Monosomy 7 Myeloproliferative Disease in Children With Neurofibromatosis, Type 1: Epidemiology and Molecular Analysis


Loss of constitutional heterozygosity is a common molecular feature of cancers in which inactivation of one or more tumor suppressor genes is thought to contribute to tumorigenesis. Recent evidence suggests that the gene responsible for neurofibromatosis, type 1 (NF-1), belongs to this class of heritable cancer genes. Children with NF-1 show an increased incidence of myeloid leukemia, including juvenile chronic myelogenous leukemia (JCML) and, perhaps, the myeloproliferative syndrome (MPS) associated with bone marrow monosomy 7 (Mo 7). We have investigated five children with Mo 7: three with NF-1 and two others with suggestive evidence of NF-1. Southern blotting experiments performed in four patients showed no loss of heterozygosity in bone marrow specimens using probes linked to the NF-1 locus on the long arm of chromosome 17. Both of our patients with familial NF-1 inherited the disease from their mothers, as did 14 of 19 other cases of myeloid leukemia in children with familial NF-1. Seventeen of these 21 children were boys. Myeloid leukemia developed in 12 boys and four girls who inherited NF-1 from their mothers, and in five boys who inherited the disease from their fathers. Father-to-daughter transmission was not observed. Taken together, the presence of chromosome 7 deletions in the leukemias of children with NF-1, a pattern of inheritance favoring maternal transmission of NF-1, and the marked predilection for boys to develop JCML and Mo 7 suggest a multistep mechanism of oncogenesis in which epigenetic factors might play a role. Further investigation is required to determine if the NF-1 genes in the leukemic bone marrows of these patients have acquired point mutations or small deletions.

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NEUROFIBROMATOSIS, type 1 (NF-1), is an autosomal dominant genetic disorder associated with an excessive incidence of childhood cancer, including brain tumors, rhabdomyosarcomas, and myeloid leukemias. In 1978, Bader and Miller observed that myeloproliferative diseases were disproportionately common among children with NF-1. Acute nonlymphocytic leukemia (ANLL) and juvenile chronic myelogenous leukemia (JCML) have been reported. The myeloproliferative syndrome (MPS) associated with monosomy 7 (Mo 7) is clinically and pathologically similar to JCML but is recognized as a separate chronic MPS in children.

Recently, five children with NF-1 and Mo 7 have been described. Three patients who presented with JCML and normal marrow karyotypes acquired Mo 7 as a new cytogenetic finding when their disease accelerated to overt acute leukemia. A fourth case had ANLL at diagnosis; cytogenetic studies were obtained 3 months later when the patient had persistent leukemia and showed 46,XX/45,XX,-7. The fifth child with NF-1 and MPS presented with marrow monosomy 7. We now report the results of molecular studies on blood and bone marrow from this patient. In addition, we have identified four new cases: two children with NF-1 and two others with suggestive evidence of NF-1, all with Mo 7. These patients strengthen the apparent relationship between NF-1 and Mo 7, and emphasize that Mo 7 is not invariably a late event in children with NF-1 who have previously been diagnosed with JCML, but may occur in patients with de novo MPS. Molecular analysis with cDNA probes from the long arm of chromosome 17 failed to demonstrate loss of constitutional heterozygosity in a total of four patients.

Two patients newly reported here, and 14 of 19 children with familial NF-1 and myeloid leukemia, inherited NF-1 from their mothers. Furthermore, boys were affected in 17 of 21 cases. Mechanisms that might partially explain these findings include: (1) an X chromosome mutation that cooperates with an abnormal NF-1 gene in leukemogenesis; (2) an increased mutation rate at the paternal NF-1 locus; (3) decreased fertility of males with NF-1; (4) genomic imprinting of the NF-1 gene resulting in either a low level of paternal gene expression in myeloid cells such that heterozygous mutation of the maternal allele is sufficient for abnormal proliferation; and/or (5) failure to reactivate an imprinted gene located on the X chromosome that normally regulates myelopoiesis as a result of the mutant NF-1 allele. As there are many clinical similarities between JCML and Mo 7, the finding that children with NF-1 are at increased risk of developing both disorders suggests that similar molecular mechanisms underlie leukemogenesis in both.

