C282Y mutation in HFE with an extremely severe form of genetic hemochromatosis. We found that this mutation may strongly affect the hepcidin promoter activity, especially by impairing its BMP/SMAD activation response, and thus could contribute to the severe phenotype of the patient.

The results of Barton *et al.*,[2] obtained from a large panel of patients selected from the HEIRS study, support the fact that this mutation is extremely rare, leading them to not recommend a large screening for this mutation in hemochromatosis patients. In addition, they found that a patient presenting with an hyperferritinemia, which was not confirmed thereafter, also has a nc.-443 C>T mutation in addition to the nc.-153 C>T in the hepcidin promoter.

We fully agree with Barton and collaborators, that from available data, there is no need to systematically search for the nc.-153 C>T hepcidin promoter mutation during population based studies and iron overload screening programs. However, in selected patients with proved and not fully explained iron overload phenotypes with high plasma transferrin saturation, future studies of the presence of the nc.-153 C>T, together with family studies, which was not possible in the patient that we reported, should provide valuable information on the clinical impact of this mutation in atypical iron overload conditions.

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Slow relapse in acute myeloid leukemia with inv(16) or t(16;16)

Acute myeloid leukemia (AML) with inv(16)(p13q22) or t(16;16)(p13;q22), resulting in *CBFβ-MYH11* fusion transcript detectable by RT-PCR and RQ-PCR, is associated with an overall good prognosis, relapses however still occur in 30-35 % of patients, and with higher frequency in older patients.[1,2] Molecular relapse generally precedes hematologic relapse in AML with balanced translocations such as t(15;17) or t(8;21), but generally by only a few weeks or a few months.[3-9] Fewer data are available in AML with inv(16)/t(16;16). In 4 of the 5 relapses we observed in AML with inv(16)/t(16;16), the interval between molecular and hematologic relapse was prolonged.

Between 2005 and 2009, 9 AML patients with inv(16) or t(16;16), with a median age of 60 years (range, 21-75) who had reached CR using French co-operative AML trials (anthracycline–cytarabine induction chemotherapy followed by consolidation chemotherapy with high-dose cytarabine, or intermediate dose cytarabine in elderly patients) at our center were prospectively monitored for minimal residual disease (MRD) based on *CBFβ-MYH11* fusion transcript levels in bone marrow samples.

RQ-PCR was performed on bone marrow cells according to the Europe Against Cancer (EAC) Program recommendations for *CBFβ-MYH11* fusion transcripts (type A, D or E), using Taqman® technology, on an ABI PRISM 7000 (Applied Biosystems).[10] Quantification of CBFb-MYH11 fusion transcripts was normalized to the housekeeping *ABL* gene. Results were expressed by the ratio *CBFβ-MYH11* copy number/*ABL* copy number x 100 (%).[10] Median follow-up after CR achievement was 18 months (range, 3-33) and median number of MRD analyses per patient was 6 (range 1-9). Molecular relapse was defined as a 10-fold or greater increase in *CBFβ-MYH11* transcript level compared to the lowest level achieved.

Five of the 9 patients relapsed, after 11-23 months, in the bone marrow (no extramedullary relapse was seen). In one of them, the interval between molecular relapse and hematologic relapse was short (one month). The 4 other hematologic relapses occurred slowly, and were preceded in all cases by molecular relapse detected in bone marrow samples, by ten (patient n. 1), six (patient n. 2), seven (patient n. 3) and eight (patient n. 4) months, respectively. Baseline characteristics of those 4 patients are shown in Table 1. Patients ns. 2 and 3 had c-*KIT* mutation in exon 8 and c-*KIT* D816V mutation, respectively (versus none of the patients who did not relapse) and patient n. 3 had *N-RAS* mutation, while no patient had *FLT3*-ITD or *FLT3*-835/I836 mutation. All 4 patients had achieved at least a 3-log reduction of the fusion transcript level, after induction therapy in 3 of them, and after the first consolidation course in patient n. 1 (Figure 1). During the period of isolated molecular relapse, blood counts and marrow aspirates remained normal in patients ns. 3 and 4, while cytopenias reappeared in

Table 1. Main characteristics of the 4 relapsing patients analyzed.

	Pt n. 1	Pt n. 2	Pt n. 3	Pt n. 4
Age (years)	58	60	64	67
Sex	M	M	M	F
BM blasts %	46	12	63	31
PB blasts %	64	34	60	11
WBC count ($\times 10^9$/L)	25,9	71,7	21,0	65,6
Karyotype	Inv(16)	t(16;16)	Inv(16)	Inv(16)
Interval between first CR and molecular relapse (months)	9	19	3	20
Interval between molecular and hematologic relapse (months)	10	6	7	8

BM: bone marrow; PB: peripheral blood; WBC: white blood cells; Pt: patient.

