Supplementary Figure 1. Upper left plot: results by mutation type. DNP= dinucleoitde mutation; TNP= trinucleotide mutation; SNP= single nucleotide mutation; ONP= oligo-nucleotide mutation; INS= insertion; DEL= deletion; MUL= multihit. Upper middle plot: representation of mutation frequencies by type. Upper right plot: frequency of point mutation types. Lower left and right plots: per-sample mutation distribution.

Supplementary Figure 2. Kaplan-Meier plot reflecting the association of *IGLV3-21* mutations with time to treatment. The blue line reflects mutated cases.

Supplementary Methods. Detailed information on the pipeline used for variant detection, filtering and driver detection can be consulted in this file.

Supplementary Table 1. Mutation data.

Supplementary Table 2. CLL drivers detected in this study. The detection method is indicated in the columns. Previously identified drivers by *Puente et al.* (2015) are labeled red, those identified by *Landau et al.* (2015) are labeled green and those reported by both studies are labeled blue. Clonal (VAF > 40%) and subclonal (VAF < 40%) mutations are indicated in the last column.

Supplementary Table 3. MuSiC2 analysis results of non-synonymous exonic mutations.

Supplementary Table 4. OncodriveFM analysis results of non-synonymous exonic mutations.

Supplementary Table 5. OncodriveClust analysis results of non-synonymous exon mutations.

Supplementary Table 6. mutation3D analysis results of non-synonymous exon mutations..

Supplementary Table 7. CHASM analysis results of non-synonymous exon mutations.

Supplementary Table 8. VEST analysis results of non-synonymous exon mutations.

Supplementary Table 9. Mutations at low frequency drivers, along with p-values for their predicted effect on protein function calculated by CHASM and VEST. Only mutations with q-values <0.25 are shown. Previously identified drivers by *Puente et al.* (2015) are labeled red,

those identified by *Landau et al.* (2015) are labeled green and those reported by both studies are labeled blue.

Supplementary Tables 10-11. Non-silent mutations association with treatment-free survival since diagnosis, unadjusted model and adjusted models respectively.

Supplementary Table 12-13. Non-silent mutations association with overall survival, unadjusted and adjusted models respectively.

Supplementary Table 14. Genes enriched in intronic mutations at a significant or suggestive level (MuSiC2 q-value <0.1 or <0.25, respectively).

Supplementary Table 15. MuSiC2 analysis results of intronic mutations.

Supplementary Table 16-17. Intronic mutations association with treatment-free survival since diagnosis, unadjusted and adjusted models respectively.

Supplementary Tables 18-19. Intronic mutations association with overall survival, unadjusted and adjusted models respectively.

Supplementary Table 20. PathScore analysis results of non-synonymous exon mutations.

Supplementary Table 21. Pathways level association with time to treatment and overall survival, unadjusted and adjusted models as stated in the headers.

Supplementary Table 22. 5' UTRs+Flanks association with time to treatment and overall survival. Data for unadjusted and adjusted models are indicated according to the corresponding headers.

Supplementary Table 23. 3' UTRs+Flanks association with time to treatment and overall survival. Data for unadjusted and adjusted models are indicated according to the corresponding headers.

Supplementary Table 24. Number of mutations included for validation and confirmed in the WGS data. Results for non-coding drivers, intronic drivers and the 5'UTR of *IGKC* are reported separately.