interval between the anonymous markers D5S672 and GATA-P1804. This locus resides within the region of loss in 12 of 27 patients with anomalies of chromosome 5; one of these cases had apparent retention of both alleles of all the telomeric loci. Fluorescence in situ hybridization (FISH) studies demonstrate that the AML cell line ML3 is disrupted at 5q13.1 by a translocation involving chromosome 3, with apparent retention of the entire chromosome 5 sequence. Our results suggest that this novel proximal locus encodes a critical gene that may be deleted or disrupted in a subset of MDS/AML patients with chromosome 5 anomalies.

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Materials and methods

Cases and cytogenetics. Routine cytogenetic analyses were performed on all MDS/AML patients seen at the Department of Hematology, M.D. Anderson Cancer Center, as detailed elsewhere. Patient samples were obtained using approved protocols. Samples from patient UPN662 described in this study were from a 37-year-old woman who was diagnosed with de novo AML in October 1993 and presented with 67% blasts. Classical cytogenetics showed a pseudodiploid clone with 45,XX,del(5)(q14),del(7)(q21q31),del(9)(q11q22),add(11)(p15),-16, and add (17)(q11). In April 1994, she was in clinical remission with no detectable cytogenetic abnormalities. Peripheral blood specimens collected at presentation (October 1993) and remission (April 1994) were used in the present study.

Cell lines. The AML cell line ML3 (a kind gift from Dr Kay Huebner, Jefferson Cancer Center, Philadelphia, PA) was grown in RPMI 1640 medium containing 10% fetal calf serum. HHW 105 somatic cell hybrid containing human chromosome 5 as the sole human chromosome was from the National Institute of General Med-

From the Department of Hematology, Division of Laboratory Medicine, The University of Texas M.D. Anderson Cancer Center, Houston, TX; and Genelabs, Inc, Redwood City, CA.

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Address reprint requests to Lalitha Nagarajan, PhD, Department of Hematology, Box 81, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030.

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2259
Chromosome 5

Fig 1. Location of dinucleotide polymorphisms, disease loci, and YACs on 5q. Polymorphic loci are designated with the D5S prefix. Distances are not to scale. Coordinates of the YACs spanning the loci D5S393, D5S399, and D5S677 are indicated. NUC, nucleophilin; SMA, spinal muscular atrophy locus that maps between the D5S112 and D5S629 loci; AML, myeloid tumor-suppressor locus on 5q31.1; RA, refractory anemia locus on distal 5q31.1; Ki1 lymphoma, nucleophilin gene from 5q35 involved in the t(2;5) in Ki1 lymphomas.

Yeast artificial chromosome. Coordinates and sizes of yeast artificial chromosomes (YACs) spanning specific dinucleotide polymorphic loci were obtained from the literature or the CEPH and Whitehead databases. Status of chimerism was established by fluorescence in situ hybridization (FISH). High molecular weight DNA was isolated from overnight cultures of yeast strains harboring the specific YAC.20

Inter–Alu PCR. Unique single-copy sequences specific for chromosome 5 (from the somatic cell hybrid HHW 105) were amplified using the dual-primer Alu PCR. The primers and amplification conditions were as described by Liu et al.21 The same primers were used to amplify single-copy sequences present in the YACs. The amplification conditions were identical to the ones described earlier except that the annealing temperature was reduced to 37°C to increase yields.

FISH. Inter–Alu PCR products from the YACs and somatic cell hybrid HHW 105 were used to localize chromosome 5 sequences. The FISHs were performed as detailed elsewhere.22 The slides were counterstained with propidium iodide (0.3 μg/mL) in antifade solution of p-phenylenediamine and examined under a Nikon (Japan) microphot SA fluorescence microscope with a triple-band pass filter to visualize both the signals and cells simultaneously. Typically, 20 to 25 metaphases were analyzed by routine microscopy and permanent records were generated by the images captured in an image analyzer system (Perceptive Scientific Instruments, League City, TX).