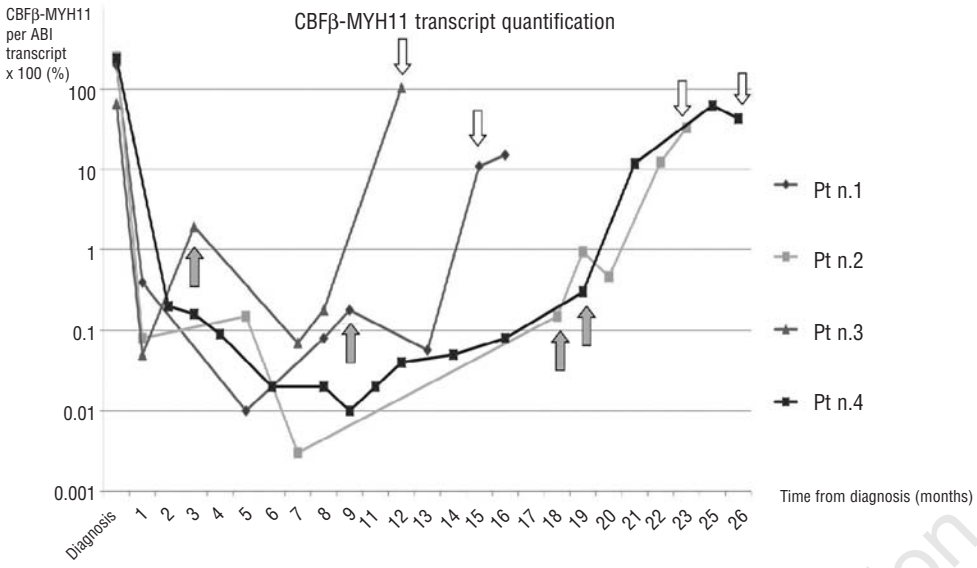

Figure 1. Minimal residual disease (MRD) sequentially measured by RQ-PCR in bone marrow samples in the 4 relapsing patients. MRD was expressed in *CBFB-MYH11* copies per /100 *ABL* gene copies. Dots on curves represent MRD examinations. Full arrows indicate molecular relapse and empty arrows indicate hematologic relapse. Follow-up is in months.

patient n. 1 and abnormal marrow eosinophils in patient n. 2. A second CR was achieved in the 4 patients with chemotherapy, combined to gemtuzumab in 3 cases. Three of them were subsequently allografted, and all 4 patients were alive 2-11 months after hematologic relapse. In acute promyelocytic leukemia (APL), the median interval between molecular and hematologic relapse was 3-4 months in published litterature[3-5] while in AML with t(8;21) it was generally less than six months[6-8] and at a median of three months in our experience.[9]

In AML with inv(16)/t(16;16), few studies are available: Schnittger *et al.* reported 6 relapses of *CBFβ-MYH11* AML with an interval between molecular and hematologic relapse ranging from 1-5 months,[8] similar to what they observed in AML with *PML-RAR* and *AML1-ETO*. By contrast, Stentoft *et al.* reported, in 4 relapsing inv(16)/t(16;16) AML, an interval between molecular and hematologic relapse of approximately one year, with a slow molecular progression rate of about 1-log per 100 days.[8] In our patients ns. 2, 3 and 4, the increase in fusion transcript levels had comparable kinetics, while in our patient n. 1, it was even slightly slower, with a molecular progression rate of about 1-log per 130 days.

Thus, AML with inv(16)/t(16;16) AML may frequently relapse more slowly than other types of AML with balanced translocations. This interval between molecular and hematologic relapse may justify frequent MRD monitoring in those patients, and therapeutic intervention before overt relapse.

