Supplemental Figure 1: Viability of CLL cells after transfection with BTK or control siRNA and coincubation with stromal cells or stimulation with IgM. BTK knockout reduced CLL cell viability even in the presence of stromal cells or after IgM stimulation. This figure represents each patient with a different symbol so that the changes in viability can be seen among conditions in each individual patient.

Supplemental Figure 2: XID/TCL1 genotype or ibrutinib treatment in vivo decreases the response to in vitro IgM stimulation in peripheral blood lymphocytes. Mice with the XID/TCL1 genotype that were untreated, TCL1 mice receiving vehicle treatment, and TCL1 mice receiving ibrutinib treatment had peripheral blood drawn and B cells selected using EasySep kit (Stem Cell Technologies) after either Ficoll density centrifugation or red blood cell lysis. Cells were then untreated or stimulated for 15 minutes with plate-immobilized IgM and then lysed. BCR stimulation, as shown by phosphorylation of ERK, was significantly diminished in mice with the XID/TCL1 genotype (4A) or WT/TCL1 mice receiving ibrutinib (4B) compared with WT/TCL1 mice undergoing vehicle treatment (4C).

Supplemental Figure 2A: XID/TCL1 mice
**Supplemental Figure 2B: Ibrutinib treated TCL1 mice**

[Immunoblot images showing pERK and ERK for different mouse groups: Mouse 1 Vehicle, Mouse 1 IgM, Mouse 2 Vehicle, Mouse 2 IgM, Mouse 3 Vehicle, Mouse 3 IgM, Mouse 4 Vehicle, Mouse 4 IgM.]

**Supplemental Figure 2C: Vehicle treated TCL1 mice**

[Immunoblot images showing pERK and ERK for different mouse groups: Mouse 1 Vehicle, Mouse 1 IgM, Mouse 2 Vehicle, Mouse 2 IgM, Mouse 3 Vehicle, Mouse 3 IgM, Mouse 4 Vehicle, Mouse 4 IgM.]

**Supplemental Figure 3: XID/TCL1 mouse spleen lymphocytes do not respond robustly to *in vitro* IgM stimulation.** Spleen cells from non-leukemic XID/TCL1 and WT/TCL1 mice were isolated using EasySep B cell selection kit (Stem Cell Technologies). Cells were then untreated or stimulated for 15 minutes with plate-immobilized IgM and then lysed. BCR stimulation, as shown by phosphorylation of ERK, was significantly diminished in mice with the XID/TCL1 genotype compared with wild type mice. Numbers below the immunoblot reflect densitometry values normalized to unstimulated condition. Black line indicates that the image is cut at this point; however, both sides are taken from the same original image.
**Supplemental Figure 4:** pErk expression is variable following ibrutinib treatment. B6/TCL1 mice with evidence of leukemia were treated for 1 week with ibrutinib. At sacrifice, spleens were processed, and B cells selected using EasySep mouse B cell selection kit (Stem Cell Technologies). Cells were then lysed, and western blots performed for pErk expression. pErk is variably expressed after ibrutinib treatment.
Supplemental Figure 5: BTK occupancy following ibrutinib drinking water administration. Following 7 days of continuous drinking water exposure, spleens were harvested and lymphocytes analyzed for BTK occupancy using fluorescent probe assay. 0.16 mg/mL formulation, corresponding to an average dose of 30.5 mg/kg/day, was used for all experiments outlined in this manuscript and produces approximately 80% occupancy of BTK [i.e. (1 - probe occupancy) * 100].

Supplemental Table 1: Average daily dose of ibrutinib in drinking water formulation. Experiments outlined in this manuscript use 0.16 mg/mL ibrutinib drinking water formulation.