

# Ig VH Gene Analysis for Chronic Lymphocytic Leukemia Prognosis

*DETECTS THE MUTATION STATUS OF THE IG HEAVY CHAIN VARIABLE REGION IN CHRONIC LYMPHOCYTIC LEUKEMIA*

## Clinical Background

- Chronic lymphocytic leukemia (CLL) is a B-cell neoplasm and the most common leukemia in the United States and Europe.
- The clinical course of CLL is variable, with approximately one half of cases being very indolent, while the other half behaves more aggressively.
- The clinical course of CLL has been shown to correlate with somatic mutations that may be present in the expressed immunoglobulin (Ig) heavy-chain variable region (VH) gene segments, with cases expressing non-mutated VH genes typically having a more aggressive clinical course.<sup>1-4</sup> Expression of the VH3-21 gene segment has been associated with poor prognosis in CLL, regardless of the mutation status.<sup>4,5</sup>

## Indications for Ordering

To determine the risk group for newly diagnosed cases of CLL.

## Interpretation

- **Non-mutated:** The VH segment is  $\geq 98$  percent identical to the most closely matched germline VH gene sequence. The VH segment and percent homology will be reported.
- **Mutated:** The VH segment is  $< 98$  percent identical to the most closely matched germline VH gene sequence. The VH segment and percent homology will be reported.
- **No clone:** No clonal VH gene could be identified.

## Limitations

- Results of this test must always be interpreted in the context of morphologic and other relevant data, and should not be used alone for a diagnosis of malignancy.
- Samples that do not yield an amplification product may either contain too few CLL cells or express VH genes with high numbers of mutations that may have compromised PCR-primer binding.
- This test is not intended to detect minimal residual disease.

## Methodology

- RNA is extracted, reverse transcribed, and then amplified with VH leader and JH primers.
- After sequencing the amplified products, identified clonal VH sequences are searched against a database of all known variable region germline sequences. The closest matching germline VH gene segment and the percent of homology to it are reported.
- Homologies measuring 98 percent and above are designated as non-mutated and those below 98 percent are designated as mutated. In addition, mutated cases with homologies between 97 and 97.9 percent are flagged as borderline and may have an intermediate clinical course.<sup>3</sup>
- CLL cells expressing the VH3-21 variable region often have a poor prognosis, regardless of mutation status. CLL clones as small as 50 percent of total B-cells can be analyzed by this test.

## References

1. Van Bockstaele F, Verhasselt B, Philippe J. Prognostic markers in chronic lymphocytic leukemia: a comprehensive review. *Blood Rev* 2009; 23 (1) :25-47.
2. Hamblin TJ. Prognostic markers in chronic lymphocytic leukaemia. *Best Pract Res Clin Haematol* 2007;20(3):455-468.
3. Hamblin TJ, Davis ZA, Oscier DG. Determination of how many immunoglobulin variable region heavy chain mutations are allowable in unmutated chronic lymphocytic leukemia – long-term follow up of patients with different percentages of mutations. *Brit J Haematol* 2008;140:320-323.
4. Ghia EM, et al. Use of IGHV3-21 in chronic lymphocytic leukemia is associated with high-risk disease and reflects antigen-driven, post-germline center leukemogenic selection. *Blood* 2008;111:5101-5108.
5. Tobin G, et al. Somatic mutations of Ig VH3-21 genes characterize a new subset of chronic lymphocytic leukemia. *Blood* 2002;99:2262-2264.

## Test Information

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*Ig VH Analysis by Sequencing*

For specific collection, transport, and testing information, refer to the ARUP Web site at [www.aruplab.com](http://www.aruplab.com).

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).