RESULTS

Retention of both alleles of the 5q31 loci in patient UPN662. During the course of our investigations on the critical AML tumor-suppressor locus, we detected retention of all of the 5q31.1 loci in the peripheral blood nucleated cells of a de novo AML patient (UPN662). Unlike the majority of the AML and MDS patients with 5q− chromosome studied in our laboratory and others, she showed heterozygosity for all the markers within the myeloid tumor-suppressor locus (AML) and the RA locus.

A systematic comparison of the dinucleotide polymorphisms in bands 5q23 to 5q31 between the peripheral blood samples collected at presentation and clinical remission is shown in Fig 2. The loci D5S421 and D5S404 map centromeric of the interleukin gene cluster on 5q23 to 5q31; the IL9 gene marks the most proximal gene within the myeloid tumor-suppressor locus that is retained in a small number of MDS/AML patients with 5q− chromosome; the D5S567 locus lies within the critical myeloid tumor-suppressor locus in 5q31.1, between the genes for IL9 and EGR1; the D5S519 locus maps between the colony-stimulating factor−1 receptor and osteonectin genes within the distal RA locus (Fig 1).

Table 1. Molecular Markers of 5q13.1

<table>
<thead>
<tr>
<th>Loci</th>
<th>cR</th>
<th>YAC</th>
<th>Insert Size</th>
<th>Chimeric</th>
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<tr>
<td>D5S672</td>
<td>848c4</td>
<td>1,370</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>AMFB347YF9</td>
<td>269.00</td>
<td>745a9</td>
<td>1,500</td>
<td>No</td>
</tr>
<tr>
<td>GATA-P10104</td>
<td>280.10</td>
<td>925e10</td>
<td>1,640</td>
<td>Yes</td>
</tr>
<tr>
<td>D5S626</td>
<td>279.09</td>
<td>965b1</td>
<td>1,060</td>
<td>No</td>
</tr>
<tr>
<td>D5S641</td>
<td>282.23</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>D5S401</td>
<td>293.87</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Microsatellite repeat loci from 5q13.1 and their map position in the radiation hybrid map (in cR units) YAC coordinates and insert sizes were obtained from the Whitehead Institute Genome database. Chimerism of YACs were determined by FISH. Note that the cR distance between D5S641 and D5S626 loci (present within the 1,050-kbp YAC 965b1) is 3.14 cR.
Surprisingly, the unique polymorphic pattern for each of the locus is identical between the samples collected at presentation and remission, denoting apparent retention of both copies of all the 5q21 to 5q31 loci.

Loss of 5q13.1 loci in patient UPN662. On further examination, both alleles of several of the 5q21 loci and distal 5q13.3 loci (D5S644, D5S401, and D5S617) were also determined to be intact (Fairman and Nagarajan, unpublished results, December 1995). As seen in Fig 3, both alleles of the 5q13.1 loci D5S626, D5S620, and GATA-P18104 were retained in the presentation sample. The first marker for which we detect loss of heterozygosity is the anonymous locus AFMB347YF9. Two other centromeric markers (D5S672 and D5S435) are deleted, indicating a contiguous deletion with a distal breakpoint between the GATA-P18104 and AFMB347YF9 loci. An examination of the databases showed the loci GATA-P18104 and AFMB347YF9 to be part of a YAC contig in the band 5q13.1 (Table 1).

The standard cytogenetic tests suggested that patient UPN662 carried a deletion of chromosome 5q14 to 5q31. Retention of all of the 5q21 to 5q31 loci (Figs 2 and 3)
showed that the deleted 5q segment may be retained elsewhere [del(11)(p) or add(17)(p)] on the genome. FISHs with chromosomes 5 and 17 specific painting probes, as well as 5q13, 5q31 and 5q35 YACs, showed that the chromosome 5q13 to 5q31 segment was inserted into 17p (L. Zhao et al, unpublished results, June 1994). This event appears to be accompanied by a submicroscopic deletion of the 5q13.1 loci shown in Fig 3. We were unable to determine the proximal limit of this submicroscopic deletion due to the restricted amount of material and the poor quality of metaphases.