CASE REPORTS

Clinical and hematologic data at diagnosis are summarized in Table 1 for cases 1 through 5. The course of each patient is briefly described in the following.

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described below. Additional details are available from the investigators.

Case 1. E.W., a 7-month-old boy, presented in 1983 with massive hepatosplenomegaly and diffuse lymphadenopathy. He had 11 cafe-au-lait spots over his trunk and extremities. His mother and several members of her family had NF-1, and three of his four siblings had cafe-au-lait spots. For 5½ years, the child received no treatment and remained well with a hemoglobin of 10 to 11 g/dL, platelets decreasing slowly to 70,000 to 80,000 \(10^9/L\), and leucocyte counts between 6,000 and 75,500 \(10^9/L\) with approximately 30% neutrophils and precursors, 30% lymphocytes, and 30% monocytes. Fetal hemoglobin was 7% at diagnosis and 0% at age 6. His spleen and liver size gradually decreased.

He was hospitalized with pneumonia and massive splenomegaly in 1989. The leucocyte count was 34,400/\(10^9\) L with 12% blasts, 31% neutrophils and precursors, 22% lymphocytes, and 31% monocytes. Marrow aspirate showed 9.2% blasts, some with monocyteid features, and Mo 7 in 20 of 21 unstimulated marrow cells. A lymph node biopsy demonstrated diffuse infiltration by monocyteid blasts and Mo 7. Epstein-Barr virus (EBV) serology testing from 1987 and 1989 showed no evidence of EBV infection.

Aggressive chemotherapy for ANLL was initiated in June 1989 (Children’s Cancer Study Group [CCSG] protocol no. 2861). Although a hypocellular marrow was ultimately achieved, 60% blasts and Mo 7 persisted. A stable chronic phase was then maintained with hydroxyurea. Massive splenomegaly, leucocyte counts of 75,000 to 150,000/\(10^9\) L, and clinical wasting recurred in late 1990 and were unresponsive to a interferon and to splene-
tomy. He died of progressive disease and pneumonia with Mo 7 present in bone marrow and spleen.

Case 2. T.P., a 5-month-old boy, presented in 1986 with vomiting and weakness. His past medical history was remarkable for numerous upper respiratory infections beginning at 2 weeks of age. Physical examination disclosed multiple cafe-au-lait spots. His mother had a spotted nevus on her forearm, but no cafe-au-lait spots. The fetal hemoglobin was 24%.

The patient remained stable for 10 months. After severe oral mucosal herpes simplex, two polyloid lesions developed on his tongue, nearly obstructing the oral cavity. Excision showed inflammatory myofibroblastic tumor. Persistent splenomegaly and a mild delay in gross motor development were noted. Blood counts were unchanged from diagnosis (Table 1). EBV serologies showed IgM antibody to viral capsid antigen (VCA) >1:20; IgG to VCA >1:640; IgG to early antigen-diffuse (EA-D) >1:40; IgG to early antigen-diffuse plus restricted (EA-D + R) >1:40.

At 24 months of age, he was brought moribund to an emergency room with fever, pneumonia, and presumed sepsis. No autopsy was performed.

Case 3. A 4-year-old boy, D.L., was hospitalized in 1988 with fever, diffuse adenopathy, bruising, and hepatosplenomegaly. He had one cafe-au-lait spot below the right axilla; one of his siblings had NF-1. Chemotherapy for mixed lineage acute leukemia was initiated, followed by CCSG "Denver" therapy for ANLL. Four months after diagnosis, hematologic remission was obtained with a normal marrow karyotype. He received an HLA-matched bone marrow transplant from his sibling with NF-1 and has no evidence of disease more than 28 months after diagnosis.

