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To the editor:

High incidence of activating *STAT5B* mutations in CD4-positive T-cell large granular lymphocyte leukemia

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Large granular lymphocyte (LGL) leukemia is a group of chronic lymphoproliferative disorders of cytotoxic T or natural killer (NK) cells frequently complicated with cytopenia and autoimmune phenomena.[1,2] In the current World Health Organization (WHO) classification, T-LGL leukemia and chronic lymphoproliferative disorder of NK cells (CLPD-NK) are included in this category.[3]

Recurrent somatic mutations in the Src homology 2 (SH2) domain of the signal transducer and activator of transcription 3 (*STAT3*) gene have been found in T-LGL leukemia and CLPD-NK,[4,5] leading to constitutive activation of STAT3 and dysregulation of genes downstream of STAT3. More recently, mutations outside the SH2 domain have been discovered in T-LGL leukemia.[6] Activating mutations in the SH2 domain of the *STAT5B* gene were also identified in 2% of LGL leukemia patients,[7] which further underlines the importance of the JAK/STAT signaling pathway in LGL leukemia.

The majority of T-LGL leukemia cases present with a clonal expansion of the $CD8^+$ LGLs. However, in a small percentage of cases, the tumor cells have a $CD4^+$ phenotype.[8-10] Cytomegalovirus-derived stimulation and restricted use of the T-cell receptor (TCR)-Vβ region has been associated with $CD4^+$ T-LGL cases,[11] but this rare disease entity still remains poorly described. To further elucidate the pathogenesis of this rare subgroup of T-LGL leukemia, we explored the mutational landscape of $CD4^+$ cases using exome and targeted amplicon sequencing. Patients diagnosed with T-LGL leukemia and CLPD-NK were recruited. The diagnostic criteria were based on the WHO classifications of 2008. Three patient cohorts (described in detail in the supplemental Appendix, available on the *Blood* Web site) were included in this study.

Exome sequencing was performed on 3 $CD4^+$ T-LGL leukemia patients' sorted tumor ($CD4^+$ or $CD4^+CD8^+$ T cells) and control ($CD4^-$) fractions. The exome was captured with Nimblegen SeqCap EZ Exome Library v2.0, and sequencing was performed with the Illumina HiSeq2000 sequencing platform. Candidate somatic mutations were identified with a bioinformatics pipeline described earlier,[4] as well as a novel pipeline described in more detail in the supplemental Appendix. Through exome sequencing, we were able to identify novel somatic missense mutations in the transactivation domain of *STAT5B* in 2 $CD4^+$ T-LGL leukemia patients. Patient 1 had a Q706L mutation at a variant allele frequency (VAF) of 45% in the $CD4^+CD8^+$ tumor fraction. Patient 2 displayed an S715F mutation (VAF, 36%) in the $CD4^+$ fraction (Figure 1A). Only wild-type (WT) STAT5B was observed in the $CD4^-$ fractions, confirming that the mutations were somatic. The third patient with $CD4^+$ T-LGL leukemia did not show any mutations in *STAT5B* or *STAT3* genes, but mutations in members of the protein tyrosine phosphatase family (*PTPN14, PTPN23)* regulating cell proliferation and tumor suppressor MLL2 were observed (supplemental Table 3).

To study the functional properties of the novel variants, we generated STAT5B expression vectors for WT, Q706L, and S715F mutations and previously described activating N642H mutation.[7] The transcriptional activity of the mutants was studied with luciferase reporter assays with and without interferon-α stimulation, and the phosphorylation status was analyzed by western blotting. In HeLa cells,

