To the editor:

ANKRD26-related thrombocytopenia and myeloid malignancies

Since the discovery that mutations in the 5’ untranslated region (UTR) of ANKRD26 are responsible for an autosomal-dominant form of thrombocytopenia (ANKRD26-RT), 1 21 affected families were reported. A study analyzing this series of patients suggested that ANKRD26-RT is characterized by normal platelet size, moderate thrombocytopenia, and absent or mild bleeding tendency. The study also found that the number of hematologic malignancies in affected families was higher than expected, but the relatively small cohort of patients precluded firm conclusions.

To gain further information on this matter, we screened for mutations in the 5’ UTR of ANKRD26 in 215 subjects with an inherited thrombocytopenia of unknown origin and found 11 mutations (3 not previously described) in 23 cases (Table 1). Analysis of family members identified another 52 affected subjects. Moreover, we found 43 additional subjects, first- or second-degree relatives of ANKRD26-RT patients, who were known to be thrombocytopenic from an early age but were not available for genetic investigation (they were dead or not willing to perform the analysis). Analysis of the new series of 75 patients with ANKRD26 mutations confirmed that ANKRD26-RT is characterized by moderate thrombocytopenia with normal platelet size and a mild bleeding phenotype.

In the extended series of 118 subjects certainly or very likely affected, we identified 10 patients who had developed myeloid malignancies: 4 acute myeloid leukemias (age at onset, 40-60 years), 4 myelodysplastic syndromes (MDS) (age at onset, 35-70 years), and 2 chronic myeloid leukemias (CML) (age at onset, 30-65 years). The total observation time was 4741 years, and the incidence of acute myeloid leukemia, MDS, and CML was 84 (confidence interval [CI], 23-216), 84 (CI, 23-216), and 42 (CI, 5-152) per 100,000, respectively. Putting together the 118 cases examined in this study and the 104 cases already reported, 4.9% of patients had acute leukemias, 2.2% MDS, and 1.3% CML. The total observation time was 8915 years, with an incidence of acute leukemias, MDS, and CML of 123 (CI, 62-221), 56 (CI, 18-131), and 34 (CI, 7-98) per 100,000, respectively, thus higher than expected in the general population (5.2, 4.5, and 1.6 per 100,000, respectively, according to the National Cancer Institute). Unlike myeloid malignancies, the incidence of lymphoproliferative disorders and nonhematologic cancers in ANKRD26-RT pedigrees was not higher than expected (data not reported). Available data are therefore compatible with the hypothesis that ANKRD26-RT, as the inherited thrombocytopenia deriving from RUNXI mutations, 3 predisposes to myeloid malignancies, in particular acute leukemias. The observation that this unfavorable outcome occurred in a limited proportion of subjects and has been observed in only 12 of 44 families indicates that the penetrance for malignancies was incomplete and other genetic and/or environmental factors contributed to the development of these disorders. Of note, the the case series described in this paper confirmed the already reported finding of unexplained high leukocyte counts in a large

Table 1. Main clinical and laboratory features of patients with ANKRD26-RT grouped by family