Case 4. M.L., a 7-year-old boy, presented in 1987 with dyspnea, petechiae, hepatosplenomegaly, and lymphadenopathy. He had multiple cafe-au-lait spots; his mother died from complications of NF-1. He was started on CCSG "Denver" therapy for ANLL. Hematologic and cytogenetic remission was achieved after two courses. However, he relapsed 4 months later with reemergence of Mo 7. After several attempts and multiple complications, remission was attained and maintained for 2 years with high-dose cytosine arabinoside, L-asparaginase, and mitoxantrone. He died in remission in August 1990 of fungal sepsis.

Throughout the course of his illness, the patient had continuously increasing EBV serologies. IgG to VCA increased from >1:1,280 at diagnosis to >1:10,240 12 months later. IgG to EA-D was consistently >1:160; IgG to EA-D + R increased from <1:10 to >1:160 over 10 months. IgG to nuclear antigen was consistently >1:8. In addition, he had extensive cutaneous warts throughout his illness.

Case 5. The clinical course of this patient has been described. Briefly, he presented at age 9 months with multiple cafe-au-lait spots, fever, and MPS with a white blood cell count of 74,000 per mm³. Remission was achieved with intensive combination chemotherapy and persisted for 6 months. He died 5 months later of resistant leukemia after two unsuccessful bone marrow transplants.

MATERIALS AND METHODS

Laboratory procedures. DNA extraction and Southern blotting were performed as previously described. DNA was prepared from the Mo 7 bone marrows of cases 1, 3, 4, and 5. In addition, DNA was extracted from peripheral blood mononuclear cells that had been stimulated with phytohemagglutinin to expand the cytogenetically normal lymphocyte populations in cases 1, 4, and 5 and from unstimulated peripheral blood in case 3. These latter samples were used to determine the pattern of polymorphic restriction fragments present in "normal" (non-Mo 7) tissues and were digested and analyzed with the marrow specimens. The study procedures were approved by the Committee for the Protection of Human Subjects at the University of California, San Francisco and by the Institutional Review Board of the Naval Hospital, Oakland, CA.

Preparation of cDNA probes. Single-copy cDNA probes were used to detect restriction fragment length polymorphisms (RFLPs) on chromosome 17. These probes included EW206, EW207, pA10-41, EW 301, p11-3C2.4, p11-2F9.8, and pHHH202. Because the amount of DNA was limited, not all probes were used in all cases. We obtained probes EW301, pA10-41, EW206, and EW207 from the American Tissue Type Collection (Bethesda, MD).

Case reviews. The patients were identified from three institutions over 7 years. Bone marrow and peripheral blood slides and cytochemical and immunophenotypic data were reviewed centrally, when available.

RESULTS

Southern analysis. A linkage map showing the probes used to analyze our patients is presented in Fig 1A. These data were derived from a multinational collaborative investigation of a large number of families with NF-1.

We found no evidence for loss of constitutional heterozygosity in three of the four children analyzed with Southern blots. Probes pA-10-41, EW301, and EW207 were informative in patient 1, EW301 and EW206 were informative in patient 3, and EW206 and p11 2F9.8 were informative in patient 4 (see Fig 1B). As shown in Fig 1B, the bone marrow of patient 5 demonstrated loss of constitutional heterozygosity with probe EW301. However, probes p11-3C4.2 and EW206, which map nearer NF-1 on the long arm of chromosome 17, showed no loss of heterozygosity in this child (Fig 1B).

Parental transmission of NF-1 and sexes of affected children. The fact that NF-1 was inherited from the mother in our patients with familial NF-1 led us to review published cases of myeloid leukemia in children with familial NF-1. We found 14 reports that specified the affected parent and recently learned of two additional children (Dinndorf P, personal communication, November 1991; and Lange BJ, unpublished observation, November 1991). As shown in Table 2, the mother was the parent affected with NF-1 in 16 of 21 patients (P = .016 by the chi-square test). Seventeen of 21 children (81%) with familial NF-1 and myeloid leukemia were boys (P = .0046 by chi-square). Of 16 affected children who inherited NF-1 from their mothers, 12 were boys and four were girls. All five patients who developed myeloid leukemia in association with paternally transmitted NF-1 were boys.