Molecular delineation of the proximal 5q13.1 breakpoint in patients with 5q anomalies. Paired peripheral blood granulocytes or blasts and Ficoll-buoyant lymphoid fractions from 26 other cases with anomalies of chromosome 5 were examined for loss of the 5q13.1 loci. Fifteen patients who showed loss of heterozygosity for the 5q31 loci retained both alleles of the 5q13.1 loci. The remaining patients showed deletions that included all or some of the loci between DSS435 and DSS401 (Fig 1). Figure 4 summarizes the loss of heterozygosity analysis of these cases for the 5q13.1 to 5q21 loci. Patients no.1 to 9 harbor large deletions spanning the entire 5q13.1 loci, as well as other 5q21 and 5q31 loci, which suggests that these are large contiguous interstitial deletions or a complete loss of a chromosome 5. The proximal limit resides between the GATA-P18104 and DSS672 in the case of a RA patient no. 10. Patient no. 11 showed retention of both alleles of DSS112 and loss of the DSS672, AFMB347YF9, and several other telomeric loci. Results on UPN662 are represented as patient no. 12. Patients no. 10 and 12 allow us to delineate the smallest region of overlap to be between the DSS672 and the GATA-P18104 loci.

The diagnosis and cytogenetic characteristics of these pa-

<table>
<thead>
<tr>
<th>Locus</th>
<th>Patient number</th>
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<tbody>
<tr>
<td>DSS435</td>
<td>1 2 3 4 5 6 7 8 9 10 11 12</td>
</tr>
<tr>
<td>DSS112</td>
<td></td>
</tr>
<tr>
<td>DSS672</td>
<td></td>
</tr>
<tr>
<td>AFMB347YF9</td>
<td></td>
</tr>
<tr>
<td>GATA-P18104</td>
<td></td>
</tr>
<tr>
<td>DSS620/ DSS626</td>
<td></td>
</tr>
<tr>
<td>DSS641</td>
<td></td>
</tr>
<tr>
<td>DSS401</td>
<td></td>
</tr>
</tbody>
</table>

Fig 4. Delineation of the critical region of loss on 5q13.1. Invariant loss of heterozygosity for the AFMB347YF9 locus in 12 patients with anomalies of chromosome 5. Paired samples of DNA from peripheral blood granulocytes or bone marrow blasts and mononuclear lymphoid cells were amplified for the multiple 5q13.1 loci. Presence of 2 distinctive alleles in the lymphoid cells rendered a given patient informative for the specific locus. Loss of heterozygosity was scored as described in Materials and Methods.
A NOVEL CRITICAL LOCUS AT 5q13

patients are summarized in Table 2. The cases are ordered based on their molecular delineations detailed in Fig 4, ie, patients no. 1 to 9 had large contiguous deletions. Further subdivision of this group between the ones with interstitial deletion and monosomy 5 categories showed patients no. 1 to 4 to be 5q- and no. 5 to 9 to be monosomic for chromosome 5. Table 2 further reveals the diagnostic classification of these cases ranged from an unusual case of RA with multiple cytogenetic anomalies (patient no. 1) to a rare AML patient with 5q- chromosome as the sole anomaly (patient no. 4). None of the monosomy 5 patients retained any of these loci on the marker chromosomes (patients no. 5 to 9). Among the patients whose proximal breakpoint resides within the 5q13.1 locus, patient 10 was a case of transfusion-dependent RA with the 5q- chromosome as the sole anomaly. Patient no. 11, who transformed to AML following an antecedent MDS, had a proximal breakpoint between the D5S112 and D5S672 loci.