<table>
<thead>
<tr>
<th>Family/No. of patients/Country</th>
<th>ANKRD26 5’ UTR mutation</th>
<th>Mean age (range) WHO bleeding score 3 (no. of patients)</th>
<th>Mean platelet count, ×10^9/L (range)</th>
<th>Mean MPV, fl (range)</th>
<th>Mean hemoglobin, g/dL (range)</th>
<th>Mean WBC, ×10^9/L (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/3 Canada</td>
<td>c.-116C&gt;G*</td>
<td>18 (6-37)</td>
<td>1 (2), 2 (1)</td>
<td>70.6 (45-107)</td>
<td>9.55 (9.4-9.7)†</td>
<td>12.85 (12.1-13.6)†</td>
</tr>
<tr>
<td>2/2 France</td>
<td>c.-118C&gt;A</td>
<td>34 (17-51)</td>
<td>2 (2)</td>
<td>63.5 (45-82)</td>
<td>10.2 (9.9-10.5)</td>
<td>15.5 (14.8-16.3)</td>
</tr>
<tr>
<td>3/1 US</td>
<td>c.-118C&gt;T</td>
<td>57</td>
<td>0 (1)</td>
<td>38</td>
<td>7.7</td>
<td>14.3</td>
</tr>
<tr>
<td>4/3 France</td>
<td>c.-119C&gt;A</td>
<td>32.6 (2-65)</td>
<td>2 (2), 3</td>
<td>55.6 (36-81)</td>
<td>10.1 (9.1-11.3)</td>
<td>13.7 (12.8-14.2)</td>
</tr>
<tr>
<td>5/1 Italy</td>
<td>c.-126T&gt;G</td>
<td>28</td>
<td>1 (1)</td>
<td>14</td>
<td>8.1</td>
<td>16.6</td>
</tr>
<tr>
<td>6/9 Argentina</td>
<td>c.-127A&gt;G</td>
<td>37.7 (6-74)</td>
<td>0 (2), 1 (4), 2 (3)</td>
<td>96.2 (68-147)</td>
<td>8.6 (7.7-9.5)‡</td>
<td>15.3 (12.9-17.7)</td>
</tr>
<tr>
<td>7/2 Italy</td>
<td>c.-127A&gt;G</td>
<td>32 (17-47)</td>
<td>0 (1), 2 (1)</td>
<td>79.5 (68-91)</td>
<td>8.8 (8.6-9)</td>
<td>14.15 (12.4-15.9)</td>
</tr>
<tr>
<td>8/3 France</td>
<td>c.-127A&gt;T</td>
<td>19 (6-38)</td>
<td>0 (1), 1 (2)</td>
<td>65.6 (47-85)</td>
<td>7.5 (7.1-7.8)</td>
<td>14.8 (12.8-17.2)</td>
</tr>
<tr>
<td>9/8 France</td>
<td>c.-127A&gt;T</td>
<td>39.25 (1-68)</td>
<td>0 (5), 1 (3)</td>
<td>39.37 (24-84)</td>
<td>10.8 (9.3-11.7)</td>
<td>14.15 (11-16.8)</td>
</tr>
<tr>
<td>10/6 France</td>
<td>c.-127delAT*</td>
<td>34.6 (1-66)</td>
<td>0 (6)</td>
<td>54.6 (26-96)</td>
<td>10.2 (8.7-11)</td>
<td>14.2 (10.4-16.6)</td>
</tr>
<tr>
<td>11/3 France</td>
<td>c.-128G&gt;A</td>
<td>63 (21-97)</td>
<td>2 (2)</td>
<td>19 (12-30)</td>
<td>8.1 (7-8.5)§</td>
<td>13.6 (13.6-13.6)§</td>
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<tr>
<td>12/2 France</td>
<td>c.-128G&gt;A</td>
<td>36.5 (26-47)</td>
<td>1, 2</td>
<td>71.5 (68-75)</td>
<td>8.4§</td>
<td>14.6§</td>
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<td>13/3 Italy</td>
<td>c.-128G&gt;A</td>
<td>20 (12-26)</td>
<td>0 (3)</td>
<td>34 (14-70)</td>
<td>7.6 (6.3-8.5)</td>
<td>15.3 (14-16.5)</td>
</tr>
<tr>
<td>14/1 Japan</td>
<td>c.-128G&gt;A</td>
<td>25</td>
<td>0 (1)</td>
<td>54</td>
<td>8.9</td>
<td>15.8</td>
</tr>
<tr>
<td>15/2 Italy</td>
<td>c.-128G&gt;A</td>
<td>52 (50-54)</td>
<td>1 (2)</td>
<td>20 (19-21)</td>
<td>8.4§</td>
<td>14.2§</td>
</tr>
<tr>
<td>16/10 US</td>
<td>c.-128G&gt;A</td>
<td>23.2 (1-62)</td>
<td>0 (4), 1 (6)</td>
<td>35.5 (19-65)</td>
<td>8.7 (7.5-10.2)</td>
<td>14.43 (12.7-16.1)</td>
</tr>
<tr>
<td>17/8 Italy</td>
<td>c.-128G&gt;A</td>
<td>40.2 (6-93)</td>
<td>0 (1), 1 (1), 2 (3), 3 (19), 4 (1)</td>
<td>18.7 (5-34)</td>
<td>8.5 (7-10.3)II</td>
<td>13.47 (11.8-16.3)</td>
</tr>
<tr>
<td>18/1 Italy</td>
<td>c.-128G&gt;A</td>
<td>38</td>
<td>2 (1)</td>
<td>48</td>
<td>9.04</td>
<td>15.9</td>
</tr>
<tr>
<td>19/2 France</td>
<td>c.-128G&gt;C*</td>
<td>20 (1-39)</td>
<td>0 (2)</td>
<td>52.5 (24-81)</td>
<td>12 (10-14)</td>
<td>13.15 (12.3-4)</td>
</tr>
<tr>
<td>20/1 Japan</td>
<td>c.-134G&gt;A</td>
<td>13</td>
<td>0 (1)</td>
<td>81</td>
<td>9.2</td>
<td>14.2</td>
</tr>
<tr>
<td>21/2 US</td>
<td>c.-134G&gt;A</td>
<td>58.5 (50-67)</td>
<td>2 (2)</td>
<td>10 (7-13)</td>
<td>8.2 (5.7-10.7)</td>
<td>11.7 (10.7-12.7)</td>
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<tr>
<td>22/1 The Netherlands</td>
<td>c.-134G&gt;A</td>
<td>34</td>
<td>2 (1)</td>
<td>24</td>
<td>11.1</td>
<td>15.5</td>
</tr>
<tr>
<td>23/1 US</td>
<td>c.-134G&gt;A</td>
<td>64</td>
<td>1 (1)</td>
<td>20</td>
<td>8.8</td>
<td>13.4</td>
</tr>
</tbody>
</table>