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Autoimmunity and risk for Hodgkin's lymphoma by subtype

Hodgkin's lymphoma (HL) is a lymphoproliferative malignancy of B-cell origin, with an age-adjusted incidence of 2.3-3.1 per 100,000 in the Western world.[1] HL is subdivided into classical HL and the rare entity nodular lymphocyte predominant HL (~5% of all HL cases). Based on characteristics of reactive infiltrates and morphology of Reed-Sternberg cells, classical HL is further divided into the following four subtypes: nodular sclerosis (NS), mixed cellularity (MC), lymphocyte-depleted (LD), and lymphocyte-rich (LR).[1] Studies have shown that these subtypes have different age-incidence curves, gender ratio, and racial discrepancy.[1]

The etiology of HL is largely unknown; however, clues about causes have been suggested by the bimodal distribution of age at diagnosis observed in developed countries and by higher risks in males, in persons with higher socioeconomic status, and in smaller families.[2] Young adult–onset HL is thought to arise as a consequence of delayed primary infection with Epstein–Barr virus.[3] Inherited genetic factors play a significant role in the etiology.[4,5]

Personal history of autoimmune diseases is consistently associated with increased risk of non-Hodgkin's lymphoma.[6] Recent data also indicate that the risk of HL is increased following autoimmune diseases.[7-9] We recently analyzed the association of a personal history of autoimmune conditions in 7,476 HL patients compared to 18,573 controls, and found several autoimmune conditions to be strongly associated with HL, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), sarcoidosis, and immune thrombocytopenic purpura (ITP).[10] We found an overall 2.7-fold increased risk for all systemic autoimmune diseases combined. Furthermore, a family history of sarcoidosis and ulcerative colitis were also associated with HL risk, suggesting a role for shared susceptibility factors. To our knowledge, no prior study has evaluated risk for HL following autoimmune disease by HL subtype.

To improve our understanding in this area, we have extended our previous study to evaluate the association of a personal history of autoimmune disease (from the Inpatient Registry) and subsequent risk of HL subtypes. Using high-quality population-based data from Sweden, we identified 9,314 HL patients (median age 49.5 years, 42% females) and 37,069 matched controls. A total of 1,601 (17%) of the patients had information regarding HL subtype using ICD10 diagnoses. We analyzed the three most common subtypes identified (NS, n=1,072; MC, n=364, and LR, n=122), and only those conditions previously identified as being significant in a multivariate analysis. Using logistic regression models adjusted for age, sex, calendar period, and region, we calculated odds ratios (ORs) and 95% confidence intervals (CIs) as measures of relative risks for each condition using logistic regression. To limit the influence of detection bias, we excluded autoimmune disease diagnosed less than one year prior to HL diagnosis.

First, in analyses including all HL cases, we found an increased risk for HL among persons with a personal history of any systemic autoimmune disease (OR=2.0; 95% CI 1.7-2.9), and specifically for RA (2.2; 1.6-2.8), SLE (5.3; 2.5-11.2), Sjögren's syndrome (4.0; 1.3-12.3), sarcoidosis (3.7; 1.9-7.4) and ITP (15.9; 1.8-142) (Table 1). Second, in analyses stratified by HL subtype, a personal history of any systemic autoimmune disease (2.6; 1.1-6.1) and RA (2.7; 1.1-6.6) were associated with and increased risk for MC HL. We did not find any significant associations between a personal history of an autoimmune disease

Table 1. Relative risk of Hodgkin's lymphoma and subtypes in relation to autoimmune disease.

	Hodgkin's lymphoma			Nodular sclerosis Hodgkin's lymphoma			Lymphocyte rich Hodgkin's lymphoma			Mixed cellularity Hodgkin's lymphoma		
	HL (9,314)	Controls (37,069)	OR* (95% CI)	NS HL (1,072)	Controls (4,274)	OR* 95% CI	LR HL (122)	Controls (485)	OR* 95% CI	MC HL (364)	Controls (1,446)	OR* 95% CI
All systemic**	98	174	2.0 (1.7-2.9)	10	22	1.8 (0.9-3.9)	2	3	2.6 (0.4-16.5)	9	14	2.6 (1.1-6.1)
Rheumatoid arthritis	80	147	2.2 (1.6-2.8)	10	20	2.0 (0.9-4.3)	2	2	4.0 (0.6-29.2)	8	12	2.7 (1.1-6.6)
Systemic lupus erythematosus	16	12	5.3 (2.5-11.2)	0	0	NA	0	1	0	2	1	8.0 (0.7-88.3)
Sjögren's syndrome	6	6	4.0 (1.3-12.3)	0	1	0	0	0	NA	1	2	2.0 (0.2-22)
Sarcoidosis	16	17	3.7 (1.9-7.4)	3	7	1.7 (0.4-6.6)	1	0	∞1	0		
Immune thrombocytopenic purpura	4	1	15.9 (1.8-142)	0	1	0	0	0	NA	0	0	NA

*ORs are adjusted for categorical year of birth, date of diagnosis, gender, and county. **Includes RA, SLE, Sjögren's syndrome, systemic sclerosis and polymyositis/dermatomyositis. NA: Not applicable.*