DISCUSSION

JCML and Mo 7 account for most cases of MPS in children. These disorders share many clinical and hematologic features including male predilection, age usually less than 2 years at diagnosis, hypercellular marrows, anemia, and hepatosplenomegaly. Children with NF-1 are at increased risk of developing leukemia, particularly JCML. The patients in this study, and a few described previously, provide evidence that NF-1 is also associated with an increased risk of Mo 7 and suggest that JCML and Mo 7 might share one or more molecular changes. However, while JCML and Mo 7 are similar in many respects, there are a number of important differences, including a higher...
Fig 1. (A) Linkage map of chromosome 17 showing the positions of the probes used in this study and of the NF-1 gene. Probes p11-3C2.4 and p11-2F9.8 were isolated from cosmids which map near the NF-1 locus. (B) Autoradiographs obtained after hybridizing Southern blots containing DNA from patients 1, 3, 4, and 5 with informative probes. Lanes containing DNA from normal tissues are marked “N,” while lanes with marrow DNA are indicated with an “M.”

incidence of recurrent infections and more dysmyelopoiesis in Mo 7, and markedly elevated fetal hemoglobin values, prominent lymphadenopathy, and a scaly skin rash in JCML. Knudson’s proposal that dominantly inherited childhood cancers might result from homozygous inactivation of a gene that normally suppresses tumor formation has been directly verified in retinoblastoma, and loss of tumor suppressor activity apparently contributes to oncogenesis and/or disease progression in a variety of other cancers. Cases of familial NF-1 with translocations in the NF-1 region, and the predilection for patients with NF-1 to develop cancer, suggested that loss of NF-1 gene function might lead to tumor formation. Recent cloning of the NF-1 gene has provided evidence in support of this putative tumor-suppressor function. Analysis of the amino acid sequence predicted from the NF-1 cDNA shows homology with the catalytic domain of mammalian guanosine triphosphatase (GTPase) activating proteins (GAPs) and with yeast proteins called IRA-1 and IRA-2. GAP normally regulates cellular growth by hydrolyzing GTP bound to the product of the ras proto-oncogene to guanosine diphosphate (GDP). By returning the ras protein to an inactive, GDP-bound state, GAP is thought to “turn off” ras and thereby limit proliferation. Experimental evidence supports this model of GAP function.

The idea that the NF-1 protein negatively regulates proliferation raises the question of whether leukemic transformation in patients with NF-1 requires inactivation of both normal alleles in a susceptible target cell. To test this hypothesis, two groups have examined soft tissue sarcomas from NF-1 patients for loss of constitutional heterozygosity. Menon et al observed deletions involving the short arm of chromosome 17 that did not extend into the NF-1 region on 17q. They demonstrated mutations within the protein coding region of the p53 tumor-suppressor gene (located on 17p) in two tumors and hypothesized that loss of p53 function was probably not a primary event but might contribute to disease progression. In contrast, Skuse et al reported loss of heterozygosity in malignant peripheral nerve tumors from 6 of 11 NF-1 patients using three probes linked to NF-1. Moreover, the NF-1 alleles retained in tumors showing loss of heterozygosity were inherited from the parent with NF-1. The possibility that both NF-1 alleles might be inactivated during leukemogenesis was suggested by a patient with NF-1 and myelodysplasia who...
acquired an unbalanced translocation in the region of the NF-1 gene in her bone marrow. We did not detect loss of heterozygosity using probes linked to NF-1 in any of our patients. The observation that our patient with a deletion of 17p presented with marked leukocytosis and had persistent Mo 7 despite intensive chemotherapy is consistent with the idea that this change is associated with biologically aggressive disease. Our results do not exclude inactivation of the NF-1 gene by mutations limited to the coding region of the gene nor do they rule out mutations of a putative tumor-suppressor gene closely linked to NF-1. Large rearrangements are uncommon in patients with NF-1 and direct sequence comparison of NF-1 cDNAs amplified from RNA prepared from normal and leukemic tissues of individual patients will be necessary to establish whether new mutations of the normal NF-1 gene accompany leukemic transformation. This type of analysis is technically daunting as the NF-1 cDNA is approximately 13 kb and the gene spans 300 kb of genomic DNA (and P.O.C., unpublished data, May 1991).

