To the editor:

Genetic evidence of *PTPN22* effects on chronic lymphocytic leukemia

The recent article by Negro et al represents a thorough investigation into the effect of Lyp, the gene product of *PTPN22*, on BCR signaling in the pathogenesis and progression of chronic lymphocytic leukemia (CLL).[1] This study shows that increased Lyp enhances Akt, a serine/threonine kinase involved in cell survival and tumorigenesis, despite a negative effect on proximal BCR signaling molecules including Lyn, Syk, and p38MAPK (inhibition of p38MAPK decreases activation-induced lymphoma B-cell apoptosis). The effect is mediated through reduced recruitment/activation of SHIP. Therefore, Negro et al reveal a critical Lyp-mediated mechanism involved in CLL susceptibility.

Over the past decade, the *PTPN22* gene has received considerable attention because of its role in autoimmunity susceptibility, response to infection, and systemic inflammation. A diverse set of studies have demonstrated that the R620W missense polymorphism in *PTPN22* (rs2476601) is involved in numerous immune-related diseases, including type 1 diabetes, rheumatoid arthritis, autoimmune thyroiditis, systemic lupus erythematosus, primary antibody deficiency, and bacterial infection.[2-4] Functional studies have painted a complex picture of how Lyp*620W affects lymphocyte function/activity: reduced Lyp protein levels, obstruction of Csk binding, lower TCR-induced Tyr-phosphorylation of Lyp, inhibited BCR-mediated apoptosis, and reduced pruning of autoreactive B cells are all proposed mechanisms.[5-8] The discovery of whether Lyp*620W confers protective or susceptible effects on CLL (ie, significantly increased/decreased in CLL cases over controls) may not only provide insight into CLL susceptibility, but also may illuminate Lyp-mediated signaling. The Negro et al study genotyped rs2476601 in a limited number of Italian CLL cases (n = 29) with 1 identified carrier, which is consistent with the expected low 620W allele frequency within an Italian population compared with northern/western Europeans (HapMap).[1] However, matched controls are absent and this small substudy suffers from less than 10% power to detect a relative risk of 1.4.

To further investigate the role of the *PTPN22* gene in CLL, we correlated rs2476601 genotypes (or a surrogate of rs2476601) with CLL using data from 2 unique studies derived from northern/western Europeans. In the Personalized Medicine Research Project (PMRP) cohort,[9] 37 of the 4235 genotyped subjects were diagnosed with CLL based on ICD9 codes within patient electronic medical records. The frequency of 620W carriers was significantly increased in CLL cases compared with 4199 controls (PMRP: 32% vs 18%, respectively, $P = .033$; Table 1). The Genetic Epidemiology of CLL (GEC) Consortium genotyped a proxy single-nucleotide polymorphism (rs6679677) in complete linkage disequilibrium (HapMap-CEU $r^2 = 1$) with rs2476601 in 407 CLL cases and 296 controls,[10] producing results supporting the PMRP finding (GEC: 24% vs 17%, $P = .019$; Table 1). Whereas these results corroborate the Negro et al report, additional verification of these preliminary findings is needed to draw strong conclusions. Given previous studies showing the 620W allele generating decreased $CD27^+$ B-cell proliferation independently of apoptotic processes,[5] these results raise the possibility that 620W pro-CLL effects may be mediated through nonproliferative mechanisms. Because Lyp exercises its pathogenic action across multiple diseases and as Lyp-targeted therapies continue to develop, understanding the potential role of *PTPN22* variation in CLL will be essential as we elucidate the molecular pathogenesis of CLL and other immunologic diseases/conditions.

Table 1. CLL genotype data for R620W variant or surrogate rs6679677

Marshfield PMRP*		
Rs2476601	**CLL+**	**CLL−‡**
GG	25	3432
AG	12	720
AA	0	47
GEC Consortium†		
Rs6679677	**CLL+**	**CLL−‡**
CC	310	247
AC	91	44
AA	6	5

*Fisher exact test (carriers vs noncarriers) $P = .033$; Cochran-Armitage Trend Test $P = .062$. AA + AG vs GG genotype odds ratio = 2.15; 95% confidence interval, 1.07-4.29.

†Fisher exact test (carriers vs noncarriers) $P = .019$; Cochran-Armitage Trend Test $P = .041$. AA + AC vs CC genotype odds ratio = 1.58; 95% confidence interval, 1.08-2.31.

‡The increased 620W frequency in GEC/PMRP controls over those in Negro et al reflects the well-described strong gradient from southern to northern/northeastern Europe.[1]

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Response

Increased expression or activity of PTPN22 may compromise negative selection of autoreactive CLL cells

The finding of Hebbring et al that the PTPN22 R620W autoimmunity risk allele is present at a higher frequency in chronic lymphocytic leukemia (CLL) patients originating from northern/western Europe than in matched controls[1] is very interesting and provides further support to the recent findings of Negro et al suggesting an important role for PTPN22 in the pathogenesis of CLL.[2]

The study by Negro et al investigated the expression of PTPN22 in a large series of CLL patients from Italy, where the PTPN22 R620W autoimmunity risk allele is relatively infrequent, and showed that PTPN22 is markedly overexpressed in the majority of investigated CLL samples.[2] Additional experiments showed that overexpression of PTPN22 attenuates BCR signals that can potentially induce leukemic cell apoptosis while simultaneously increasing the activity of the AKT kinase, a key survival signaling molecule in CLL cells. This selective uncoupling of AKT from downstream proapoptotic BCR pathways was shown to protect CLL cells from activation-induced cell death. Overall, these data suggested that the purpose of PTPN22 overexpression in CLL could be to protect the malignant B cells, which frequently express autoreactive BCRs, from immunologic tolerance mechanisms that eliminate autoreactive lymphocytes.

A similar mechanism is believed to be responsible for the increased risk of autoimmune disease in subjects carrying the PTPN22 R620W allele.[3] The risk allele has been shown to inhibit antigen-receptor signaling more strongly than the wild-type protein,[4] suggesting that it could compromise autoantigen-induced negative selection of autoreactive lymphocytes. Therefore, the finding by Hebbring et al that the PTPN22 R620W autoimmunity risk allele is present at a higher frequency in northern/western European CLL patients than in matched controls suggests that both