The AFMB347YF9 locus and the D5S620/D5S626/D5S641 cluster flank an inverted coupling translocation in an AML cell line. The delineation of the critical 5q13.1 region could be further characterized by identification of a model AML cell line. Previous cytogenetic analysis had determined that the AML cell line ML3 carried a normal chromosome 5, del(5)(q13q35) chromosome, and a der(3), which contains all of the deleted chromosome 5q13 to 5q35 material.25 Analogous to UPN662, this cell line retains heterozygosity for all of the microsatellite and restriction fragment-length polymorphisms in the chromosome 5q21 to 5q35 region tested to date (Fairman and Nagarajan, unpublished results, May 1994).

FISH results depicted in Fig 5A demonstrate that there are three distinct chromosomes with chromosome 5 sequences: (1) the normal chromosome 5; (2) the 5q- chromosome with deletion of 5q13 to 5q35; and (3) a large der(3) chromosome, with insertion of chromosome 5 sequences. The condition of the inserted 5q13 to 5q35 segment on the derivative chromosome was investigated with nonchimeric YACs. The YAC 880g9, which lies within the AML tumor-suppressor locus,8 and the YAC 746b2, which is telomeric of the nucleophosmin locus in 5q35,24 were used in these studies. The results shown in Fig 5B allow us to make several conclusions: (1) both the 5q31 and 5q35 YACs are excluded from the 5q- chromosome; (2) the deleted 5q13 to 5q35 is inserted in an inverted orientation on a der(3) chromosome as the signal from YAC 746b2 (5q35) is proximal to the signal from the YAC 880g9 (5q31); and (3) the AML tumor-suppressor locus and the RA locus are grossly intact on the der(3) chromosome.

To define the 5q13.1 breakpoint, inter-Alu PCR products from YACs were hybridized to metaphase preparations from the ML3 cells. The results obtained with the two of the nonchimeric YACs are shown in Fig 6. The inter-Alu PCR products from the YAC 956b1 containing the locus D5S620/D5S626/D5S641 show a detectable signal on the der(3) chromosome containing the 5q sequences (Fig 6A). Figure 6B shows identification of the chromosome 5 sequences on the same metaphase (Fig 6A) with a chromosome 5-specific painting probe. In contrast to Fig 6A, the YAC 745a9, which spans the AFMB347YF9 locus, hybridizes to homologous sequences on the normal chromosome 5 and close to the telomere of the q arm of the 5q- chromosome (Fig 6C).

Table 2. Characteristics of Patients With Loss of Heterozygosity for 5q13.1 Loci

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Previous Malignancy</th>
<th>Diagnosis</th>
<th>Age (yr)/Sex</th>
<th>Cytogenetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>N</td>
<td>AML</td>
<td>58/F</td>
<td>46,XX,del(5)(q13q33),-7,+t[12]/47,iderm,+19[4]/46,XY[9]</td>
</tr>
<tr>
<td>3</td>
<td>N</td>
<td>RAEB-T</td>
<td>60/M</td>
<td>44,XY,del(5)(q11-13q33-35),t(7;12)(q1?q7),-8,18,21(q?q7),-12,add(12)(p11),del(13q?q7),-14,add(15)(p11),add(16)(q7),add(17)(p11),-22(20)</td>
</tr>
<tr>
<td>4</td>
<td>N</td>
<td>AML</td>
<td>64/F</td>
<td>46,XX,del(5)(q13q33)19,46,XX[5]</td>
</tr>
<tr>
<td>5</td>
<td>N</td>
<td>RAEB</td>
<td>20/F</td>
<td>44-46,XX,t(3;9)(q7;p7),-5,add(6)(q?),add(6)(p?),del(11)(q?),-13,-20,-21+4mer[24]/46,XX[12]</td>
</tr>
<tr>
<td>6</td>
<td>Y</td>
<td>t-RAEB</td>
<td>50/F</td>
<td>44-XX,-5,-13,add(17)(p11.2),add(19)(q13.3)[18]/46,XY,-5,+8,add(17)(p11.2),idic(22)[p11]</td>
</tr>
<tr>
<td>7</td>
<td>Y</td>
<td>t-RAEB-T</td>
<td>71/M</td>
<td>41-48,XY,-5,-7,der(7)(q7;12)(p22;q13),add(11)(q23),-12,der(12;13)(q10;q10),-14,-15,add(17)(p11.2),-18,+2-3mar[cp7]/46,XY[13]</td>
</tr>
<tr>
<td>8</td>
<td>Y</td>
<td>t-RAEB</td>
<td>82/M</td>
<td>45-48,XY,-2,-5,15(12)(q10;10),del(7)(q21),-8,-13,-16,+1-2r+1-4mar[cp16]/46,XY[4]</td>
</tr>
<tr>
<td>9</td>
<td>N</td>
<td>AML</td>
<td>55/M</td>
<td>43-44,XY,add(4)(q35),-5,-7,-8-10+1-3mar+3min[cp6]</td>
</tr>
<tr>
<td>10</td>
<td>Y</td>
<td>RA</td>
<td>87/F</td>
<td>45,XY,del(5)(q13q33)[23]/46,XY[2]</td>
</tr>
<tr>
<td>11</td>
<td>Y</td>
<td>AML</td>
<td>75/M</td>
<td>44,XY,del(5)[q13-15],-8,del(7)(q21q31),-13,(13;15)(q7;q7),-17,+mar[11]</td>
</tr>
<tr>
<td>121</td>
<td>N</td>
<td>AML</td>
<td>39/F</td>
<td>45,XX,del(5)[q14],del(7)(q21q31),del(9)(q11q22),add(11)(p15),-16,add(17)(p11)[25]</td>
</tr>
</tbody>
</table>