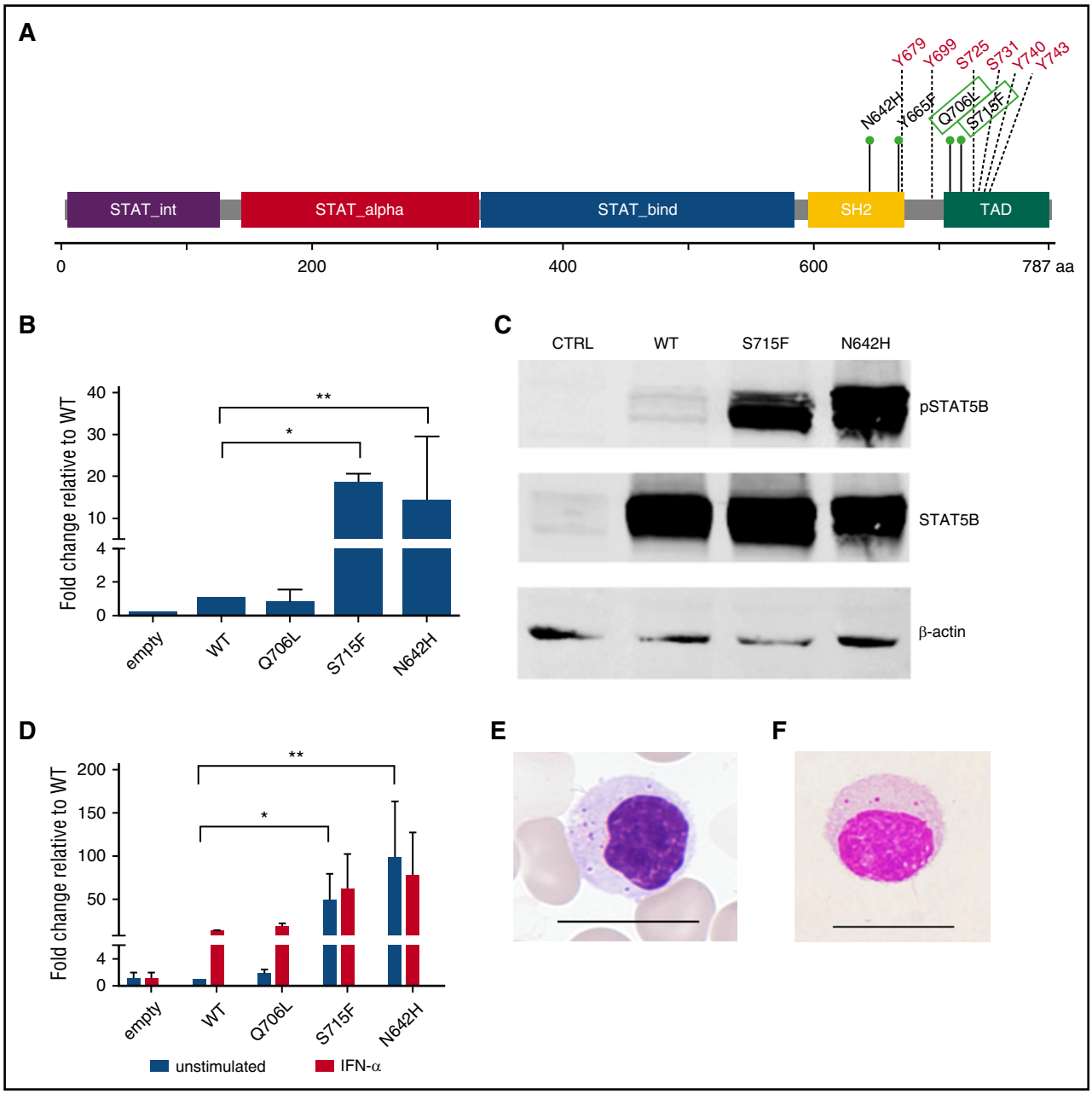

Figure 1. *STAT5B* mutation characterization. (A) Linear representation of the STAT5B protein structure. Previously known LGL leukemia mutations in STAT5B are marked in the SH2 domain, whereas the novel Q706L and S715F mutations in the transactivation domains are marked with green boxes. Multiple tyrosine and serine phosphorylation sites are marked in red. (B) STAT5B reporter assay results. Mutated STAT5B constructs (pCMV6-XL6 *STAT5B*) were generated through site-directed mutagenesis followed by transfection and expression of WT and mutated STAT5B (Q706L, S715F, N642H) in HeLa cells together with a STAT5B reporter. Dual-reporter luciferase assay was used to determine activation and phosphorylation of mutated STAT5B. The experiment was repeated 3 times. Columns represent mean of the fold-change activity. Error bars indicate the standard error of the mean (SEM), and the statistical significance was calculated with a 1-way analysis of variance (ANOVA; $*P < .05$, $**P < .001$). (C) To investigate the phosphorylation status of the variants, HeLa cells transfected with the abovementioned variants were analyzed by western blot with a phosphoSTAT5 (Tyr694) specific antibody. Protein lysates of the different variants were separated on an sodium dodecyl sulfate-polyacrylamide gel electrophoresis gel and transferred to a nitrocellulose membrane. STAT5 protein levels of the different variants were used to normalize for the transfection efficacy. β-Actin was used as a loading control. (D) Transfected HeLa cells were stimulated with 100 ng/mL interferon-α for 6 hours. A dual-reporter luciferase assay was used to determine activation and phosphorylation of mutated STAT5B. The experiment was repeated 2 times. Columns represent mean of the fold-change activity. Error bars indicate the SEM, and the statistical significance was calculated with a 1-way ANOVA ($*P < .05$, $**P < .001$). (E) Typical morphology of a representative LGL cell in a *STAT5B* mutated T-LGL patient. Scale bar, 15 μm. (F) Morphology of lymphocyte expressing CD4, CD56, and TCRαβ in a healthy individual. $CD4^+CD56^+$ and TCRαβ-type lymphocytes were sorted by the FACS method and stained with Wright-Giemsa stain. A representative cell is shown. Scale bar, 15 μm.