MPV, mean platelet volume; US, United States; WBC, white blood cell; WHO, World Health Organization.

*New mutations.
†Data from 2 of 3 patients.
‡Data from 7 of 9 patients.
§Data from 1 of 2 patients.
||Data from 7 of 8 patients.
proportion of subjects. Further observation is required to ascertain whether the higher leukocyte counts are related to eventual development of leukemia.

In conclusion, ANKR26-RT is an insidious form of inherited thrombocytopenias that exposes patients to a low risk of bleeding but predisposes them to hematologic myeloid malignancies. Recognizing this disorder and its attendant risks is important for proper management of affected subjects.6

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To the editor:

Plasma hepcidin of Ethiopian highlanders with steady-state hypoxia

Hepcidin impedes iron absorption and is suppressed when erythropoietic iron requirements are increased. Recent studies show that during acute exposure to high-altitude hypoxia, plasma hepcidin concentrations drop when iron demands for erythropoiesis and hemoglobin synthesis are sharply increased. However, the effects of chronic exposure to high-altitude hypoxia with stable erythropoietic iron requirements have not been examined. We hypothesized that plasma hepcidin would not be suppressed in iron-replete individuals chronically adapted to high altitude.

People of Amhara and Oromo ethnicity have been living at high altitude in Ethiopia for more than 5000 years and about 500 years, respectively, and have been shown to differ from one another in hemoglobin and oxyhemoglobin percentage. Healthy volunteers from 3700 to 4000 m (high altitude) and 1200 to 1500 m (low altitude) were recruited, and they provided blood samples for analyses (see the supplemental Video(s)/Data Set(s) link at the top of the online article for genetic analysis methodology). The sample reported here had normal calculated body iron stores, accounting for 22% of the variation in covariate-adjusted hepcidin level. Allele A of rs7700582 increased hepcidin levels by 8.1 ng/mL only among Amhara, although allele frequency was similar in all 4 subsamples.

Hepcidin was not suppressed in Amhara or Oromo highland samples under steady-state hypoxia, likely because erythropoietic drive was stable. It is interesting to speculate that the higher plasma hepcidin of highlander Amhara, compared with Oromo, is due to lower iron demand indicated by lower hemoglobin and erythropoietin concentrations and higher body iron stores. Variants in GRAMD3 are associated with macular degeneration, a retinal disease that has been related to abnormalities in hepcidin and iron accumulation. Another variant near GRAMD3 (rs1366100) has been associated with erythrocyte counts, consistent with the idea that this region plays a role in iron metabolism. Thus, the genetic results also support the idea that iron stores are primary regulators of hepcidin levels in hypoxic populations without increased erythropoietic drive. Previous work has shown that various highlander populations demonstrate different responses to hypoxia, which may also be the case with iron regulation.

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