To the editor:

**Clinical manifestations, management, and molecular genetics in congenital factor VII deficiency: the International Registry on Congenital Factor VII Deficiency (IRF7)**

Factor VII deficiency is a rare bleeding disorder in which premature death may occur from severe bleeding. Up to now, our scientific knowledge on factor VII deficiency has been mainly based on reporting of single cases and groups of patients from confined geographical areas. To improve our insight and understanding of the epidemiology and the heterogeneity of factor VII deficiency through detailed study of the relationships among causative mutations, polymorphic modifiers, phenotype variances, the nature of bleeding manifestations, and the clinical complications and the efficacy of bleed management, a task group has recently been formed to study, compile, and publish such information.

The steering committee of the International Registry on Congenital Factor VII Deficiency (IRF7), as originally proposed by G. Mariani, has recently widened its scope to add further expertise, in particular on molecular genetic, biologic, and clinical aspects.

As of today, 10 treatment centers have reported a total of around 90 patients to IRF7. An additional 145 patients suffering factor VII deficiency have been identified by task group members in their respective centers. Most of those patients have already been assigned a mutation diagnosis. Eligible patients reported so far (n = 86) display a wide distribution of phenotypic variance. In 37% of patients, less than 2% of normal factor VII:C activity was reported. No less than 70% of patients had undergone at least one surgical procedure, and 4 patients had experienced a thrombotic episode occurring in close relationship with surgery.

Because enrolled or identified patients are almost exclusively of European Caucasian origin, the IRF7 steering committee clearly recognizes the need for an expansion of the study. The IRF7 data collection may create a unique opportunity to improve the existing knowledge on congenital factor VII deficiency, and so the steering committee wishes to invite colleagues worldwide to report patients to the registry.

Entering candidate patients requires filling out a 1-page form. Interested colleagues are advised to contact IRF7 chair Dr G. Mariani, Hematology and Bone Marrow Transplantation Unit, University of Palermo, Via del Vespro 129, IT-90127 Palermo, Italy; e-mail: marianigu@tin.it. The enrollment form can be submitted by e-mail or by surface mail. The registry may require supplementary information once the patient is registered, depending on the nature of the information disclosed in the entry form. Colleagues are advised to consult their respective institutions’ review boards or ethics committees, as required.

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**References**


To the editor:

**No germline ATM mutation in a series of 16 T-cell prolymphocytic leukemias**

In their review, Vanasse et al state that up to half of the individuals without ataxia telangiectasia who contract T-cell prolymphocytic leukemia (T-PLL) were heterozygote carriers of mutations with the ATM gene. But no evidence for this assertion could be drawn from the cited references. In the 4 series of patients with T-PLL analyzed to date for ATM mutation, ATM was inactivated by deletion or mutation in at least two-thirds of the leukemias. In our initial work, we reported that the 3 mutations identified in the tumor DNAs were not present in the paired germline DNAs, demonstrating that these mutations were of somatic origin and that no carrier of ATM mutation was present in this series. Similarly, Yuille et al reported 2 ATM mutations in T-PLL samples which were absent in remission samples.

Furthermore, since these initial reports, we thoroughly investigated 16 patients with T-PLL. The loss of heterozygosity (LOH)
### Analysis of ATM alleles in T-PLL