the mutated *STAT5B* S715F construct significantly enhanced the transcription of the cotransfected STAT5 reporter (18-fold compared with WT STAT5B) similarly to the N642H mutation (Figure 1B), whereas the Q706L mutation activation was equal to WT. In the western blot analysis, S715F and N642H mutations showed significantly increased phosphorylation compared with WT STAT5B (Figure 1C), whereas no increased phosphorylation was observed with the Q706L mutation. The location of the novel S715F mutation in a serine phosphorylation site is likely to increase the phosphorylation of STAT5B. Stimulation with interferon-α revealed that the Q706L mutation behaved

Table 1. Clinical features of CD4$^+$ T-LGL leukemia patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11
STAT5b mutation (% VAF)	Q706L (45)	S715F (36)	N642H (25)	N642H (46)	Y665F (31)	N642H (27)	None	None	None	None	None
Vbeta expansion (CD4$^+$ population)	Vb.13.1: 98%	Vb.8: 86%	NA	NA	NA	NA	Vb.13.1: 78%	NA	NA	NA	NA
Age (years)	61	70	74	79	82	66	80	67	58	70	79
Sex	M	F	M	F	M	M	F	F	F	F	F
WBC count (10^9/L)	8.5	10.2	9.0	8.7	13.9	9.4	8.7	6.8	5.5	6.1	8.2
Neutrophil (%)*	40	16	12	5	51	32	33	35	32	42	26
LGL (%)*	52	72	71	91	39	63	57	44	54	55	69
Hb (g/L)	134	124	119	126	155	141	135	142	73	135	120
Platelets (10^9/L)	399	204	144	186	245	265	241	143	200	229	156
Other neoplasias	None	None	None	None	None	None	None	None	None	None	None
Other diseases	Diabetes	None	None	Gastrointestinal hemorrhage	None	Lung cancer	Osteoarthritis, hypothyroidism	None	None	None	None
Observation period	5 years	7 years	14 years	6 months	3 years	2 years	3 years	12 years	6 years	12 years	15 months
Outcome	Alive	Alive	Death	Alive	Alive	Alive	Alive	Alive	Alive	Alive	Alive

F, female; Hb, hemoglobin; LGL, large granular lymphocyte; M, male; VAF, variant allele frequency; WBC, white blood cell.

*Neutrophil and LGL percentage from whole white blood cell population. From patients 1, 2, and 3, germline DNA was available for sequencing to confirm the somatic nature of the STAT5b mutations.

as the WT, whereas stimulation was not able to further increase the transcriptional activity of the S715F and N642H mutants (Figure 1D).

To elucidate whether *STAT5B* mutations are more prevalent in CD4$^+$ T-LGL leukemia cases, deep amplicon sequencing was used for screening of the SH2 and transactivation domains of *STAT5B* in CD4$^+$ (n = 8), *STAT3*-mutated CD8$^+$ (n = 37) and nonmutated CD8$^+$ (n = 58) T-LGL leukemia patients. Targeted *STAT5B* amplicon sequencing covering exons 14 to 19 was done with an in-house–developed deep amplicon sequencing panel using the Illumina Miseq platform.[7] The data were analyzed with a bioinformatics pipeline described previously.[12] A variant was called when the variant base frequency was 0.5% of all reads covering a given a position. Additionally, the same regions were screened with Sanger sequencing in Japanese and Chinese LGL leukemia cohorts consisting of CD8$^+$ and CLPD-NK cases (n = 57). None of the patients with CD8$^+$ T-LGL leukemia or CLPD-NK had *STAT5B* mutations. In contrast, 4 of 8 CD4$^+$ T-LGL leukemia cases had *STAT5B* mutations. Of the 4 patients with *STAT5B* mutations, 3 possessed the earlier described N642H mutation and 1 the Y665F mutation. Sanger sequencing–negative patients and healthy controls (n = 50) were also screened with allele-specific PCR for N642H and Y665F mutations, but no additional mutations were found. Altogether, the *STAT5B* mutation frequency in CD4$^+$ T-LGL leukemia patients in our cohort was 55% (6 of 11 patients). This is significantly higher than in the previous study (2%) of 211 CD8$^+$ T- and NK-cell LGL leukemia cases where *STAT5B* SH2 domain mutations were initially discovered.[7] Most of the *STAT5B* mutations found in CD4$^+$ T-LGL leukemia have also been seen in various T-cell neoplasms, including γδ hepatosplenic T-cell lymphoma,[13] T-cell acute lymphoblastic leukemia,[14,15] T-cell prolymphocytic leukemia,[16] type II enteropathy-associated T-cell lymphoma,[17] and extranodal NK/T-cell lymphoma,[18] suggesting that these are shared with other T-cell malignancies. The analyses of STAT5 target genes with chromatin immunoprecipitation sequencing have shown that STAT5B is a key factor in T-cell development, binding to molecules such as DOCK8, SNX9, FOXP3, and IL2RA.[19] Together these results suggest that the STAT5B pathway plays a central role in the development of T-cell neoplasms.