Abbreviations: N, no; Y, yes; M, male; F, female.
* These patients did not undergo chemotherapy or radiation.
† This is UPN682.
Fig 5. AML cell line ML3 carries an inversion-coupled translocation of 5q13 to 5q35. Arrow denotes normal chromosome 5, arrow head indicates 5q– chromosome, and double arrow head points to the der(3) chromosome. (A) Hybridization with chromosome 5–specific painting probe. A representative metaphase hybridized with the chromosome 5–specific probe shows signals on the normal chromosome 5, 5q– chromosome, and der(3) chromosome. (B) Localization of 5q31 to 5q35 sequences. A representative metaphase hybridized with the 5q31 YAC 880g9 and the 5q35 YAC 746b2 detects signals on the normal chromosome 5 and the der(3) chromosome. Insert shows the reverse order of these YACs on the der(3) chromosome in comparison to the normal chromosome 5.

to narrow down the critical 5q13.1 locus between these two loci. Data shown in Table 1 reveal that the cluster DSS641/DSS620/DSS626 contained within the 1.05-Mb YAC 965b11 spans 3.14 cR units based on radiation hybrid analyses. Thus, the physical distance between the loci GATA-P18104 and AFMB347YF9 corresponding to 6.1 cR units can be estimated to be less than 2.0 Mb.

DISCUSSION

Cytogenetic and molecular analyses by a number of groups have identified invariant loss of band 5q31.1 in more than 150 patients with the 5q– chromosome, and the deletions extend to 5q11 to 5q13 in a significant proportion (>45%) of these cases. Additionally, there have been sporadic descriptions of translocations or deletions of the bands 5q11 to 5q13. Three cases of unbalanced translocations of chromosome bands 5q11 to chromosome 7,13 a case of MDS with t(5;21)(q13.1;q22) involving the runt homolog on chromosome 22,25 a case each of paracentric inversion involving 5q14 to 5q35, and t(5;17), and three cases of three-way translocations involving 5, 17, 12, and 5, 17, and 18 have been identified;16–12 a single

Fig 6. The 5q13.1 break point lies between the AFMB347YF9 and the DSS620/DSS641/DSS626 cluster in the AML cell line ML3. (A) A representative metaphase hybridized with the inter–Alu PCR product from YAC 965b11 spanning the loci DSS620/DSS641/DSS626 detects signals on the normal chromosome 5 and on the q arm of the der(3) chromosome. (B) Chromosome 5 painting of the metaphase shown in A. (C) A representative metaphase hybridized with the inter–Alu PCR product from YAC 745a9 spanning the locus AFMB347YF9 detects signals on the normal chromosome 5 and on the q arm of the 5q– chromosome and not the der(3).
case of RA with a 5q− chromosome showed retention of all of the 5q31 loci.14