<table>
<thead>
<tr>
<th>Patients</th>
<th>LOH analysis</th>
<th>ATM mutation analysis</th>
<th>Germline ATM mutation</th>
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<tbody>
<tr>
<td>TP2 (Lee)</td>
<td>LOH*</td>
<td>C7370T*</td>
<td>51 S2394L Rad3 C7370T</td>
</tr>
<tr>
<td>TP3 (Bat)</td>
<td>LOH*</td>
<td>4182ins29*</td>
<td>28/29 frameshift ND</td>
</tr>
<tr>
<td>TP4 (Ver)</td>
<td>No LOH*</td>
<td>9216del3</td>
<td>65 L2448 Y PI3K 9216del3</td>
</tr>
<tr>
<td>TP8 (Mal)</td>
<td>LOH*</td>
<td>G8350T</td>
<td>58 D2721 Y PI3K G8350T</td>
</tr>
<tr>
<td>TP10 (Imb)</td>
<td>LOH*</td>
<td>G7530T</td>
<td>52 D2448 Y G7530T</td>
</tr>
<tr>
<td>TP13 (Van)</td>
<td>LOH*</td>
<td>G8861A</td>
<td>62 G2891D PI3K G8861A</td>
</tr>
<tr>
<td>TP15 (Ber)</td>
<td>LOH*</td>
<td>A7499G</td>
<td>52 Y2437C A7499G</td>
</tr>
<tr>
<td>TP19 (Jun)</td>
<td>LOH*</td>
<td>G8861A</td>
<td>62 G2891D PI3K G8861A</td>
</tr>
<tr>
<td>TP21 (Big)</td>
<td>LOH*</td>
<td>2891insT*</td>
<td>20 frameshift 2702insT</td>
</tr>
<tr>
<td>TP22 (Bul)</td>
<td>LOH*</td>
<td>C7645G</td>
<td>52 R2486G PI3K C7645G</td>
</tr>
<tr>
<td>TP27 (Dai)</td>
<td>LOH*</td>
<td>6536del105*</td>
<td>46 del35aa Rad3 GIVS46+1A</td>
</tr>
<tr>
<td>TP32 (LOH)</td>
<td>LOH*</td>
<td>C8284T</td>
<td>57 P2699S PI3K C8284T</td>
</tr>
<tr>
<td>TP33</td>
<td>LOH*</td>
<td>G8945A</td>
<td>62 G2919D PI3K G8945A</td>
</tr>
<tr>
<td>TP34</td>
<td>LOH*</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td>TP35</td>
<td>No LOH*</td>
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<td>ND</td>
</tr>
<tr>
<td>TP36</td>
<td>LOH*</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

Numbering of nucleotides is based on the ATM transcript sequence (Genbank accession number U33841).

Abbreviations: LOH, loss of heterozygosity; ND, not determined; PI3K, phosphatidyl inositol 3 phosphate kinase homology domain; Rad3, Rad3 homology domain; aa, amino acid.

*Results previously reported.4
†LOH deduced from the homozygosity for the A7499G mutation (see text).

analysis, performed as previously described,4 identified deletion of one copy of the 11q23 region in 81 percent of the cases (13 of 16). Because missense mutations of ATM were frequent in the tumors, contrasting with the truncating mutations representing most of the germline mutations, we used the fluorescence-assisted mismatch analysis (FAMA) technique to search for mutation.6 Briefly, after reverse transcription of the messenger RNA, ATM transcripts were amplified by the polymerase chain reaction (PCR) using fluorescent primers. The PCR products were denatured and reannealed with germline PCR products to form heteroduplexes, and subjected to conventional cytosine- and thymine-specific modifications. Cleavages occurring on opposite strands were detected by denaturing gel electrophoresis using an automated DNA sequencer. The identified cleavage regions were then sequenced using specific primers. Thirteen aberrations of ATM transcripts were identified in 12 patients. Case TP15, without detectable LOH using polymorphic markers, was found homozygous for an A7499G mutation (single-letter amino acid code), which was absent in germline DNA. This was interpreted as a small-sized allelic deletion of the ATM gene. Alterations of ATM by deletion or mutation were found in all but one patient (Table). Considering a model in which ATM is consistently inactivated on both alleles in T-PLL, 18 mutated alleles were expected. The 13 identified mutations were consistent with this model, considering the sensitivity of the FAMA technique to detect ATM mutations, estimated at 72% from the analysis of a series of ataxia telangiectasia patients (Lauge et al, unpublished data). The genomicmutation responsible for the aberrantly spliced transcripts in case TP3 was not identified, precluding the determination of its somatic or germline origin. The 12 ATM mutations in 11 patients, identified in the tumor DNAs, were absent in the corresponding germline DNAs obtained from paired lymphoblastoid cell lines generated from the tumor samples. Thus this analysis of a larger series confirmed the somatic nature of ATM mutations in T-PLL and did not identify ATM heterozygotes suffering from T-PLL.

