EBV infection in AIDS-DLBCL is consistently linked to plasmacytoid/plasmablastic differentiation.[4]

Although latency programs predominate in EBV-driven tumors, lytic EBV replication may also be of pathogenic relevance, at least in the early phases of cell transformation.[5,6] This finding is particularly relevant for AIDS-related lymphomagenesis, since the underlying impairment of immune responses may favor uncontrolled activation of EBV lytic replication in latently infected B lymphocytes. Importantly, regarding tumor microenvironment, EBV infection is implicated in angiogenic mechanisms.[5-7] In conclusion, the results reported by Liapis and colleagues[1] are consistent with genetic and virological data suggesting that in AIDS-DLBCL, neovascularization is linked to EBV status of tumor and to immunoblastic features.

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To the editor:

No familial aggregation in chronic myeloid leukemia

There is a fivefold to sevenfold elevated risk of myeloproliferative neoplasms (MPNs) among first-degree relatives of MPN patients.[1,2] In contrast, aside from early-onset patients, there is no significant familial aggregation in acute myeloid leukemia (AML).[3]

The molecular underpinnings of the development of chronic myeloid leukemia (CML) are unclear. Ionizing radiation in high doses is the only known risk factor.[4] Benzene and benzene-containing products have been reported to be significantly related to morbidity and mortality from CML,[5] although recent case-control literature indicates the opposite.[6] Apart from extremely rare pedigrees with multiple cases of CML/myeloproliferative disorders,[7] there is essentially no data on familial aggregation of CML in the population. According to The National CML Society, "Occasionally, there are families that may have other members living with leukemia, however, there is no conclusive evidence that family members are predisposed to develop leukemia."[8]

Taking advantage of high-quality registry data from Sweden, we conducted a population-based registry study to evaluate risk of CML, MPN, AML, and other malignancies among 9491 first-degree relatives of 4619 patients (45% females) with CML compared with 42 474 first-degree relatives of matched controls. Our methods have been previously described.[3] In brief, using the Swedish Cancer Registry, we identified all patients with a primary diagnosis of CML diagnosed between 1958 and 2004. For each CML patient, 4 population-based controls (matched by sex, year of birth, and county of residence) were chosen randomly from the Swedish population database. All control individuals had to be alive at the time of CML diagnosis for their corresponding case patient and without a hematologic malignancy at the date of CML diagnosis for their corresponding case patient. We obtained information on all first-degree relatives of cases and controls from the Swedish Multigenerational Registry, which includes data on parent-sibling-offspring relations for all Swedish citizens born in 1932 or later. We used a marginal survival model to calculate familial aggregation.

We found that neither CML (relative risk, 1.62; 95% confidence interval, 0.52-5.11), AML (0.94; 0.44-2.0), nor MPN (1.11; 0.58-2.17) aggregated significantly in relatives of patients with CML (vs relatives of controls) (Table 1). In addition, the relative risks for any lymphoproliferative, hematologic, or solid tumor were not significantly increased. We also analyzed the risks in relatives by gender and age at diagnosis of proband ($\leq$60 vs $>$60 years) and could not reveal any significant associations (data not shown).

CML patients may worry about their family members having a potentially increased risk of developing CML or other cancer. In this population-based study, including all age groups of patients with CML, we found no significant familial aggregation for CML, AML, MPN, lymphoproliferative neoplasm, or any other cancer among relatives of CML patients (vs relatives of matched controls). Our findings are in sharp contrast to those observed in MPNs where an increased familial aggregation supports the notion that genetic susceptibility genes may play a strong role in these patients.

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Table 1. Risk of myeloid, lymphoid, and solid malignancies in relatives of patients with CML

Outcome in relatives	CML, n = 9491	Controls, n = 42 474	RR	95% CI
Myeloid				
AML	8	38	0.95	0.44-2.0
MDS	0	7	—	—
AML/MDS	8	45	0.81	0.38-1.70
CML	4	11	1.62	0.37-7.2
MPN	11	44	1.14	0.59-2.20
Any myeloid malignancy	23	100	1.04	0.64-1.68
Lymphoid				
NHL	35	145	1.1	0.75-1.60
HL	3	26	0.52	0.16-1.71
CLL	14	52	1.2	0.69-2.20
WM	0	2	—	—
MM	11	52	0.96	0.50-1.85
Any lymphoproliferative malignancy	65	276	1.07	0.80-1.41
ALL	4	9	1.98	0.61-6.40
Any hematologic malignancy	92	383	1.09	0.86-1.37
Any solid tumor	998	4312	1.04	0.97-1.12
Any cancer	1089	4695	1.05	0.98-1.12

ALL, acute lymphoblastic leukemia; CI, confidence interval; CLL, chronic lymphocytic leukemia; HL, Hodgkin lymphoma; MDS, myelodysplastic syndrome; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; RR, risk ratio; WM, Waldenström macroglobulinemia; —, not computed.

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To the editor:

A missense mutation in ANKRD26 segregates with thrombocytopenia

Inherited thrombocytopenias form a heterogenous group of diseases characterized by decreased platelet count and increased risk of bleeding. Mutations in at least 17 genes have been associated with autosomal-recessive, autosomal-dominant, and X-linked forms of the disease (recently reviewed by Balduini and Savoia[1]). Autosomal-dominant nonsyndromic thrombocytopenia-2 (THC2; MIM 188000) is characterized by decreased platelet count, mild propensity to bleeding, normal platelet function, normal numbers of megakaryocytes, and normal maturation stages, suggesting defective platelet production or release.[2] Morphologically, platelets and megakaryocytes appear normal under light microscopy, but a recent study suggests the presence of particulate cytoplasmic structures in ANKRD26 platelets and megakaryocytes when examined under electron microscopy.[3] Genetic studies have identified mutations of the 5′ untranslated region (UTR) of the ANKRD26 gene as the underlying cause of the phenotype.[4] Since the initial report, additional mutations have been described in the same 22-nucleotide stretch of the 5′ UTR in a total of 21 pedigrees that are postulated to cause THC2 by upregulation of ANKRD26 expression.[2,4]

We carried out a whole-exome sequencing experiment on 2 individuals, an affected father-daughter pair, from a 4-generation Saudi Arabian family with autosomal-dominant nonsyndromic thrombocytopenia (Figure 1). The proband, a 4-year-old girl, presented with a history of bruising. Initial investigations revealed mild thrombocytopenia and iron deficiency anemia requiring only 3 transfusions since birth. Laboratory investigations revealed the following: hemoglobin, 12.2 g/dL; white blood cells, 11.08×10^9/L; neutrophil count, 5.7×10^9/L; platelet count, 26×10^9/L (mean platelet