Thus far, there have been no systematic attempts to delineate the interstitial 5q deletions using the PCR-based microsatellite polymorphism analyses to detect allele loss. Availability of a large number of such markers from the genome mapping efforts15 facilitates this approach and overcomes the technical problems of minimal patient material, as well as lack of informativeness of polymorphic loci. The results described in the present study demonstrate disruption of a critical 5q13.1 region by translocation or deletion. In UPN662, this is characterized by a submicroscopic deletion coupled to juxtapositioning of the chromosome 5q13 to 5q31 segment to chromosome 17p, which may be analogous to the previously reported unbalanced t(5;17) in therapy-induced MDS.12

Involvement of the same locus in the inversion seen in the ML3 cell line suggests that this locus may also be affected in the previously described paracentric inversions of 5q14 to 5q35 associated with secondary MDS.11 The translocation of the 5q13.1 to 5q35 segment in an inverted orientation in the ML3 cells results in a disruption of a 5q13.1 locus, which is telomeric of the sequences present in the YAC 745a9 and centromeric of the YAC 965b11. Similarly, the 5q13.1 breakpoint described by Nuñofira et al in a case of t(5;21)(q13.1;q23) is flanked by YACs from the D5S12 and DSS617 loci, suggesting the same fusion partner may be involved in all of these cases (Roulston and Nagarajan, unpublished results, September 1995). Alternatively, there may be more than one critical gene within this interval. Nonetheless, an integration of these results indicates that a novel locus, which maps telomeric of the AFMB347YP9 locus and centromeric of the marker GATA-P18104, is a site of inactivation/activation by deletions or translocations. The physical distance between these two loci is estimated to be less than 2.0 Mb based on the cR units of radiation hybrid map available from the databases (Table 1).

The finding on UPN662 is an important example of the need for rigorous molecular analysis for accurate interpretation of the standard cytogenetic findings. Interestingly, the proximal breakpoints within the 5q13.1 region are seen in two other cases (Fig 3, patients no. 10 and 11) with interstitial deletion of chromosome 5. As suggested by Thangavelu et al,13 translocations involving 5q11 to 5q13 regions may be underreported due to the resemblance between a 5q− chromosome and one harboring a small translocated autosomal segment at 5q13.1.

Molecular cloning of genes residing at chromosomal breakpoints in myeloid leukemias has provided evidence for submicroscopic deletions accompanying the juxtapositioning of critical genes to variant loci.96 There appears to be a repertoire of gene activation/inactivation events in MDS and myeloid neoplasms. The critical locus disrupted in the cases described here may also be lost in patients with 5q− chromosome belonging to the del(5)(q13q33) and del(5)(q13q35) subsets and may be a possible tumor-suppressor. Positional cloning of this locus will be facilitated by the characterization of the translocations, analogous to the isolation of the NFI tumor-suppressor gene on chromosome 17q12, which was pinpointed by a couple of rare cases with translocation coupled deletion of the candidate gene.27,28 Availability of high-density maps and YAC contigs has equipped us with the required preliminary reagents for these endeavors.

The long arm of human chromosome 5 contains 4.5% of the haploid genome, and the physical loss ranging from 60% to 75% to 100% of this chromosome associated with the deletions 5q13 to 5q33, 5q13 to 5q35, and monosomy 5 cases, renders room for point mutations at more than a single locus in the remaining "normal" chromosome 5. We have previously described such a case of MDS in a patient who had lost the entire 5q11 to 5q31 loci and harbored a submicroscopic deletion of the CSF1R locus on the 5q− chromosome.29 Localization of a novel locus in the band 5q13.1 in this report in conjunction with the two other previously characterized loci on 5q31.1 are the necessary first steps in the isolation of the genes that may act singly or in combination.

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