We found striking imbalances with respect to both the sexes of children with familial NF-1 who developed myeloid leukemia and the sex of the parent transmitting NF-1. Males account for most cases of JCML and Mo 7 among children who do not have NF-1 (and our unpublished data, November 1991). While boys who inherit NF-1 from either parent are at risk of developing myeloid leukemia, maternal transmission was associated with 12 cases and paternal NF-1 with only five. The four girls with myeloid leukemia and NF-1 all inherited NF-1 from their mothers. These data suggest a number of possible genetic mechanisms.

The fact that 17 of 21 patients were boys raises the possibility of a gene on the X chromosome which interacts with a mutation (or mutations) at NF-1 to deregulate growth in a myeloid progenitor. Boys who inherited NF-1 from their fathers and developed leukemia would have received a mutant X chromosome from carrier mothers who did not have NF-1. The 20% of cases seen in girls might be explained by unbalanced Lyonization, by coinheritance of NF-1 mutations which are particularly deleterious, or by alternative disease mechanisms. A model that postulates an X-linked disease susceptibility locus is appealing because it is consistent with the general predilection of males to develop JCML and Mo 7. However, it does not explain why girls who inherit NF-1 from their mothers appear more likely to develop leukemia than those who inherit NF-1 from their fathers. Furthermore, this model predicts the existence of pedigrees with female carriers who have brothers and multiple male offspring with both NF-1 and myeloid leukemia. To our knowledge, no such families have been reported.

Alternatively, the finding of maternal transmission of NF-1 in over 75% of children with familial NF-1 and myeloid leukemia might be explained by either an increased rate of mutation at the paternal NF-1 locus or by decreased fertility of males with NF-1. The first possibility is consistent with the data of Jadayel et al., who found that new mutations causing heritable NF-1 occurred on paternal chromosomes in 12 of 14 families and postulated that paternal NF-1 genes are more susceptible to mutation than the maternal alleles. However, a simple model based on the proposal that paternal NF-1 alleles are more likely to sustain a "second hit" does not account for the striking excess of boys with leukemia. Similarly, boys and girls should be at approximately equal risk of leukemia even if there were differences in fertility between men and women with NF-1.

Genomic imprinting has been defined as "the differential expression of genetic material, at either a chromosomal or allelic level, depending on whether the genetic material has come from the male or female parent." Two lines of evidence suggest that imprinting is important in susceptibility to some types of familial cancer. First, while Knudson's model explains the genesis of retinoblastoma, the familial predisposition to develop cancer does not map within commonly deleted segments of DNA in some cases of Wilms' tumor, rhabdomyosarcoma, and Mo 7. Second, paternal alleles are preferentially retained in Wilms' tumors, osteosarcomas, and rhabdomyosarcomas. These findings led to the hypothesis that paternal tumor-suppressor alleles might be inactivated by the action of a mutant "imprinting" gene that is not physically linked to the imprinted target gene. The recent observation that children with sporadic Beckwith-Wiedeman Syndrome show uniparental disomy for the region of chromosome 11 to which the disease locus has been mapped provides direct evidence implicating imprinting in the development of some genetic cancers. However, while genomic imprinting of paternal NF-1 alleles might explain a higher risk of leukemia associated with maternal transmission of NF-1,

### Table 2. Parental Origin of Familial NF-1 in Children With Myeloproliferative Disease

<table>
<thead>
<tr>
<th>Age and Sex of Patient</th>
<th>Diagnosis</th>
<th>Parent With NF-1</th>
<th>Reference</th>
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<td>3 yr/M</td>
<td>JCML</td>
<td>Father</td>
<td>14</td>
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<tr>
<td>5 yr/M</td>
<td>AML</td>
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<td>15</td>
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<tr>
<td>23 mo/M</td>
<td>JCML</td>
<td>Mother</td>
<td>16</td>
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<tr>
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<td>JCML</td>
<td>Mother</td>
<td>17</td>
</tr>
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<td>JCML</td>
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<td>3</td>
</tr>
<tr>
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<td>JCML</td>
<td>Mother</td>
<td>22</td>
</tr>
<tr>
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<tr>
<td>5 mo/M</td>
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<td>Mother</td>
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<td>13</td>
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<td>7 mo/M</td>
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<td>Mother</td>
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† Lange BJ, and the Children's Hospital of Philadelphia Greater Delaware Valley Tumor Registry; unpublished data.
this mechanism does not account for the marked excess of affected boys.