Considering the potential anxiety and unjustified medical care that could be generated by the statement made by Vanasse et al, it should be stated that, surprisingly, there is no evidence so far for an increased risk of T-PLL in ATM carriers. But our data do not exclude a relative risk (RR) inferior to 3. Given $P_{TPLL}$, the frequency to observe no heterozygote in a series of 11 cases with a probability $P$ below .05 estimated at $.25 P = (1 - .25)^11 = .042$, and $P_{ATM}$, the frequency of ATM heterozygote in the general population estimated at .01, the maximal relative risk (RR) in ATM heterozygotes for T-PLL was deduced from the formula $P_{TPLL} = (P_{ATM} \times RR) / (P_{ATM} \times RR + (1 - P_{ATM}))$. But even with such a risk, considering the extremely low incidence of T-PLL in the general population, this risk for ATM carriers would be minor. Finally, the apparent absence of overrepresentation of ATM carriers in the patients suffering from T-PLL and the differences in the mutations observed in ataxia telangiectasia patients (most often truncating mutations) and in T-PLL (often missense mutations in the phosphatidyl-inositol 3 phosphate kinase homology domain) may indicate important functional differences in these mutant ATM proteins.7

**References**

Response:

Somatic versus germline origin of ATM mutations in T-PLL

We thank Dr. Stern and his coworkers for their timely letter, which brings new data to bear on the origin of ATM mutations in sporadic cases of T-PLL. Because nontumor DNA was not studied in conjunction with most of the previously reported cases, it has not been possible to determine the relative contributions of 2 models for how these mutations arise: (1) two somatic mutation events occur in the course of T-PLL pathogenesis, each of which inactivates one ATM allele in a cell, or (2) T-PLL arises in a subset of A-T heterozygotes with specific germline mutations, accompanied by a single somatic mutation event inactivating the normal ATM allele.

The latter model, in which ATM acts as a classic tumor suppressor gene, is appealing because of the precedent provided by other genes such as Rb, p53, and so forth and because A-T patients (homozygotes) are susceptible to this unusual malignancy. As noted by Stoppa-Lyonnet et al and other investigators, the preponderance of ATM mutations reported in T-PLL are point mutations clustering in the 3′ portion of the gene, whereas mutations seen in A-T more often represent protein truncations and are spread throughout the gene. Given these observations, coupled with the fact that T-PLL and A-T are rare conditions, it would seem extremely unlikely to observe the same mutation, either in multiple T-PLL patients or in T-PLL and A-T patients by chance alone. In their letter, however, Stoppa-Lyonnet et al indicate that 2 of 12 T-PLL patients shared the same missense mutation in the ATM gene and report 1 additional T-PLL mutation (G [IVS46+1]A), which has been previously detected in an A-T patient. Additional examples of ATM mutations common to either multiple T-PLL patients or T-PLL and A-T patients can be found in the literature. The mutation T7271G has been detected in leukemic cells from a T-PLL patient but has also been detected in normal cells from patients in 2 A-T families. Two additional ATM mutations reported in T-PLL, 7636del9 and C9139T, are relatively common in A-T, the former having been seen in 15 different A-T families and the latter in 5 different families of different ethnic origins. There are 2 separate reports of the mutation C9022T in T-PLL patients, and this mutation has also been reported in an A-T family. Recurrence of these mutations does not fit well with a strictly somatic origin for ATM mutations in T-PLL. As a result, many investigators, ourselves included, have tacitly accepted that biallelic ATM mutations in at least some cases of T-PLL arise from germline heterozygosity, despite the limited evidence available to date. Stoppa-Lyonnet et al now provide important new data that suggest that a substantial fraction of ATM mutations in T-PLL cases are strictly somatic mutation events.

We did not comment in our review about potential cancer risks for heterozygous carriers of ATM mutations. This remains a subject of considerable controversy, with most current concern centered around the increased risk for breast cancer. Given that the exact spectrum of ATM mutations that contribute to T-PLL, the frequency of carriers for these mutations in the general population, and the degree of overlap between this set of mutations and those that lead to A-T are all unknown, it would be difficult to evaluate any risk for T-PLL associated with A-T carrier status. But given the rarity of T-PLL and the overall estimated carrier frequencies for A-T of approximately 1%, these risks are likely to be small.

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References