In contrast to other more aggressive T-cell malignancies with *STAT5B* mutations, the disease course in our CD4$^+$ T-LGL leukemia cohort was indolent, and none of the patients with *STAT5B* mutations needed therapy during the observation time (median follow-up, 4 years). Rheumatoid arthritis (RA) is commonly associated with CD8$^+$ T-LGL leukemia, and especially patients with multiple *STAT3* mutations more often have RA.[12] In our cohort, none of the 11 cases with CD4$^+$ T-LGL leukemia suffered from RA. Two patients showed neutropenia and 1 patient had anemia (Table 1).

All *STAT5B* mutated CD4$^+$ T-LGL cases possessed a TCRαβ T-cell phenotype with CD16$^-$CD56$^+$ and CD57$^+$ (Figure 1E). Two cases were CD8$^-$, 2 were weakly positive for CD8, and 2 were clearly positive for CD8 (supplemental Table 4). This is in accordance with the earlier reports[8-10] of monoclonal CD4$^+$ T-LGL cells, which have shown expression of TCRαβ, variable levels of CD8, and a typical cytotoxic (granzyme B$^+$, CD56$^+$, CD57$^+$, CD11b$^{+/-}$) and activated/memory T-cell (CD2$^{+\,bright}$, CD7$^{-/+\,dim}$, CD11a$^{+\,bright}$, CD28$^-$, CD62L$^-$HLA-DR$^+$) phenotype. Interestingly, all 6 patients with *STAT5B* mutations had large monoclonal TCR-Vβ expansions where the mutations were located, whereas significant proportions of *STAT3* mutations in CD8$^+$ T-LGL leukemia and CLPD-NK are detected in small subclones.

Because the CD4$^+$CD56$^+$TCRαβ$^+$ immunophenotypes recognized on *STAT5B*-mutated T-LGL leukemia cells have been poorly defined, we also investigated whether normal lymphocytes with similar phenotypic features exist in peripheral blood of healthy subjects. Among 27 healthy controls, the median percentage of CD4$^+$CD56$^+$ TCRαβ$^+$ T cells in lymphocytes was 0.2, and it varied from less than 0.02% to 6.5% (supplemental Figure 2). Fluorescence-activated cell sorter (FACS)-sorted CD4$^+$CD56$^+$TCRαβ cells possessed LGL morphology with cytoplasmic azurophilic granules (Figure 1F; N = 3). Thus, phenotypically similar cells as observed in CD4$^+$ T-LGL leukemia cases can also be observed in healthy individuals in small quantities. However, deep amplicon sequencing of sorted CD4$^+$CD56$^+$ cells from 5 healthy subjects revealed no mutations in the SH2 or transactivation domains of *STAT5B*.

In conclusion, activating *STAT5B* mutations can be found in the majority (55%) of CD4$^+$ T-LGL leukemia cases, whereas among patients with CD8$^+$ T-LGL leukemia or CLPD-NK, these are very rare. *STAT5B* mutations can be considered as a novel diagnostic marker for this specific disease subtype.

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Contribution: E.I.A., T.T., S.M., and F.I. designed the study, coordinated the project, analyzed the data, and wrote the paper; E.I.A., T.T., T.K., S.L., K.M., and P.E. performed sequence analysis and validated mutations; E.I.A., V.R.G., and Sabrina Bortoluzzi designed and performed the functional experiments; S.E., Stefania Bortoluzzi, A.C., and A.B. designed and performed the bioinformatics analysis; N.S., T.M., N.F., S.N., N.S., H.S., H.N., Y-L.K., T.P.L., and J.P.M. provided patient samples; and all authors read and approved the final manuscript.

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To the editor:

Cardiac involvement in Erdheim-Chester disease: an MRI study

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Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis (<1000 cases reported in the literature), characterized by tissue infiltration by $CD68^+$ $CD1a^-$ "foamy" histiocytes. ECD commonly causes long bone osteosclerosis, retroperitoneal (periaortic and perirenal) fibrosis, central nervous system (CNS) lesions, but also involves the lung, the skin, and various endocrine axes.[1] Cardiovascular manifestations are also common (~40% of the cases) and include infiltration of the myocardium (eg, pseudotumoral atrial masses), the pericardium (eg, pericarditis sometimes complicated by tamponade), and the aorta, with the typical aspect of "coated aorta."[2,3] Patients with ECD with cardiovascular involvement are reported to have a poorer prognosis[1,4,5] and are therefore usually treated aggressively, but