A final possibility is that mutant NF-1 alleles prevent reactivation of an imprinted gene on the X chromosome which normally regulates hematopoiesis. In females, one allele of this gene would normally be inactive due to imprinting, while males would have a single active (unimprinted) locus. According to this model, boys with NF-1 who develop myeloid leukemia would receive an imprinted X chromosome from their mothers. Inheriting NF-1 from either parent would inhibit reactivation of the critical X-linked gene. Girls would be at lower risk of leukemia because of the protective effect of two X chromosomes. Finally, expression of a mutant NF-1 allele during oogenesis might more strongly inhibit reactivation of imprinted alleles than if NF-1 is inherited from the father. This could account for both the preferential maternal transmission of NF-1 to children who develop leukemia and for the fact that the only cases of leukemia in girls with familial NF-1 occurred in patients who inherited the disease from their mothers. While this model is highly speculative, the observation that maternal transmission of NF-1 has previously been associated with the highest incidence of serious childhood complications related to the disease50 suggests that imprinting may modify the severity of NF-1. In that report, the only children who developed cancer (one with a brain tumor, the other with leukemia) were sisters who inherited NF-1 from their mother.48 The peculiar inheritance of fragile X syndrome led Laird52 to propose a model based on the failure to reactivate an imprinted gene on a maternal X chromosome in retarded males. The molecular genetics of the fragile X locus has yet to be resolved with certainty; some in retarded males. The molecular genetics of the fragile X locus has yet to be resolved with certainty; however, the recent observation of hypermethylation in some patients implicates aberrant imprinting in its pathogenesis.51

Two of our patients are interesting from the perspective of how NF-1 mutations are expressed clinically. Cawthon et al61 reported an apparently normal mother of a patient who had been diagnosed with the nonhereditary form of NF-1 who shared a novel mutation of the NF-1 gene with her son. The fact that our patient 3 has a brother with NF-1 suggests that he inherited the disease even though he showed no cutaneous stigmata. Similarly, the mother of patient 2 has a spotted nevus on her forearm. Additional studies are necessary to clarify the range of phenotypic expression of NF-1, and to define the role that inherited and acquired NF-1 mutations play in sporadic cases of Mo 7 and JCML.

Some children with Mo 7 show abnormal responses to viral infections. Patient 4 had persistent elevations of antibodies to EBV and intractable cutaneous warts. Patient 2 also had markedly elevated antibodies to EBV and developed striking inflammatory myofibroblastic tumors immediately after a severe oral infection with herpes simplex virus. A JCML-like myeloproliferative illness, which may be transient, has also been associated with persistent EBV infection in children without NF-1.52,53

The association of NF-1 with both JCML and Mo 7 suggests a multistep model of leukemogenesis in which mutations of the NF-1 gene interact with male sex, chromosome 7 deletions, and, perhaps, persistent EBV infection. The observation of familial cases of Mo 72,34 and the fact that JCML and Mo 7 predominantly affect young children implicate genetic factors in patients who do not have NF-1. Important questions include whether inactivation of the single normal NF-1 allele is a necessary step in leukemogenesis in children with NF-1 and what role acquired mutations of the NF-1 gene play in cases of JCML and Mo 7 seen in patients who do not have NF-1. The presence in many children with JCML and Mo 7 of a well-defined chronic phase preceding evolution to AML should facilitate investigation of the molecular events responsible for disease progression. The NF-1 gene provides a logical starting point for these studies.

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Monosomy 7 myeloproliferative disease in children with neurofibromatosis, type 1: epidemiology and molecular analysis

KM Shannon, J Watterson, P Johnson, P O'Connell, B Lange, N Shah, P Steinherz, YW Kan and JR Priest